AN EVALUATION OF COMPLIANCE IN CANCER PATIENTS

AND NON-INSULIN DEPENDENT DIABETICS

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ABSTRACT

A novel electronic recording device for monitoring patient compliance with oral therapy was described and the method of its construction explained. The accuracy of the device under various conditions of use was evaluated. To interpret the output data from the monitor new compliance measures were devised describing the "overall compliance", the "daily irregularity" and the "hourly irregularity".

The device was used to assess the compliance in three groups of patients attending out-patient oncology clinics in London hospitals. These patients were suffering from small-cell lung cancer, or ovarian cancer or lymphoma. The influence on patterns of drug administration of factors such as their quality of life, including experience of drug side-effects, the number of cycles of chemotherapy they had received and the complexity of their dosage regimens was considered.

In a further study, a group of non-insulin dependent diabetics were recruited from two general practice surgeries in London. They were all being treated with the oral hypoglycaemic agent glibenclamide. Their compliance was assessed using the electronic monitor, by blood levels of the drug, by the physicians' estimation and by counting the number of tablets returned in the device at each visit. Possible correlations between compliance and the patients' health beliefs and biochemical measures of diabetes control were investigated.

Patient compliance with the short term courses of oral chemotherapy was found to be very high in all the patient groups and suggests that inadequate compliance with oral chemotherapy would not account for any significant lack of clinical response in these patients. This finding inspires confidence in the use of self-administered oral

chemotherapy, having as it does advantages in convenience to the patient and cost of treatment. More surprisingly, compliance with long term oral hypoglycaemic agents was also found to be high and reasons for this are discussed.

The ethics and advantages of using electronic devices to monitor compliance are discussed in the light of these findings.

To my mother

the late

Maureen Fold Lee

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CHAPTER 1

THE ASSESSMENT OF PATIENT COMPLIANCE

1.1 COMPLIANCE

1.1.1 Definition of Compliance

Compliance has been defined as the extent to which a person's behaviour, in terms of taking medications, following diets, or executing other life-style changes, coincides with the clinical prescription (Sackett & Haynes 1976). Other terms have been used in place of compliance , such as adherence, because compliance is seen by some as implying that the clinician has a dictatorial relationship with the patient (Fletcher 1989). Compliance, however remains the most commonly used term (Fletcher 1989, Feinstein 1990).

1.1.2 The Importance of Compliance Assessment

Accurate assessment of a medication's safety and efficacy in a clinical trial is made increasingly difficult when, in addition to inter-patient variability in drug handling, patients are also receiving varying doses of a drug at different frequencies due to varying levels of compliance. Significant non-compliance in a clinical trial could result in the conclusion that an effective drug is ineffective or result in the overestimation of the minimal effective dose (Rudd et al 1990). In the Lipid Research Clinic Coronary Primary Prevention Trial a compliance distribution was demonstrated. The mean reduction in coronary heart disease (CHD) was 19-24% among the cholestyramine treated group as compared with the control group. However, when the compliance data was taken into account it was projected there could have been up to a 49% reduction in CHD if all subjects had taken the full dose (Lipid Research Clinics Program 1984).

Compliance assessment is also important for the general practitioner. If a medication appears to be ineffective it may be due to it being the wrong medication for the condition, the dose being too low or needing augmentation, or it may be just that the patient has failed to take it as prescribed. The consequences of increasing the dose or changing to, or adding, a more powerful drug when the medication is ineffective solely because of non-compliance, include a likely increase in adverse reactions and greater costs (Rudd 1987).

If a practical, accurate and sensitive measure of compliance were available compliance bias in clinical trials could be eliminated and the clinician would be better able to assess ambiguous clinical responses.

1.2 Methods used to Assess Compliance

One of the major problems in compliance research has been the lack of a valid way to measure compliance. Haynes, Taylor & Sackett (1979) reviewed 537 original studies and found that less than 40 satisfied their methodological requirements. Methods are generally broadly divided into indirect or subjective methods such as interviews, questionnaires and pill-counts and direct or objective methods such as drug assays of body fluids (Gordis 1979). No single method is entirely satisfactory, but, direct methods generally give higher figures for non-compliance than indirect methods (Evans & Spelman 1983). More recently, new medication monitors have been devised which offer a break-through in compliance measurement in that they allow the continuous monitoring of a patient's drug administration patterns.

1.2.1 Indirect Measures

1.2.1.1 Treatment Outcome

With most medications, assuming the diagnosis is correct, a patient is more likely to have a full therapeutic response if they comply with the regimen than if they do not. Leistyna (1966) showed that there is a relationship between compliance demonstrated by pharmacokinetic methods and treatment response in a group of patients with streptococcal pharyngitis treated with penicillin. Compliance was judged by urine assays for penicillin; there were more negative urine assays in patients who had positive culture on re-examination and were not responding to drug therapy. However, the approach is not very sensitive because even when patients comply a satisfactory outcome is not guaranteed. In a study by Cheung et al (1988a), patients treated with antibiotics for clinically proven urinary tract infections had their compliance assessed by electronic medication monitor. Outcome was monitored clinically and no difference was found in both the total compliance or pattern of compliance in patients who were cured and those not cured. Kass et al (1986b) monitored compliance using an electronic eye-drop medication monitor in patients on pilocarpine treatment for glaucoma. None of the clinical measurements, including intra-ocular pressure, pupillary diameter and pupillary reactivity to light, distinguished patients with lower rates of compliance from those with higher rates of compliance. Compliance should be viewed as a moderator of clinical response (Dunbar et al 1989), so whilst therapeutic outcome is important in the assessment of treatment efficacy it should not be used to measure treatment compliance.

1.2.1.2 Prescription Refill

Pasty (1990) used the method of prescription refill to identify patients who had recently stopped taking their beta-blockers and assessed the subsequent risk of coronary heart disease. In another study in the USA a retrospective review of Medicaid-paid prescription data was carried out to look at the relationship between compliance and dosing schedules in patients treated with non-steroidal anti-inflammatory drugs for arthritis (Jacobs 1988). The method has not been compared with other compliance measures and would generally only be applicable to those patients on long-term medications for chronic disorders. The method has the disadvantage that even if the patient has the prescription dispensed this does not ensure the medication is taken or used.

1.2.1.3 Patient Interviews or Questionnaires

For the general practitioner the cheapest and most practical way to assess patient compliance is to ask the patient in a non-judgemental manner whether they take their tablets (Sackett 1979). In a study of a group of diabetic patients the best correlate of medication compliance, as assessed by pill-count, was simple questioning of the patient (Diehl et al 1987). Weaker correlations were obtained with certain other demographic, and socioeconomic variables which were considered. However, the sensitivity, calculated as the proportion of patients with less than 80% compliance by pill count who reported taking their medication less than every day, was only 22-50%. In another study Inui et al (1981) examined the relationship of verbal self-report to independent pill counts in patients with hypertension. Their estimate of sensitivity was 40-55% and they concluded that the predictive value of a patient's report of any

non-compliance was sufficiently high to be of clinical value. Stewart (1987) interviewed patients and conducted a pill-count ten days after they had visited their family physician. The percentage of true non-compliers, as assessed by pill-count, identified by the questionnaire ranged from 40-80% depending on the patient subgroup.

As the figures for sensitivity show, although some patients who are non-compliant may be identified by direct questioning many will not. A study by Bergman & Werner (1963) in patients with streptococcal pharyngitis treated with penicillin showed that negative urine assays for penicillin identified more non-compliant patients than either pill-counts or patient interviews. On ten occasions over a period of two years, Roth & Caron (1978) measured the intake of antacids in patients with peptic ulcer. Compliance was measured by an elaborate system of bottle counts which was validated by blood levels of a tracer substance added to the antacid. Patients were also questioned in a "sympathetic" way about their intake. A small correlation was found between patients' statements of intake and bottle count; however, the mean (SD) actual intake by bottle count was 47% (27%) and the mean (SD) stated intake was 89% (17%) of the prescribed amount. Moreover, patients who admitted missing only an occasional dose actually missed substantially more doses than those who claimed 100% compliance. For patients who claimed they took 100% of the prescribed dose, intake varied from 2% to 130% with a mean of 59%. For those who described missing an occasional dose (80-95% compliance) the mean actual intake was 40%. Norell (1981a) used an electronic eye-drop monitor to record the compliance of patients treated with pilocarpine to prevent visual loss from glaucoma. Patient interviews identified 7 out of 16 patients who missed doses at least once in the

previous week (44% sensitivity). There was a small correlation between interview data and monitor data (r= 0.38). However, under-reporting of missed doses was a major problem in determining medication compliance by interview. Of 73 patients interviewed, only 4% reported two or more missed doses during the previous week whereas monitor records showed that 33% of the patients missed at least 2 doses and 16% at least 6 doses over the same period. Kass et al (1986b) used an electronic eye-drop medication monitor in a similar group of patients and reported that subjects administered a mean (SD) of 76% (24%) of prescribed pilocarpine doses whereas when interviewed they reported using a mean (SD) of 97% (6%) of doses. There was a small correlation (r= 0.20) between a patient's report and compliance as recorded by the monitor. Patients are likely, therefore, to be at least as and possibly 2-3 times as non-compliant as indicated by interview. Estimates of non-compliance may therefore be misleading when interviews are used to determine the proportion of non-compliant patients or the frequency of missed doses (Norell 1981a).

There are a number of reasons why asking the patient is not an accurate measure of compliance. People naturally present themselves in a good light so are likely to overestimate their compliance. Paradoxically this may be even more likely to occur in a good doctor-patient relationship where the patient wants to protect the relationship (Caron 1985). The most common reason for patients omitting doses is probably forgetfulness so asking the patient to remember when they forgot is unlikely to provide accurate information. Patient recall deteriorates when the interval exceeds two weeks (Rudd 1979), so it is best to ask the patient how many doses they omitted in the preceding week for the information to be the most accurate. However, it has been shown by electronic monitoring that compliance in the five days preceding a

clinic visit is significantly higher than that in five days a month before the visit (Cramer et al 1990). The imminent clinic visit seems to serve as a reminder to take the tablets. Reliance on pre-visit behaviour to formulate a report of usual compliance could therefore lead to overestimation of adherence (Dunbar et al 1989).

1.2.1.4 Physicians' Assessment

Doctors often have to make judgments about the level of compliance of their patients. Moulding (1970) showed that there was a correlation between physicians' and nurses' predictions of compliance and actual compliance as assessed by a medication monitor. However, neither physicians or nurses could accurately predict the compliance of all patients. In a study of antacid compliance, Roth & Caron (1978) showed that the physicians' estimates were more accurate than the patients' statements but averaged 50% higher than actual intakes. The correlation between actual intakes and physicians' estimates was 0.48 indicating that physicians' judgements were significantly better than chance but nevertheless low in accuracy. In a study of glaucoma patients by Norell (1981a) physicians and ophthalmology assistants were asked to estimate their patients compliance and this was compared with an electronic monitor record. Both the physicians' and assistants' estimates showed a small correlation with the monitor record. However, there was no correlation either between the estimates of the physicians and those of the assistants or the self-report of the patients themselves. It was therefore concluded that neither the physicians' nor assistants' estimates were useful in determining compliance. In a similar study of pilocarpine administration to glaucoma patients, physicians estimated their patients compliance (Kass et al 1986b). This was only moderately correlated (r= 0.20) with

the data derived from an eye drop monitor and physicians were unable to distinguish patients with lower rates of compliance from those with higher rates of compliance. Interestingly, the accuracy of the physicians' prediction was not affected by how well they knew the patient. The best independent predictors of compliance were found to be weight of medication used, the physician's estimate and pupillary reactivity; however, these three factors together accounted for only 15% of the variation in compliance.

There are a number of reasons why doctors are not able to make an accurate assessment of the compliance of a particular patient even though the doctor has access to the patient's clinical data, possibly the patient's report of compliance, a knowledge of the patient and experience. The clinical data may be misleading since some patients remain well or get better even though they do not comply with the treatment and other patients have disease progression despite rigid adherence (see section 1.2.1.1). The patients' self report is likely to be an overestimation of their compliance (see section 1.2.1.2) and knowledge of the patient has been shown to be unrelated to ability to predict compliance (Kass et al 1986b).

1.2.1.5 Pill-Counts

The pill-count or return tablet count is the most commonly used method of assessing compliance in clinical trials since it is simple, cheap and noninvasive. It is usually performed by dispensing more tablets than required and asking the patient to return any remaining at the next visit. These are then counted and related to the number expected to give a measure of the overall compliance. By dispensing more than required it is hoped that the patients who are non-compliant, and just dispose of

all the tablets before returning, are more easily identifiable.

That pill-counts are more accurate a measure than patient interviews has been demonstrated in a number of studies (Bergman et al 1963, Roth & Caron 1978, Diehl et al 1987, Maenpaa et al 1987b). However, studies comparing pill-counts with the more direct measures of pharmacologic indicators or electronic monitors are critical of the approach. Pullar et al (1989) assessed compliance using both a pharmacologic indicator (low-dose phenobarbital) and a return tablet count in 225 patients. Of the 161 patients who had compliance by tablet count in the range 90-109%, 77 or 48% had low plasma phenobarbital concentrations when compared with those of "age-related" volunteers. They concluded that tablet-counts overestimate compliance although this assumes that patients and volunteers are handling the drug in a similar manner.

Cheung et al (1988a) studied compliance in patients treated for urinary tract infections using an electronic medication monitor. They found that although counting the number of openings of the monitor overestimated compliance, counting the residual tablets grossly overestimated it. Roth & Caron (1970) used a bottle count and a tracer (a low level of sodium bromide) to assess the compliance of patients being treated with antacid for peptic ulcer. An elaborate system was devised for conducting the bottle count using a 'delivery man' who collected the empty bottles and delivered a new supply every 30 to 60 days. Nevertheless, they found that there was only a moderate correlation between bottle counts and their matched bromide levels and the correspondence was particularly poor when bottles were "missing". They concluded on the basis of their experience a substantial number of "clinic" tablet or bottle counts are invalid.

Rudd et al (1989) assessed compliance by pill count in an antihypertensive drug trial. Patients were selected for high rates of compliance and the mean compliance rates did in fact approximate 100%. However, they found a wide variability in weekly pill counts between patients and within patients over time, which was obscured by long-term averages. In the subset of patients who were over-compliant by pill-count, the reduction in blood pressure was similar to the group who were under-compliant by pill-count, and in both these groups the reduction in blood pressure was lower than the patients who had good compliance by pill count. The authors concluded the best explanation for this was that patients who appeared over-compliant were not actually ingesting the tablets. This study highlights the problem of how to interpret data when the subject fails to return the container, or when they return an empty container when there should be tablets remaining. In the study previously mentioned in this section by Pullar et al (1989), 6 out of 10 patients with compliance by return tablet count greater than 110% and 4 out of 12 who failed to return their container had plasma phenobarbital concentrations that were suggestive of non-compliance.

In summary, pill-counts are subject to manipulation by patients and care must be taken to carry out the "counting" as unobtrusively as possible (Caron 1985). Although it has been said: "if the tablets are in the bottle they are not in the patient" (Pearson 1982), the assumption that patients who return approximately the correct number of tablets have good compliance is likely to be wrong for about one half to one third of the patients (Pullar et al 1989).

1.2.2 Direct methods

1.2.2.1. Drug assays of body fluids

The use of pharmacokinetics and therapeutic drug monitoring has had an important impact on the current practice of pharmacy and medicine, finding uses from drug development and formulation to individualised dosage regimens (Backes & Schentag 1991). Therapeutic drug monitoring has also been used to determine patient compliance with their medication.

Most studies measure the drug or a marker in either the plasma or urine. Measuring the drug itself is the best method when there is a clear relationship between dose and steady-state blood level. Therapeutic drug monitoring is used routinely with some drugs such as theophylline and the anticonvulsants, and for these low drug concentrations are often used as a predictor of non-compliance. However, Kossoy et al (1989) found that in certain of their patients persistently low or erratic plasma concentrations of theophylline were due to abnormal disposition of the bronchodilator rather than non-compliance. For other drugs the time and expense of working up a suitable assay and obtaining reference plasma concentrations for each medication you wish to study is probably not feasible and, indeed, may not be possible, if there is no clear relationship between dose and plasma level and where the drug pharmacokinetics are not well understood. Often this method would merely provide a non-quantitative "marker" which would indicate whether a dose of the drug has been ingested during the past few hours.

A solution to this is to add a pharmacologic marker to the medication to be studied. Roth & Caron (1970) used a tracer substance added to a liquid antacid to

measure the compliance of patients being treated for peptic ulcer. Maenpaa et al (1987a) used minimal doses of digoxin as a marker to assess compliance in a primary prevention study of coronary heart disease. Feely et al (1987) have developed a method using low-dose phenobarbital as a marker which they have used in a number of studies (Feely et al 1988, Pullar et al 1988, Pullar et al 1989). They have also compared the use of a short half-life marker (low-dose isoniazid), a long half-life marker (low-dose phenobarbital), and measurement of the drug itself (controlled release metoprolol) in a volunteer study with simulated partial (two thirds) compliance (Hardy et al 1990) They found measurement of phenobarbital was much superior to isoniazid or metoprolol measurements in reflecting partial compliance over the previous 1 to 4 weeks. Using a long half-life marker enables you to assess compliance over a longer period of time and therefore distinguish between fully compliant patients and those that have just been compliant in the few days prior to the visit. The marker technique has one potential problem that does not seem to have been addressed, in that, if the marker chosen has completely different pharmacokinetics from the drug under study, the results could be misleading.

Detection of a drug or marker in the body as a means of identifying non-compliant patients has been compared with other compliance measures. In all cases, the method has given higher figures for non-compliance than pill-counts or patient interviews and physicians' reports. Roth & Caron (1970, 1978) found that the tracer technique was superior to either bottle count, patient interview or physicians' report. Pullar et al (1989) showed that a low-dose phenobarbital marker identified more non-compliant patients than pill-count. Maenpaa et al (1987b) showed that a digoxin marker identified more non-compliant patients than capsule counting or patient

questionnaire.

A couple of studies of compliance using electronic medication monitors have cast doubt on the usefulness of monitoring the drug to predict compliance. Cheung et al (1988b) assessed compliance by electronic monitor in 22 patients on anti-tuberculous therapy. Patients also provided a urine sample to test for the medication, an accepted way to assess compliance in these patients. Of the two patients with negative urine results one was fully compliant according to the monitor and the patient with the poorest compliance had a positive urine test. It is unlikely that the patient who was fully compliant by the monitor was actually non-compliant since the patients were unaware of the monitor. The patient with the positive urine test who was non-compliant could have taken the medication on the few days prior to the clinic and therefore appeared more compliant than he was. Cramer et al (1989) measured compliance with anti-convulsant therapy by drug serum concentration and an electronic medication monitor. Coefficients of variation of drug serum concentrations had no significant relationship to compliance rates from the electronic monitor and the authors concluded finding a drug serum concentration within the therapeutic range or small variations in repeated levels cannot be assumed to reflect good compliance.

The greatest advantage of this method over the measures of compliance discussed previously is that, if the drug is detected, one can be sure the patient has ingested it. However, the great limitation of the method is that there are so many variables other than compliance that may influence the concentration detected (Backes & Schentag 1991). Possible variables include time of drug ingestion in relation to sampling (not known in an ambulatory setting), variations in drug handling between patients and within patients over time, and drug pharmacokinetics. Unlike patient

interviews, where if a patient reports they have missed some doses they are likely to be at least as non-compliant as they say (see section 1.2.1.3), and pill-counts, where if the tablets are in the bottle they are not in the patient (see section 1.2.1.4), with drug assays if a low level of the drug is detected this may not necessarily indicate poor compliance. That is, unlike pill-counts and patient interviews assessing compliance by blood levels of the drug can produce false negatives.

1.2.3 Summary of Indirect and Direct Measures

All the above measures of compliance have the limitation of not defining exactly when pill consumption began, how dosing frequency proceeded or whether periods of over-compliance and under-compliance were such as to cancel each other out (Rudd 1987). Furthermore, their use is distant in time from the actual medication taking event. At best, therefore, they are crude measures resulting in research which has reduced the multiple patterns of medication usage into an overly simplistic dichotomy of compliant and non-compliant (Dirks et al 1982). Furthermore, as Rudd (1987) has concluded such measures all show disappointing levels of sensitivity, that is they are able to detect few of the patients who have imperfect compliance. Because of the continuity of record afforded by medication monitors, they can provide a more accurate indication of the pattern of drug administration and thereby may prove of more practical use in clinical trials and treatment.

1.2.4 Medication Monitoring Devices

A number of medication devices that automatically record when they are used

have been developed. The information obtained gives far more detail than any other compliance measure. This detailed pattern of medication usage allows analysis of dosing intervals, frequency of over and under-dosing and trends in compliance over time (Norell 1983, Cramer 1991). The major criticism of the monitors is that you do not know whether the medication was actually used or ingested. However, it is most unlikely that a person would regularly use a medication container and not be using the medication especially if they were unaware it contained a recording device. In this context, the ideal medication monitor should be similar in appearance to medicine bottles in common use to minimise the impact it might have on patient behaviour (Norell 1983).

1.2.4.1 The First Medication Monitor

In 1962 Moulding described a specially designed dispenser containing a minute amount of radioactive material and photographic film to record the regularity with which medication was removed. This was subsequently modified to a dispenser containing individual boxes of medication in a stack which was used to study compliance with antituberculosis therapy (Moulding et al 1970). Each box contains a day's medication. A small piece of uranium is fixed to the top of the medication stack and a strip of photographic film is fixed down one side. As each box is removed from the bottom of the stack a spring forced the uranium downwards exposing different places on the film, appearing as a record of dots on the film after development. If the boxes are removed regularly a series of dots of equal intensity are seen. If no boxes are removed for a few days a darker dot is seen, and then if a number of boxes are removed in one go to "catch up", no dots are seen. There are

a number of disadvantages of the monitor. Because of its size and appearance it is likely it would alter compliance behaviour. It is not portable so patients would be likely to transfer tablets to another container if they were travelling. It is only useful for medicines with once daily dosing and even then does not allow assessment of dosing intervals. It is not possible to tell accurately from the intensity of the dot how may days medication has not been removed.

1.2.4.2 Electronic Medication Monitors

Electronic monitors provide accurate time information. They all contain a crystal clock system and a random access memory. Some action, such as opening the container, causes a record to be made in the location of the memory corresponding to the time of the action. The size of the memory and the power of the batteries dictate how long data collection can be carried out. When the monitor is returned it is connected to a reader device which accesses the memory allowing the stored data to be read out. The first electronic monitors developed were for eye-drop bottles, and subsequently monitors have been developed for aerosol inhalers and for tablets.

1.2.4.2.1 Eye-Drop Monitors

In 1974 Yee et al described a monitor which consisted of a plastic container with two compartments. One compartment was sealed and contained the electronics; the other compartment held a conventional eye-dropper bottle. The action of opening the lid of the medication compartment transferred a signal to the memory. One bottle opening an hour could be recorded for three weeks. The container was 10 x 9 x 3 cm so was portable, but the eye drop bottle needed to be removed from the compartment

to use it and it is therefore likely it may not be replaced. The monitor has not been used in any published studies.

Norell et al (1980a) developed an improved model consisting of a plastic box with a holder for a 25ml medication bottle. The removal of the eye-dropper cap from the bottle transfers a signal to the memory, the bottle remaining held in the monitor. One bottle opening an hour could be recorded for three weeks. The monitor has been used in a study of compliance with pilocarpine eye drops in patients with glaucoma (Norell et al 1980b). The container was smaller than that developed by Yee et al (1974). Both these monitors have an unusual appearance and may influence compliance behaviour as a result.

In 1984 Kass et al reported the development of a far superior model. This consisted of a 30ml plastic dropper bottle into which the electronic components were sealed and which was similar in appearance to commercially available eye-drop bottles. The monitor records the patient's use only when the cap is removed from the bottle and the bottle is inverted. Both these actions are necessary to administer a dose and this solves the problem of false results when the bottle is left without the cap on. The monitor can record four openings an hour for a six week period. It has been used to study compliance in glaucoma patients with pilocarpine (Kass et al 1986a) and timolol (Kass et al 1987).

1.2.4.2.2 Aerosol Inhaler Monitor

In 1985 Spector reported a device for monitoring metered-dose inhaler (MDI) usage in subjects with asthma. It is a portable electronic device that holds any standard MDI canister. The device records each of up to 256 actuations of the MDI.

The major disadvantage of this device is that the canister can be removed, and because the device looks different from a normal inhaler it may influence compliance.

1.2.4.2.3 Tablet Monitors

In 1981 Rudd et al reported the development of an electronic tablet monitor which could record 256 events. They did not give any description of the device except to say it represented compromises in size, weight and portability. The device has not been used in any published studies.

In 1986 Dickins et al reported the development of a pill-box consisting of a plastic box fitted with an inner container which holds the medication. The electronic components are concealed under this inner container. The device records an opening when the box is opened and is able to record 15 openings per hour for six weeks. The device has been used in two studies; one of compliance with antibiotic treatment for urinary tract infection and one of compliance with anti-tuberculous therapy (Cheung et al 1988a, Cheung et al 1988b). The container does not look like a tablet bottle and measures 11x9x3.5 cm so is likely to alter compliance. The authors found that the number of box openings tended to be high and erratic when a patient first received the device but then fell into some sort of pattern, so data for the first 24 hours after the patient had received the device were ignored (Cheung et al 1988b).

A third tablet monitor was described by Eisen et al (1987). This consists of a plastic case containing two blister sheets which can hold a total of 42 tablets. The paper used to seal the tablets in the blisters contains loops of conductive wires. The action of tearing the paper to remove a tablet interrupts the circuit and results in a signal to the memory. The device has been used to study compliance with anti-

hypertensive medications (Eisen et al 1990). The device is quite bulky being about 20 cm long and is therefore not very portable. Having tablets blister packed as opposed to being in a conventional tablet bottle has been shown to increase compliance in itself (Wong & Norman 1987).

None of the above tablet monitors resemble conventional tablet bottles and are therefore open to the criticism that they will in themselves alter compliance behaviour. Most recently an electronic monitor has been developed by the Aprex Corporation (Fremont, CA) which conceals the electronics in a child-proof lid which can be fitted to a standard tablet container. There is little visible difference between the device and a usual medication cap. The action of both opening and closing the lid is recorded by the device. It can record 1100 events and as well as giving the date and time of each opening also gives the duration of the opening. This has now been used in a number of studies including, compliance with anti-convulsants in epilepsy (Cramer et al 1989), 31 ambulant patients with diverse chronic conditions (Kruse et al 1990a), and a clinical trial of an anti-hypertensive drug (Rudd et al 1990).

CHAPTER 2

FACTORS AFFECTING PATIENT COMPLIANCE

2.1 INTRODUCTION

Many studies have attempted to correlate compliance with various patient characteristics to try to identify a non-compliant type of person. The effect of various treatment characteristics on compliance has also been studied. When assessing the relative importance of findings in these studies it is important to bear in mind the method used to analyse compliance and its limitations and disadvantages. In the following review, an attempt has been made to cite only those papers considered to have used a valid measure and definition of compliance. The measures involved the use of long half-life markers, unobtrusive pill-counts or electronic medication monitors. Factors considered were classified as patients characteristics, treatment characteristics, the disease, and characteristics of the doctor/patient relationship. The clinical significance of the relationship of any of the these factors with compliance is not discussed.

2.2 PATIENT CHARACTERISTICS

2.2.1 Demographic Variables

General reviews (Griffith 1990, Evans & Spelman 1983) report that the literature is conflicting on the association between demographic variables and compliance and that there are no easily identifiable characteristics which are indicative of non-compliance. Sackett (1976) suggests that demographic factors are related to a patient's utilization of health services but are not so important when considering their compliance when under medical care.

2.2.1.1 Age

It might be reasonable to assume that an elderly person becoming increasingly forgetful and confused is likely to be less compliant with medication; however, the age at which this becomes important is going to vary considerably. Adolescents who tend to be asserting their independence from authority figures such as their parents and who wish to be identical to their peers may also have problems complying with medication.

Cramer et al (1989) monitored compliance in epileptic patients and found that delayed verbal memory and increasing age accounted for the greatest proportion of variance in compliance but the finding was not statistically significant. The mean age of the study population was not given. In contrast Cheung et al (1988b) monitoring compliance in a group of TB patients, mean (SD) age 42 (12) years, found there was a weak positive correlation between increasing age and the totality of compliance. Similarly, Jacobs et al (1988) monitoring compliance with NSAIDs in arthritis found that patients greater than 50 years old were significantly more compliant than younger patients. However, Cheung et al (1988a) in a different study with an older population, mean (SD) age 69 (9) years, failed to show any correlation between compliance with antibiotic therapy and age, short term memory or ability to calculate. Kruse et al (1990a) monitored compliance with long-term drug treatment for various diseases and also found no association between age and compliance in a group of patients ranging from 14 to 87 years old, mean 50 years.

2.2.1.2 Gender

There is no logical reason why gender should be related to compliance and neither Cheung al (1988a & 1988b) nor Kruse et al (1990a), in the studies mentioned

in the above section, found any association. However, Jacobs et al (1988) found a small but significantly higher compliance in males compared with females for compliance with NSAIDs in arthritis.

2.2.1.3 Race

Similarly to gender there is no logical reason why race *per se* should be related to compliance. A couple of studies from the USA have, however, reported higher compliance in whites than non-whites (Jacobs et al 1988, Roth & Caron 1978). This has possibly got more to do with other factors such as perceptions of health care and socioeconomic status.

2.2.1.4 Socioeconomic Status

Some studies have reported lower compliance in social classes IV and V and the unemployed (Griffith 1990) although the majority found no association (Evans & Spelman 1983). Roth & Caron (1978) reported a positive correlation between social class and compliance but found that education and IQ were not related to compliance. Cramer et al (1989) also found that education and IQ showed very low correlations with compliance.

2.2.1.5 Summary of Demographic Variables

It seems likely that there are no easily identifiable patient characteristics that have a large bearing on patient compliance. However, some of these variables may have a small but significant effect on compliance, in particular diseases or patient groups.

2.2.2 Patients' Beliefs and Attitudes

Peoples' beliefs and attitudes influence their behaviour and various sociological models have been proposed to try to explain peoples' behaviour in relation to health. The approaches tend to share a number of common themes; the patients' perceptions of the threat posed by the disorder, the benefits and costs of any treatment, the amount of control which the patient believes they have over the disorder and the likelihood that treatment will be successful (Shillitoe 1988). Two models that have received much attention are the "Locus of Control" model and the Health Belief Model.

2.2.2.1 Health Locus of Control

The concept of "locus of control" was developed by Rotter in 1954 and is based on the amount of personal control over a situation that the individual believes they have. People who believe that an outcome tends to be under their own control are said to have an "internal" locus of control. People who believe that outcomes are under control of external factors, such as other people, or chance, are said to have an "external" locus of control. This model is clearly too simplistic since if a person believes that an outcome is under the control of their doctor this is different to believing it is due to luck. Wallston & Wallston (1976) subdivided externality into "powerful others" and "chance". When studying locus of control in relation to health, "medical control" can be substituted for the term "powerful others". Using the model it has been postulated that patients with an internal locus of control would know more about their condition, and take greater responsibility in their treatment and be more compliant than those with external locus of control. Wallston & Wallston (1976) suggested that in the management of a chronic disease high scores for internal control

and medical control may be equally important.

There is no reason to suppose that locus of control is static and indeed it probably changes as a patient experiences new situations in their disease management. Locus of control covers only one aspect of health behaviour and as such is best used alongside another model such as the Health Belief Model.

2.2.2.2 Health Belief Model

This is one of the best known models of health-related behaviour. It was initially devised by Rosenstock in 1966 to predict preventative health behaviours such as immunization, and has been further developed by Becker and others to include the prediction of behaviour during illness. The model covers a number of factors such as the perceived seriousness and risks of a disease and the perceived benefits of taking the particular course of action or treatment being offered. It can be postulated from the model that if a person considers that they are susceptible to a health problem they perceive to be serious, and they consider the treatment benefits outweigh the barriers then they are likely to be compliant with the recommended course of action.

2.2.2.3 Overview of Beliefs and Attitudes

Research using the Locus of Control model and the Health Belief Model has generally shown that their usefulness in predicting health behaviours is low. The relationship between beliefs and behaviour is not well understood and little work has been done to assess changes in beliefs with time. One of the major difficulties in this area is that non-specific instruments have been used to evaluate patient attitude to disease. More recently validated questionnaires specific to a particular disease have

been devised (see chapter 3 section 3.2.3).

2.3 TREATMENT CHARACTERISTICS

Treatment characteristics have on the whole shown to be more consistently related to compliance than characteristics of the patient. However well motivated a person is to comply, if the treatment demands are too difficult then they will be unable or unwilling to comply fully.

2.3.1 Treatment Complexity

2.3.1.1 Prescribed Daily Frequency

In studies using electronic medication monitors it has generally been found that compliance with medication decreases as the prescribed daily frequency increases. Kass et al (1987) found that overall the totality of compliance with timolol eye-drops (84.3%) prescribed twice daily was better than that with pilocarpine eye-drops (77.7%) prescribed four times daily in patients using both medications for the treatment of glaucoma. Cheung et al (1988a) monitored compliance with two antibiotics for urinary tract infection and found that both the totality and consistency of compliance were lower with the four times daily regimen than with the twice daily regimen. 61% and 30% of the patients had less than the ideal number of openings for the twice daily and the four times daily regimens, respectively. In a study in epileptics, Cramer et al (1989) found that the percentage of days with the prescribed number of doses decreased from once daily through to four times daily with the values of 87%, 81%, 77% and 39%, respectively.

In contrast to Kass et al (1987) and Cheung et al (1988a), Kruse et al (1990a)

found no difference in the totality of compliance between those patients presicrbed daily frequencies reported as once daily (77.1%) or more than once daily (77.4%). However, similar to Cramer et al (1989), they did find a significant difference between the percentage of days with the prescribed number of doses for medications presicrbed once, twice and three times daily which were 76.5%, 61.4% and 46.6%, respectively.

Other studies, not using medication monitors, have found differences in compliance between prescribed daily frequencies. In a study in which placebo was given to diabetic patients, Pullar et al (1988) found that compliance with once and twice daily schedules was similar but that both were superior to three times daily. Taggart et al (1981) found similar results in patients on digoxin therapy prescrbed once, twice and three times daily. Jacobs et al (1988), monitoring compliance vith NSAIDs for arthritis, found that compliance decreased as the prescribed diily frequency increased from one through to four.

Norell (1981b) monitored compliance with pilocarpine eye drops prescrbed three times daily and found that of the doses missed 54% were the noon dose 29% the evening dose and 19% the morning dose which suggests that patients are more likely to comply with a regimen which involves the instillation of eye drops on one occasion in the morning.

It does therefore seem that for both chronic and acute illnesses compliance decreases as the prescribed daily frequency increases especially above twice daily. The clinical significance of these differences will depend, in part, on the treatment and the disease.

2.3.1.2 Number of Medications to be Taken Daily

Increasing the number of treatments prescribed is generally considered to be inversely related to compliance (Evans & Spelman 1983); this may be particularly so in the elderly when polypharmacy is common and is one of the reasons it has been recommended that elderly patients should be prescribed no more than three or four drugs. However, Cheung et al (1988a) did not find that the number of daily dosage units of concurrent medication, mean (SD) 2.9 (3.5), was related to compliance with antibiotics in a study of the middle aged and elderly with urinary tract infections. Similarly, Kruse et al (1990a) found no association between the number of concurrent drug prescriptions, mean 1.4 range 1-6, and compliance. In a study by Kass et al (1987) with medication for glaucoma, compliance with timolol as a single agent was worse than compliance with timolol when given in conjunction with pilocarpine. This is the opposite of that expected and it was suggested that the patients on two medications may have considered their glaucoma to be more serious and were therefore more compliant.

Despite the general perception it does not seem that the number of medications is directly related to compliance and presumably other factors play a role.

2.3.2 Duration of Treatment

It has been postulated that the longer a person has been on treatment the more likely they are to be compliant with the treatment, on the basis that if a patient is unhappy with the treatment they are more likely to stop taking it (Haynes 1976). This hypothesis appears to be supported by the findings of Kass et al (1986a) who found that the subset of patients in the study who were monitored from the initiation of

treatment for glaucoma had a significantly lower totality of compliance than those who were monitored using a long established regimen of the medication.   However, other researchers have held the view the longer a person is on treatment the more likely it is that they inadvertently forget to take the medication or to refill a prescription on time.   This is particularly likely if the missing of doses has no immediate adverse consequence. Patients may then decide that they no longer need the medication or become more lax in taking it. In a study of compliance with TB therapy, Cheung et al (1988b) found that patients on the intensive phase of the treatment were more compliant than those on maintenance therapy. This illustrates that compliance with regimens for chronic diseases may decrease over time.

2.3.3 Size, Shape and Colour of Medication and Route of Administration

Patients may balk at the idea of having injections, or using suppositories and even with oral administration, patients may find large tablets difficult to swallow, small tablets fiddly to handle, or subconsciously dislike the colour of the medication. To what extent these factors affect compliance is probably influenced by the patients' perception of the severity of the disease and the usefulness of the treatment and although they therefore may be important on an individual basis they are unlikely to be significant factors in compliance generally.

2.3.4 Side-Effects

A number of authors have noted that side-effects are a reason given by patients for non-compliance (Evans & Spelman 1983) although the association between side-effects and compliance has not been much studied. However, in one study of

compliance with a 7 day hormone course in patients with primary infertility, Kruse et al (1990b) found that in patients who took more than 65% of the drug there was a statistically significant negative relationship between compliance and reporting of adverse drug reactions, r=-0.71 p<0.01.

2.4 THE DISEASE

In his review, Haynes (1976) stated that with the exception of psychiatric illness, where compliance is generally lower, it is not possible to identify a non-complier by his diagnosis, nor by features of his disease. This has been interpreted as there is no relationship between compliance and the type of disease (Griffith 1990, Evans & Spelman 1983).

2.5 THE PATIENT/DOCTOR RELATIONSHIP AND INFORMATION

Compliance is likely to be affected by the quality, duration and frequency of consultations with the doctor (Griffith 1990). Patients who are seen promptly have been found to be more compliant than those kept waiting for long periods (Carr 1990). If the patient feels that the doctor has understood their concerns and has provided an appropriate solution they are more likely to comply.

Although there is no direct link between knowledge and compliance, if the patient does not understand the medical advice or treatment regimen they are not in a position to comply. Patient information leaflets and other written information seems likely to improve patient knowledge of disease state and the treatment. In a recent review 60% of all studies in this area reported that written information led to improved compliance (Carr 1990).

CHAPTER 3

PATIENT COMPLIANCE IN CANCER AND DIABETES

3.1 COMPLIANCE WITH CYTOTOXIC AGENTS IN THE TREATMENT OF MALIGNANT DISEASE

3.1.1 The Use of Cytotoxic Agents in the Treatment of Malignant Disease

Malignant disease or cancer can be broadly defined as a disease in which there is uncontrolled multiplication and spread within the body of abnormal forms of the body's own cells. It is one of the major causes of death in the developed nations; one in five of the populations of Europe and North America can expect to die of cancer. There are three main treatment approaches for dealing with established cancer - surgical excision, radiotherapy and chemotherapy. Cytotoxic agents may be used either as an adjuvant to surgery or radiotherapy or in situations in which surgery or radiotherapy have been found to be ineffective or are not possible. Moreover, in an increasing number of cases they are used as the first line of treatment. Therapy is aimed at effecting a cure or to prolong life and palliate symptoms.

Cytotoxic agents act by inhibiting cell division and do so in a variety of ways. The two main groups of cytotoxics are the alkylating agents and the antimetabolites. Alkylating agents include the nitrogen mustards and nitrosureas which act by arresting cell division by alkylating and cross linking bases in DNA. The antimetabolites include the folate antagonists and pyrimidine or purine analogues. They act by blocking enzymes involved in the synthesis of DNA. Other cytotoxics which do not fit into these two groups include the cytotoxic antibiotics, doxorubicin and bleomycin, the plant alkaloids vincristine and vinblastine and etoposide which is a semi-synthetic derivative of podophyllotoxin. A number of other agents which affect the growth and proliferation of malignant cells are used in the treatment of cancer including

procarbazine and tamoxifen.

Glucocorticoids are used in association with cytotoxic agents in the treatment of some malignant diseases, particularly leukaemia and lymphomas. Other hormones, for example oestrogens and androgens, are used for specific cancers.

The toxicity of cytotoxic agents is generally a function of their therapeutic activity. Although they have different modes of action, their antineoplastic effect is dependent on a cytotoxic action which is not selective for malignant cells but tends to affect all rapidly dividing cells. However, in general malignant cells are either more sensitive than normal cells or the malignant cells surviving treatment recover less rapidly than normal cells. Since the agents do not all act at the same sites or at the same stage in cell division, combination therapy including several agents together or in sequence has generally been found to be more effective than treatment with a single agent. Furthermore, since all agents do not possess the same toxicity profile a lower spread of side-effects is achieved with combination therapy which is preferable to the frequently crippling toxicity which occurs with high doses of single agents.

Certain adverse effects are common to all antineoplastic agents in varying degrees. These may be divided into acute effects occurring shortly after administration, delayed effects occurring days or weeks after and long term effects which may not become evident for years. Acute effects include anorexia, nausea and vomiting, allergic reactions and local irritant effects when given by the iv route. Delayed or long-term effects generally result from the action of antineoplastic agents on rapidly dividing normal cells in the bone marrow, gastrointestinal mucosa, skin and gonads. The most common serious effect is probably bone-marrow depression giving

rise to leucopenia, anaemia, thrombocytopenia and immunosuppression. The attendant increased risks of infection and haemorrhage can themselves be life threatening. The severity and time course of myelosuppression varies for different cytotoxic agents with some causing a serious cumulative delayed depression. Adverse effects on the gastrointestinal tract include mouth ulcers, abdominal pain and diarrhoea. The active cells of the hair follicles are sensitive to some agents causing reversible alopecia. Some agents cause infertility which may be irreversible. The most serious of the long term effects of the alkylating agents in particular, is that they are carcinogenic and may cause second malignancies in patients who have previously undergone successful cancer chemotherapy.

Because of the toxicity of these agents they are only used where there is a reasonable chance of success and treatment is carried out under the direction of staff qualified in the field of malignant disease.

3.1.2 Review of Compliance Studies

Of the potential factors contributing to non-compliance described in chapter 2 many apply to the treatment of cancer with cytotoxic agents. The treatments are often complex requiring the administration of a number of medications some as injections at a clinic and some as oral medication to take at home. As described, many of the medications cause distressing side-effects. This coupled with the fact that a cure is not guaranteed might cause a patient to be an erratic complier or to completely default from the treatment program. On the other hand, patients fear of cancer and a feeling that chemotherapy is their only hope might lead to meticulous compliance.

There are a number of types of non-compliance possible in cancer patients.

Once they have entered a treatment protocol they may fail to keep appointments or may refuse aspects of the therapy. They may withdraw from the protocol which is considered to be non-compliance (Hoagland et al 1983). With self-administered therapy they may fail to get the prescription dispensed or to take the recommended doses or to take the medication at the prescribed frequency (Given & Given 1989). Considering the large volume of literature on compliance, surprisingly little work has been done in the field of cytotoxic chemotherapy.

3.1.2.1 Physicians' Assessment

The only study assessing physicians' views of non-compliance in this field was carried out by Hoagland et al (1983). They sent questionnaires to oncologists to assess their views on the extent of and reasons for the non-compliance of their patients. Oncologists average estimate of the frequency of non-compliance in cancer patients was 14%, however the range of estimates was 0-95%. Compliance aspects of appointment keeping, adherence to out-patient and in-patient treatment and adherence to taking self-medication were covered in the questionnaire. The non-compliant behaviour seen by the greatest number of oncologists as a problem was that of a patient who accepts treatment and then fails to complete the protocol. This is probably because this is the aspect the physician is most aware of. The primary reason oncologists gave for their patients' non-compliance was psychological, such as denial of the disease, fear and familial or peer pressure. They saw this as more of a problem than side-effects such as nausea.

3.1.2.2 Appointment Keeping and Intravenous Chemotherapy Received

A number of studies have examined medical records to assess the compliance with scheduled appointments and with the amount of iv therapy received. In an inner city hospital serving patients with multiple social and financial problems, Garrett et al (1986) prospectively evaluated compliance in clinic attendance over a 12 month period. Patients were being treated for a number of malignancies with chemotherapy, hormonal therapy or supportive therapy alone. 89% of the scheduled appointments were kept with 53% of patients keeping all their appointments. No difference in clinic attendance was found according to, sex, age, tumour category or mode of therapy. Reasons for missing appointments included forgetfulness, the weather, transport difficulties and clerical error with only one case of refusal of further chemotherapy. The authors concluded this high rate of appointment compliance demonstrated that these patients were appropriate candidates for treatment protocols requiring frequent clinic visits.

Lee et al (1983) looked at patients' compliance and total dose achieved with adjuvant chemotherapy for breast carcinoma. About 77% of the patients remained on the treatment program for at least 6 months and 50% for 12 or more months. Compliance was unrelated to age.

Taylor et al (1984) assessed compliance with iv chemotherapy for breast cancer by interviewing patients and by studying their medical record. In spite of severely unpleasant side-effects, compliance was 92%. Of the 8% non-compliant, 2 patients rejected chemotherapy outright and 2 utilised alcohol chronically to decrease their white blood cell count so that chemotherapy would be delayed.

Berger et al (1988) assessed compliance with an aggressive combined treatment

program in medically indigent patients with neglected breast carcinoma. Patients were evaluated for compliance by review of their medical record. Compliance was defined as overall compliance, the percentage completing the protocol as prescribed: and as appointment compliance, the percentage of appointments scheduled that were attended. The compliance with the oral self-administered part of the protocol was not assessed. 75% of the patients completed the protocol as prescribed and the appointment compliance was 91.7%. Compliance was not found to vary significantly with age, marital status, nationality, the presence of treatment related complications (side-effects) or the time of delay before diagnosis. The only factor found to correlate with non-compliance was duration of therapy. There was 100% overall compliance at 2 months, 82% at 6 months and 75% at one year. The authors concluded that complex treatment regimens were feasible as well as effective for these patients who although they had initially neglected their disease were well motivated once in therapy.

In conclusion it would seem that among adult patients compliance with appointments and intravenously administered chemotherapy appears to be high.

3.1.2.3 Compliance with the Oral Component of Chemotherapy

Few studies have assessed compliance with the oral component of cancer chemotherapy. In one such study Smith et al (1979) reported a method to assess the compliance of children with prednisone therapy using a urine 17-ketogenic steroid assay. They measured random urine 17-ketogenic steroids in three groups; in-patients receiving prednisone, out-patients receiving prednisone and a group of out-patients not receiving prednisone. They found that the assay was clearly able to differentiate those patients taking prednisone from those who were not. The assay results implied that

one third of the out-patients prescribed prednisone were not complying and this fraction increased to 0.59 when the adolescent age group was considered separately. The authors suggest that these low compliance levels may in part explain why children with the same disease on the same therapy show such a wide variation in response and why adolescents with acute leukaemia have a poorer prognosis than younger children and they postulated that the reasons for non-compliance could be linked to the unpleasant side-effects on the therapy including embarrassing weight gain and skin changes especially when a patient is in remission.

Tebbi et al (1986) also examined compliance in children with cancer. Parents and patients over 10 years old were interviewed separately at 2 weeks, 5 months and 1 year post diagnosis. The results of self-reported compliance were corroborated by serum assay of corticosteroids in 35% of the patients and were reported to agree with the self-report in all cases although no further details were given. Patients were considered non-compliant if they reported missing occasional doses (one or two) or frequent doses (three or more) in the previous month. 18.8% of the patients were considered non-compliant by this measure at 2 weeks, 39.5% at 20 weeks and 35% at one year. No significant correlations were found between compliance and stage of disease, number or type of drugs used, complexity of the regimen, degree of satisfaction with information given, understanding of the disease or belief in medication efficacy. A significant correlation was found between age and compliance with children over 10 years found to have a greater compliance problem. However, one wonders to what extent this was due to the fact that only the parents were interviewed when the children were under 10 years. More compliers than non-compliers were in agreement with their parents regarding who was responsible for the

administration of the medication. The authors suggest that in the development of protocols for the treatment of the adolescent age group, less reliance should be placed on self-administered oral therapy.

In adults only two studies have been carried out that assessed patients' compliance with oral chemotherapy. Using test and control groups, Levine et al (1987) assessed the influence of an intervention package on compliance with prednisone and allopurinol in patients with newly diagnosed haematologic malignancy. Compliance was assessed by serum samples obtained monthly over six months which were analyzed for the presence of the drugs. Each monthly level was classified as fully compliant, under-compliant and non-compliant depending on the level of drug present. If patients failed to attend for a monthly clinic appointment, a blood sample was not collected and they were classified as non-compliant for that month. The control group of patients were fully compliant with allopurinol only 16.8% of the time. This increased to 44% of the time for the group of patients who received an intervention package aimed at improving compliance. Control patients were fully compliant with prednisone only 26.8% of the time and this was not increased in the group who received intervention. Only a very small proportion of the tests were classified as under-compliant so non-compliance was occurring 56-83% of the time. The authors also recorded monthly appointment keeping and reported that control patients kept appointments an average of 66.4% of the time. This is lower than in other studies recording appointment keeping (Garrett et al 1986, Berger et al 1988). The patients in the intervention groups attended between 84 and 93% of their appointments which is comparable with these other studies but even these patients were found to be 56-73% non-compliant with the oral therapy. The relationship of

symptoms of the disease and side-effects to non-compliance was also investigated and reported separately (Richardson et al 1988). Patients reported nausea, fever and pain as the most difficult physical effects to tolerate but, neither the occurrence, frequency, or difficulties associated with these effects related to non-compliance with either of the two self-administered medications. This finding is not surprising since neither allopurinol or prednisone are cytotoxic agents so they would not cause the side-effects associated with chemotherapy, such as nausea, vomiting or hair loss. Patients reported difficulties associated with particular side-effects did however, relate to non-compliance with clinic appointments to receive iv chemotherapy.

Lebovits et al (1990) assessed compliance in patients with breast cancer on protocols that included oral cyclophosphamide and/or prednisolone. Patients were interviewed at four points over a six month period and were classified as non-compliant if they reported ingesting 90% or less, or 110% or more of either of the medications at any one of the four interviews. By this measure 43% of patients were classified as non-compliant. However, over half these were classified as non-compliant by reporting over-compliance so only 20% of patients were actually non-compliant by reporting under-ingestion. The criteria of non-compliance seem rather stringent and are not related in any way to data on efficacy of the drugs. In addition, given the problems of self-reported compliance the results are of doubtful validity.

In summary only two studies to date have looked at patient compliance with the oral component of cancer chemotherapy regimens and neither of these employed measures of compliance that allowed assessment of the pattern of administration or the overall amount of medication ingested. The only study looking at compliance with an oral cytotoxic agent used a measure of self-report (Lebovitis et al 1990).

3.2 COMPLIANCE WITH ORAL HYPOGLYCAEMIC AGENTS IN THE TREATMENT OF NON-INSULIN DEPENDENT DIABETES MELLITUS

3.2.1 Background to Non-Insulin Dependent Diabetes and its Treatment

The prevalence of known diabetes in the UK is about 1.2% (Williams 1985) and an additional 0.5% of the population probably have undiagnosed diabetes (Forrest et al 1986). About 75% of people with diabetes have non-insulin dependent diabetes mellitus (NIDDM) which is characterised by deficient pancreatic beta-cell function and impaired insulin sensitivity in target organs. NIDDM occurs typically in adult life, and has a gradual onset: it may remain undetected for years since many patients are asymptomatic with much higher than normal blood glucose levels. 80-90% of NIDDM patients are obese (Jaspan 1987) and since weight loss can help normalise both blood glucose levels and the lipid abnormalities seen in diabetes diet is an important aspect in the treatment of the disease. About 30% of patients may have their diabetes controlled by diet alone (BDA 1988) but the remaining require additional therapies to achieve normoglycaemia. This normally takes the form of oral hypoglycaemic agents, of which the sulphonylureas are generally the first choice to which a biguanide may be added. Oral hypoglycaemic agents are not always effective in NIDDM and if they are effective the duration of usefulness is often limited with 20% of patients eventually requiring insulin injections. The sulphonylureas act principally by stimulating the release of insulin from the pancreas, the older agents generally being of lower potency than the new "second generation" agents. They are well tolerated with the most serious adverse effect being the risk of hypoglycaemia. This risk is increased in elderly patients in whom the shorter acting, lower potency

agents are generally prescribed. Since sulphonylureas tend to increase body weight, the biguanides are preferred in very obese patients. The only biguanide licensed for use in the UK is metformin. It has a short duration of action and therefore needs to be taken three times a day. The sulphonylureas have longer half-lives and are prescribed to be taken once daily or occasionally with higher doses twice daily. A rare but serious side-effect of the biguanides is lactic acidosis so their use is contraindicated in patients with renal insufficiency. The mechanism of action of the biguanides is poorly understood but it does not involve the stimulation of insulin secretion and perhaps due to this they rarely cause hypoglycaemia (Gerich 1989).

Because the treatment of NIDDM is less demanding than that for insulin-dependent diabetes it is often viewed as a mild form of the disease, however it is in reality a disabling condition (MacFarlane 1988) Poor metabolic control causes tiredness, polyuria and infections and all diabetics are at risk of developing circulatory complications resulting in ischaemic damage to organs. Microvascular damage occurs especially in the retina and the renal tubules, and results in failing vision and renal problems. Macrovascular complications occur in the large blood vessels resulting in atherosclerosis, cardiovascular disease and reduced life expectancy. Diabetic neuropathy also occurs and this, coupled with the microvascular changes in the feet, may lead to ulceration and gangrene; this complication of diabetes being the single largest cause of amputations in the UK. It is generally accepted that maintaining near normoglycaemia will reduce the incidence of complications (Holman & Turner 1988, Jaspan 1987), however there is much debate as to how energetic this should be (MacFarlane 1988). Overenthusiastic prescribing of sulphonylureas leads to weight gain and hypoglycaemic episodes. In patients with complications at diagnosis there

is no evidence that tight control will reverse these changes. In elderly patients with severe complications, strenuous efforts to normalise blood glucose are unlikely to improve their quality of life (MacFarlane 1988).

Other authors consider that many NIDDM patients are not receiving adequate treatment. In addition to characteristics of the disease, Assal (1988) attributes the generally poor control of NIDDM to the attitudes or compliance of both the health care team and of the patients. Patients may be poorly motivated to control their diabetes efficiently due to lack of symptoms of the disease. They may be reluctant to change their dietary habits if they consider obesity to be a normal family characteristic. They may be unaware of the possible complications or may consider that they cannot influence the outcome of the disease. Because of what was seen as a shortfall in the treatment of NIDDM there have been a number of publications on the subject from the World Health Organisation, the European NIDDM Policy Group and the British Diabetic Association (Tasker 1988, Alberti & Gries 1988). It is recommended that NIDDM patients are reviewed at least annually.

Metabolic control may be assessed by monitoring blood levels of cholesterol, triglycerides and glucose. Urine glucose testing, although not directly related to blood glucose, is useful to detect major hyperglycaemic excursions in patients with known normal renal threshold for glucose (Alberti & Gries 1988). Random blood glucose (RBG) measurements are of little value because they are dependent on the timing and size of the last meal, making their exact interpretation difficult (Holman & Turner 1988) although RBG measurements above a certain level are indicative of poor control. Fasting blood glucose is stable from day to day in most patients with NIDDM and provides a reliable criterion of blood glucose control. Haemoglobin and

other blood proteins are glycosylated non-enzymatically and irreversibly according to glucose concentration (Boucher & Ross 1988). Glycosylated haemoglobin therefore, gives a measure of blood glucose control over the preceding 8-10 weeks, based on the half-life of haemoglobin. Its measurement is invaluable in assessing diabetic control because, unlike measurements of blood glucose, the result cannot be manipulated by the patient, who may improve their compliance to their treatment in the week prior to a review to try and improve the test results. Fructosamine or other glycated serum proteins can also be measured and since their half-lives are shorter than haemoglobin they reflect control over a shorter time span (Armbuster 1987).

3.2.2 Compliance in NIDDM patients

The treatment of diabetes involves behavioural and dietary changes as well as taking medication. Diabetes compliance therefore, consists of an interdependent network of regimen behaviour and level of compliance to one aspect of the regimen is often unrelated to degree of adherence to another (Glasgow et al 1985). In addition, for some aspects of the regimen, especially diet and exercise, the "prescription" is non-specific, which makes the analysis of compliance in these areas difficult (Glasgow et al 1985). Possibly because NIDDM is considered to be less serious, there have been fewer studies on compliance in NIDDM than in IDDM. These studies have used self-report, prescription refill and pill-counts as the method of compliance assessment and the limitations of these methods need to be taken into account when evaluating the results, (see Chapter 1). To date, no studies have monitored compliance with oral hypoglycaemic agents using electronic medication monitors.

3.2.2.1 Studies of Medication Compliance

Using questionnaires Ary et al (1986) assessed the levels of adherence to different aspects of the diabetes regimen, including medication compliance, in a group of diabetics in the community of whom 88% were NIDDM patients. In the previous three months patients reported that they had, on average, taken 87% of their medication on time. However, over the same period they had only adhered to their diet, exercise program and tested their blood or urine for glucose 50% of the time. The authors did not give the distribution of responses. Men reported exercising and glucose testing more than women and older people reported glucose testing more than younger people. Obese subjects reported less adherence to exercise. This study demonstrates that levels of compliance to different aspects vary and correlations among the different regimen areas were found to be low. Limitations of the study include the problems of response bias in self-reporting and that patients reported their compliance on the basis of what they understood their prescription to be which could well differ from the prescription as written by their physician.

Chan & MacFarlane (1988) questioned 50 consecutive patients with NIDDM at a hospital out-patient clinic about their medication. They were all being treated with oral hypoglycaemic agents. Patients were asked to name all the tablets they were taking and to explain why they were taking each one, then they were asked how frequently they missed doses. Only 28 of the 50 patients could name, or make a reasonable guess at the name of their oral hypoglycaemic drug. Several patients thought the oral hypoglycaemic drug was prescribed for another purpose and more than half the patients admitted that they sometimes forget to take their diabetic tablets. Given the fact that when questioned, patients are likely to present themselves in a

good light (see chapter 1 section 1.2.1.3) this level of compliance is a matter for concern although it is difficult to know how to interpret "sometimes" forgetting to take tablets.

Using an anonymous questionnaire, Davis & Strong (1988) assessed compliance in 100 randomly selected diabetics attending a hospital out-patient department. They did not classify the diabetics as NIDDM or IDDM. 96% of those on insulin or oral hypoglycaemic agents stated they took their medication exactly as prescribed, over half admitted being non-compliant with glucose monitoring and over 75% admitted to a significant degree of dietary non-compliance. Almost a quarter of the sample said they had at some time fabricated results of blood or urine testing. Like the studies previously mentioned, the questionnaire-based assessment of patient behaviour has problems although this study was conducted anonymously. No distribution of responses was shown.

In a study of factors affecting compliance with diet, medication and clinical control, Peterson et al (1984) assessed compliance in NIDDM patients attending a hospital diabetic clinic by questionnaire and prescription refill frequency. 47% of the patients stated they adhered strictly to their diet. 72% of the patients on oral hypoglycaemic therapy were considered compliant on the basis of prescription refill frequency: a patient was classified as non-compliant if the interval between prescription renewals exceeded that expected by a week or more at least once in the previous year. The authors reported that self-reported medication compliance was closely correlated with compliance by prescription refill frequency but gave no figures for the self-reported compliance. Interestingly they found that although compliance with diet and hypoglycaemic medication was correlated, only compliance with diet

was related to diabetic control. They give no justification for their classification of non-compliance by prescription refill and no information on the distribution of compliance. In addition there is no guarantee that if people refill prescriptions regularly that they take the medication as prescribed.

Physicians believe that compliance problems are greater in patients on insulin therapy than if tablets are prescribed. To test this hypothesis, Diehl et al (1985) conducted a trial to assess compliance with chlorpropamide and insulin in patients recently requiring medication for NIDDM. Patients were randomly assigned to receive chlorpropamide or insulin for 24 weeks and were then crossed over to the other medication for 24 weeks. Compliance was assessed by return tablet count and weight of returned insulin vials at 4 points in the 24 weeks. The mean compliance for chlorpropamide was 95.3% and that for insulin was 97.4%. 70% or more of patients were at least 80% compliant at each visit. Subjects estimated they actually took their medication a mean of 6.5 days per week or more. Including those patients who dropped out of the study as non-compliers the authors estimated the mean compliance as 78%.

3.2.3 The use of Health Locus of Control and the Health Belief Model in understanding Compliance in Diabetes

Health Locus of Control and the Health Belief Model are psychological frameworks which have been used to study patient compliance (see chapter 2, section 2.2.2). Both the models have been used in studies with diabetic patients.

3.2.3.1 Locus of Control in Adults with Diabetes

There are a number of Locus of Control scales that have been developed. The most widely used scale designed specifically to assess perceived control over health is the Health Locus of Control Scale (HLOC) of Wallston et al (1976). This scale attempts to distinguish between the dimensions of internality and externality but further divides externality into "chance" and "powerful others". Thus external expectations of no personal control are subdivided to specify whether outcomes are believed to be controllable by powerful others such as the doctor, or essentially uncontrollable and due to chance factors.

Alogna (1980) used the HLOC scale in a sample of insulin dependent diabetics to assess whether control expectancy was related to compliance with a weight control program. They reported that compliant subjects tended to exhibit more of an internal locus of control but this did not reach significance.

Schlenk & Hart (1984) studied the relationship between Health Locus of Control and compliance in a sample of insulin dependent diabetics. They assessed compliance with insulin, diet, hypoglycaemia management, exercise and foot care by a measure of self-report and direct observation. They measured health locus of control using the scale developed by Wallston et al. A statistically significant relationship was found between compliance and "powerful others" health locus of control and compliance and internal health locus of control. All the patients complied with at least 70% of the points assessed.

Bradley et al (1984) proposed that the generally non-predictive results obtained using locus of control scales in diabetes are due to the scales of Rotter or Wallston being too general for use in individual diseases. They developed diabetes-specific

control scales for adults requiring insulin (Bradley et al 1984). The scales were designed to examine attributions of responsibility for, and control over, both positive and negative outcomes concerning diabetes management. They found that patients were more likely to make internal attributions for their diabetes control than attributions to medical treatment and attributions to medical treatment were made in preference to attribution to external factors. Bradley et al (1990) further adapted this scale to measure perceived control of adults with tablet-treated diabetes. Stronger perceptions of personal control were associated with lower glycated haemoglobin levels, lower percent ideal body weight, less anxiety, greater positive well-being and greater satisfaction with treatment.

The value of locus of control in understanding diabetes has not yet been proven although with newer more specific scales its use may be clarified. However, the determinants of health behaviour are multifactorial and it is simplistic to believe that any single construct can predict much of the variance in individual health behaviours. The Health Belief Model looks at behaviour and attitudes in a wider context and as such may be more useful (Shillitoe 1988).

3.2.3.2 The Health Belief Model in Adults with Diabetes

The health belief model, like locus of control, has evolved over the years with different studies using different versions. In a study of compliance with a weight reduction program Alogna (1980) used a perception of severity of disease index based on the health belief model. She found that compliant subjects viewed their illness as significantly more severe than the non-compliant patients although compliance was divided into only two categories on an arbitrary degree of weight loss.

Cerkoney & Hart (1980) interviewed 30 patients on insulin treatment with predominantly NIDDM using a HBM questionnaire. They looked at the relationship between compliance, as assessed by self-report and direct observation, and the components of the HBM. The beliefs of patients regarding the severity and susceptibility to the disease and the benefits of and barriers to the treatment were positively correlated with compliance; however, only that for perceived severity reached statistical significance.

Harris & Linn (1985) examined the health beliefs of 93 male NIDDM patients and correlated their beliefs with metabolic control and compliance. Compliance was assessed using a combination of the patients' self-report and the nurses evaluation. There was no significant correlation between compliance and a combination of areas of health beliefs. However, belief in the disease severity was significantly correlated with compliance although the degree of correlation was small. They found that health beliefs were better correlated with metabolic control than with compliance however the measure of compliance used is subject to bias.

The use of diabetes specific health belief scales has been advocated in order to improve the power of the scales (Bradley et al 1984 & Lewis et al 1989). Scales have been designed for use in insulin dependent diabetics (Bradley et al 1984) and tablet-treated NIDDM patients (Lewis et al 1989). Lewis et al found patients who were more overweight and/or had higher glycosylated haemoglobin levels perceived their treatment to be less "cost-effective", rated complications as being more severe, and reported greater vulnerability for themselves and the "average person" with diabetes to these complications.

3.2.3.3 Overview of Locus of Control and the Health Belief Model

Many of the published studies are difficult to interpret due to the unsatisfactory

measures of compliance and metabolic control and the eccentric patient selection

criteria in addition to the dubious validity of the instruments (Williams 1988). Use

of the newer instruments (Bradley et al 1990b Lewis et al 1989) and the availability

of better methods of assessing compliance may throw some light on this obviously

important area.

CHAPTER 4

CONSTRUCTION AND TESTING OF THE

ELECTRONIC TABLET MONITOR

AND ANALYSIS OF DATA GENERATED

4.1 CONSTRUCTION AND TESTING OF THE DEVICE

In order to assess the degree of compliance of patients with oral, solid-dosage medication a tablet container was developed to electronically record the time at which the lid was removed (Nicholson, 1991). Although other devices have been described which accomplish this, (see chapter 1 section 1.2.4), at the time of carrying out this work none resembled the type of tablet bottle in common usage. The device described here was designed to ensure that the patient would be unaware that monitoring was taking place, as knowledge of such monitoring may influence compliance behaviour (Norell 1983). It was designed to give an objective, continuous measure of compliance, a method which is probably a more reliable measure of compliance than any of the others currently available (Rudd 1987).

4.1.1 Description of the Device

The device consists of a tablet bottle with an electronic device concealed between an inner container and the outer surface of the bottle (see figure 4.1). The lid and outer surface of the inner container are light proof and a photocell is concealed at the bottom of the inner container. The small amount of light that enters when the lid is removed is sufficient to cause a change in the resistance of the photocell. This is recorded in the location of the electronic memory corresponding to the hour in which the opening occurred. The memory can store one event (ie bottle opening) for each of 1024 hourly signals (ie 6 weeks). Read-out of the data stored is achieved by connecting up to a reader device. Data is then processed by computer, to give the dates and times of opening and a graphical print out, an example of which is shown in figure 4.2.
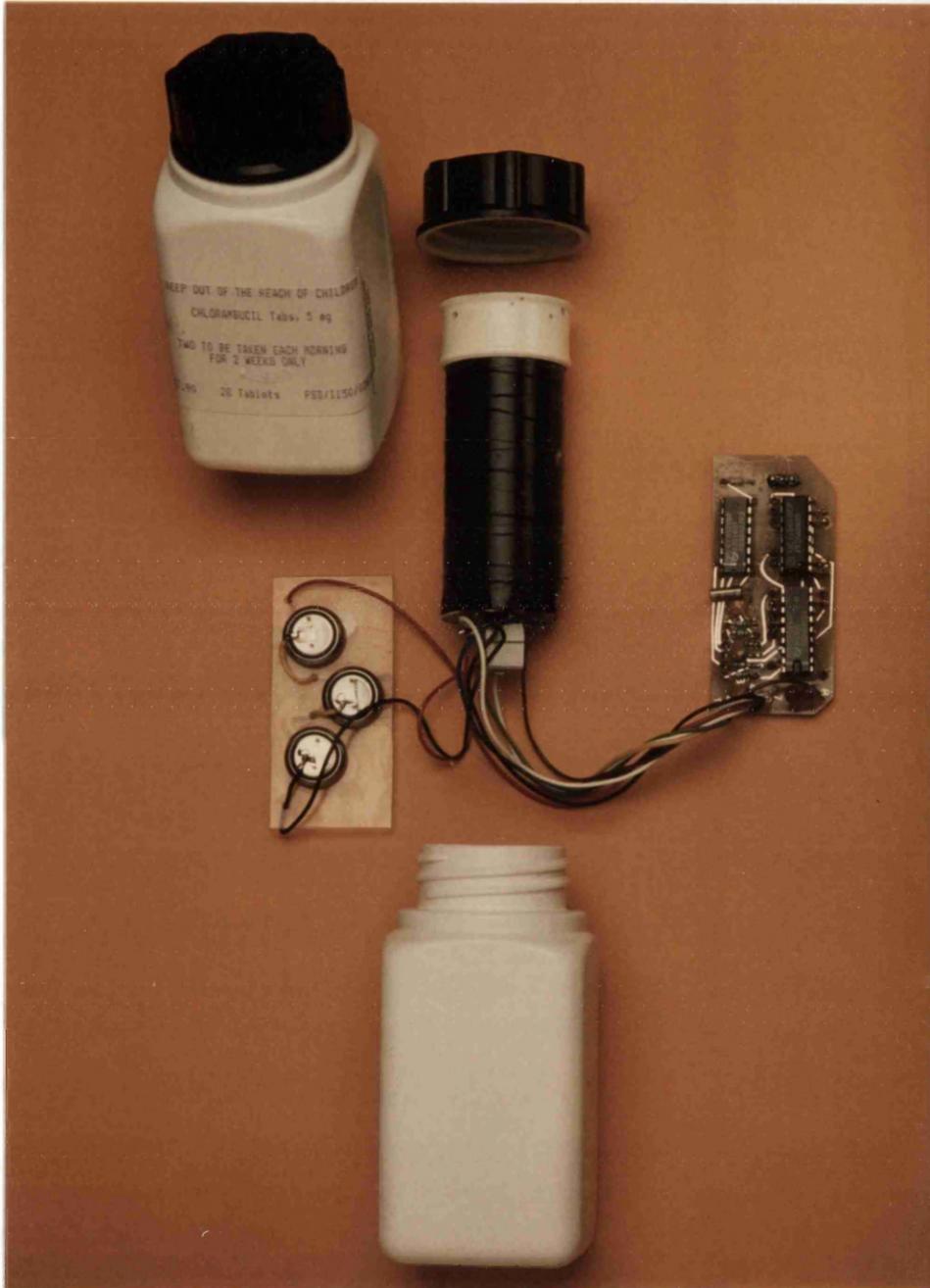
Figure 4.1 Photograph of the Electronic Recording Device and its Component Parts
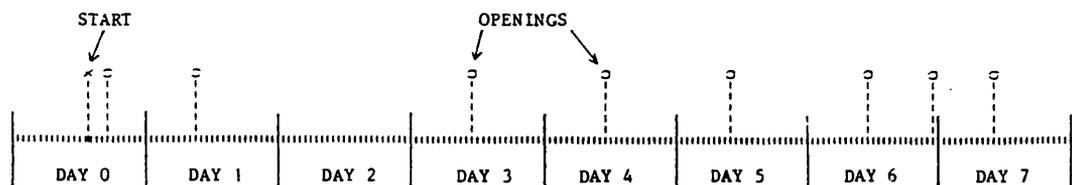
*Figure 4.2 A Portion of a Computer Generated Data Record
from the Device in Graphical Form.*

The memory can be erased by the reader device and re-initiated for subsequent

use. The circuit is powered by three 60mAh NiCad button cells which provide ample

capacity for the 42 day data gathering period and can be recharged without removal

from the device.

4.1.2 Construction of the Device

4.1.2.1 The Container

Standard blow-moulded white polyethylene tablet bottles (10 x 4.8 x 4.8 cm)

were donated by Stuart Pharmaceuticals Ltd for use in the project as an outer

container. Each bottle was received complete with cap which had a Stuart emblem

on top. A small hole, 1.5cm in diameter, was drilled in the base of the bottle which

allowed access to the connector when the device was completed.

The inner container was constructed from transparent plastic centrifuge tubes

(Nalgene Centrifuge Ware). The rounded base of the tube was sawn off before

placing the tube in a mould and a flat base added using ~0.9g clear Araldite[1] resin, (see figure 4.3 (a)). The base had to be flat to allow the photocell to be affixed. To conceal the presence of the photocell, a translucent Araldite layer (~0.6g) was then applied by combining some white pigment with the resin, (see figure 4.3 (b)). The tube was then removed from the mould and inverted before a small cadmium sulphide photoconductive cell was attached to the base in the centre using clear Araldite, (see figure 4.3 (c)). Copper tape was then put around the base of the tube to form a well into which was poured ~0.6g of Araldite resin containing white pigment,(see figure 4.3 (d)). The copper tape was removed and the edges of the white layer turned down on a lathe to make them square. Another well was formed with copper tape and ~0.9g of Araldite resin containing black pigment was added to make the base light-proof, (see figure 4.3 (e)). The outside of the tube was then sprayed with two coats of white paint to make it appear white from the inside, (figure 4.3 (f)), before applying a light-proof layer of black PVC insulating tape, (figure 4.3 (g)). This arrangement ensures the outer surface of the tube is light-proof so that light can only enter through the top to activate the photocell. The tube acts as a light pipe such that even when it is full of tablets light finds its way to the photocell in the base. A nine pin electrical socket was attached to the base of the tube on the top of the photocell, (figure 4.3 (h)). To secure this inner container firmly into the bottle a collar of white pigmented Araldite was applied using a silicone rubber mould, (figure 4.3 (i)). When the collar had hardened the top of the tube was removed so that it was flush with the collar.

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[1] *Araldite is a registered trademark of Ciba-Geigy Plastics. In all instances where Araldite was used it was set in an oven at 40°C.*

Clear

White (f)

Light-proof
covering (g)

Collar (i)

outer
container

Circuit
Board

Battery
Board

Translucent

(b)

(a)
(d)
(e)

Photocell (c)

Socket (h)

(j)
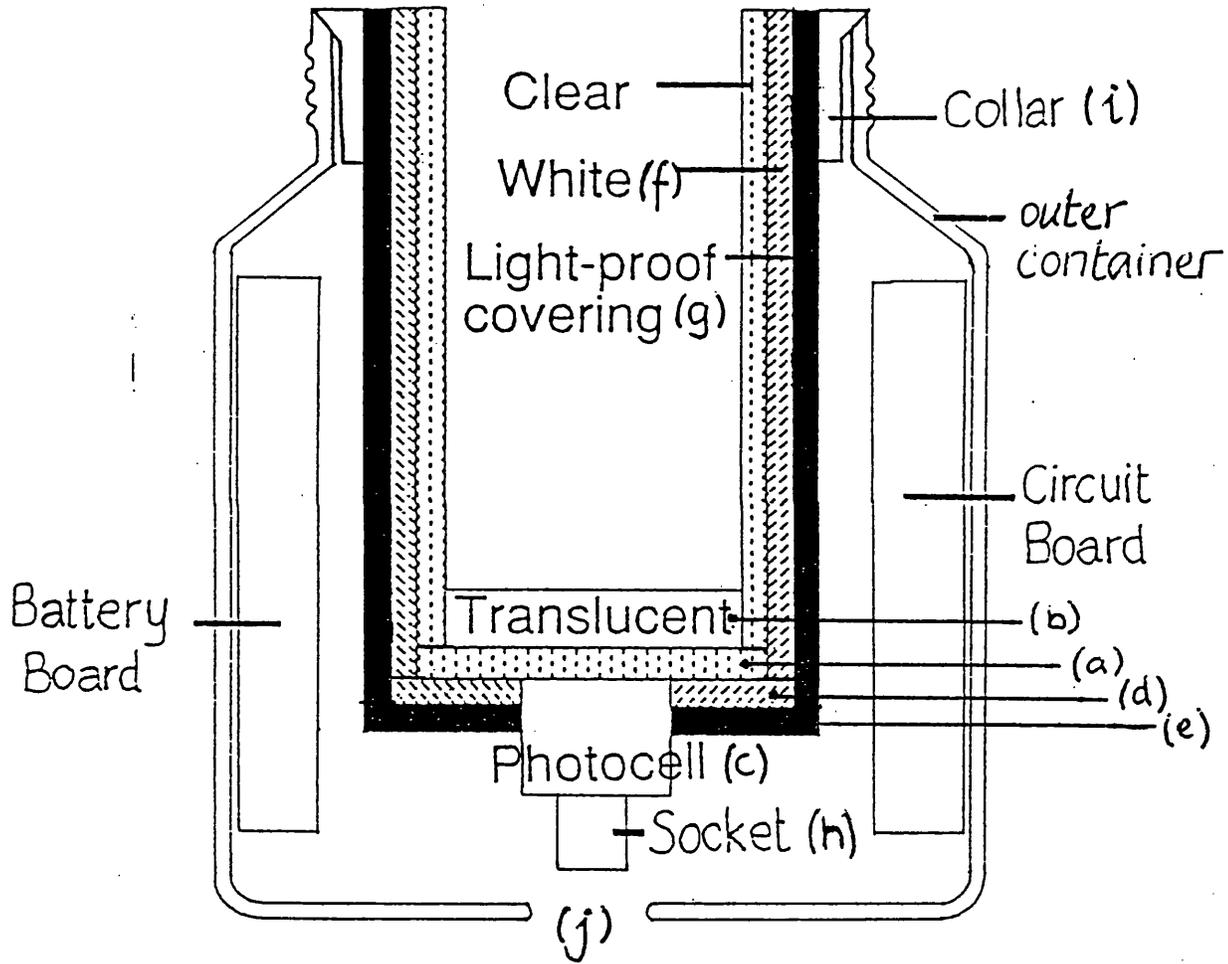
*Figure 4.3 Diagrammatic Representation of a Cross Section of the Device.
For an explanation of the letters see text.*

The inner container then fits snugly into the bottle and access to the electrical socket can be gained through the hole in the bottom of the bottle, (figure 4.3 (j)). This hole is concealed with a label when the device is in use. The screw cap had the Stuart emblem removed on a lathe and was light proofed by spraying with black lacquer.

4.1.2.2 The Electronic Components

Strips of positive resist, double sided copper clad board were cut 65 x 30 mm. The black protective film was removed from the laminate and each strip was exposed with the artwork for the circuit using a UV light source. The strips were exposed for four minutes on each side making sure the artwork was in good contact with the laminate. The strips were then immersed in a developer solution (Farnell Electronic Components) and agitated gently for 3 minutes at room temperature. The exposed copper was then removed by etching in ferric chloride solution for approximately 5 minutes. The positive resist was left on the copper tracks after etching to protect them, and removed, prior to soldering, by rubbing with a glass fibre brush. The pads were drilled using a 0.8mm drill except for those for the through-pins which were drilled with a 1mm drill. The through-pins, capacitors, resistors and the crystal were then soldered into place on the board. Five CMOS integrated circuits were then soldered into place ensuring the board, equipment and the operator were properly earthed. The wires were then soldered to complete the board.

To hold the batteries securely a piece of clear plastic was cut 30 x 60mm and three 15mm holes were drilled in it and 1mm holes for the wires. Three button cells of diameter 15mm were secured in the holes using Rapid Araldite. The batteries were then wired in series.

4.1.2.3 Assembly of the Device

With the inner container removed from the bottle the circuit board and the batteries were wired to the photocell and the electrical socket. The wires used were 14cm in length to allow enough slack to insert the electronic components into the bottle before the inner container. The circuit board and the battery board were then slipped into the bottle and fixed to opposite sides using adhesive pads (DRG Sellotape products). The inner container was then inserted taking care not to pinch any of the wires. Figure 4.4 shows a block diagram of the circuit.

4.1.3 Testing the Device

4.1.3.1 Testing the Electronic Components During Assembly

During construction the functioning of each device was tested at a number of stages. Prior to soldering any of the components on the printed circuit board all the tracks were examined carefully for breaks. After soldering all the solder points were examined under magnification. At this stage the design of the circuit allowed for testing in a "minute mode", advancing the memory every minute instead of every hour so greatly reducing the time for testing. Instead of connecting the circuit to the photocell and battery board, at this stage it was connected to a switch and a 3V power supply. The wires from the board were soldered to a plug which connected to the reader device. Using the reader device the memory was erased and then it was checked that the memory contained zero in every location.
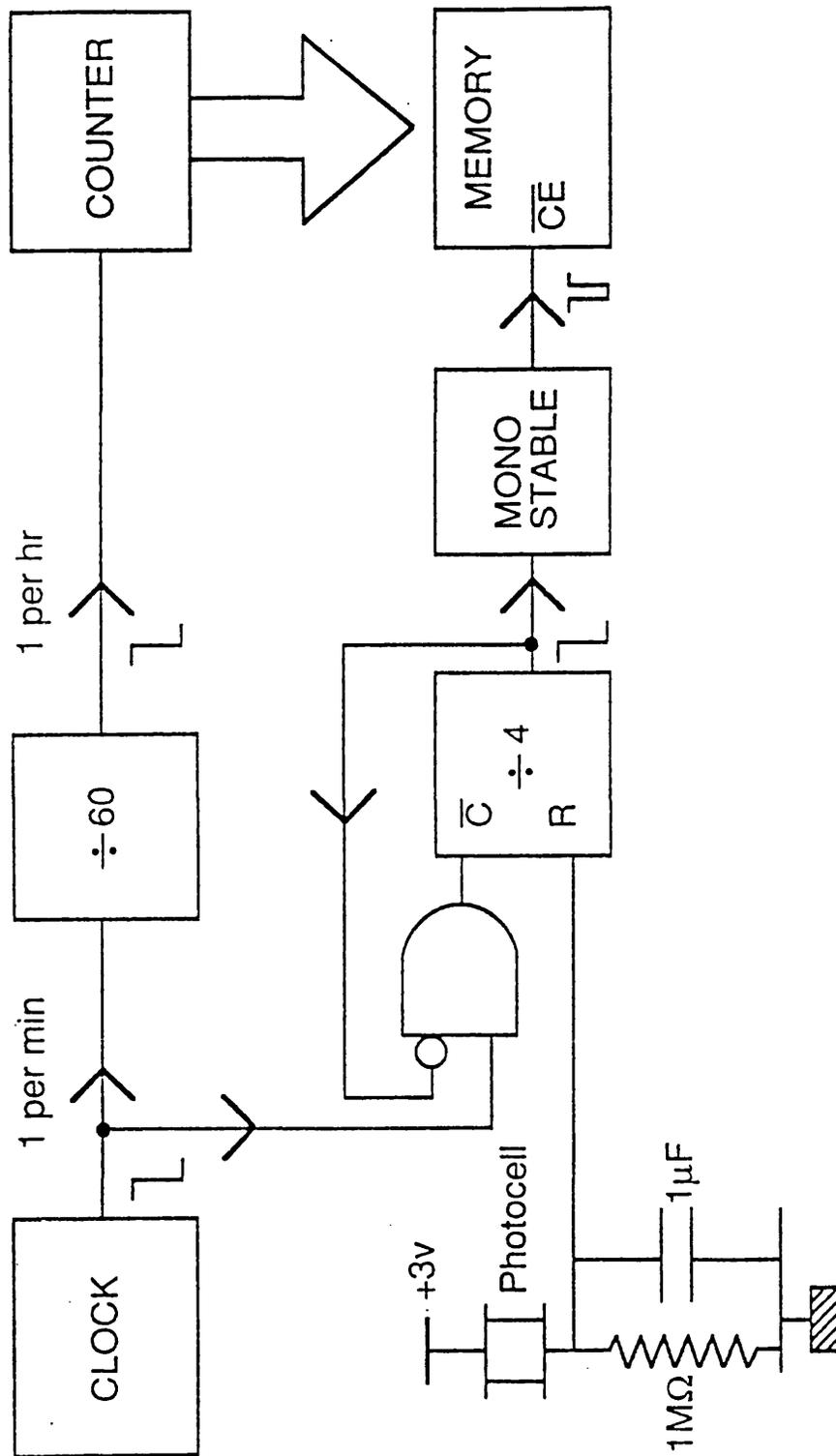
Figure 4.4   Block Diagram of the Circuit of the Device.

If the erase function did not work this indicated there was most likely to be a soldering fault on the circuit. Using an oscilloscope it was possible to determine which part of the circuit was faulty. If the erase function was working then the circuit was initiated and the time accurately recorded. The switch (simulating the photocell) was depressed at recorded times over a period of 10 minutes or so, then the memory was read-out and it was checked that these openings were in the correct locations.

If the circuit board was functioning properly in "minute mode" it was then changed to the hourly mode and wired up to the photocell and electrical socket attached to the inner container and also to the battery board. The components were not assembled into the bottle at this stage; instead the end of the outer container was covered with black tape such that a piece of the tape could be removed and replaced to let light enter, simulating an opening of the container. The memory was erased and checked then it was initiated and the time recorded. At intervals over a period of 7 hours light was allowed to enter the inner container and then the memory was read to ensure the times recorded were correct.

If functioning correctly the components were finally fitted into the bottle . The memory was again erased, checked and initiated before testing over a period of 24 hours.

4.1.3.2 Light-tightness of the Device

Early versions of the inner container had ~0.9g of black Araldite applied around the photocell on the base, (see figure 4.3 (e)). In initial trials with the device it was found that when the container was left sitting on a windowsill in sunlight records were occasionally found in the memory when the container had not in fact

been opened. To measure the resistance across the photocell the inner container was removed from the bottle and the circuit board, batteries and socket detached then the top covered with black tape. In the room the resistance measured was greater than $20M\Omega$ which was as expected. On the windowsill the resistance varied from ~8-$11M\Omega$ which was satisfactory; however, when the sun was shining the resistance went down to ~3-$4M\Omega$ which would be low enough to cause a record to be made in the memory. To detect which part of the container was leaking light, a beam of light was directed on different parts of the container using a piece of card with a small hole in it. The light source used was an overhead projector lamp which was shown to give a beam more intense than sunlight. It was shown that the resistance of the photocell remained greater than $20M\Omega$ wherever the beam of light was directed on the inner container except for the sides and back of the photocell itself when the resistance was much lower. To solve this it was decided to cover the whole of the photocell with black pigmented Araldite requiring ~3.5g. This totally solved the problem of spurious records when the device was left in direct sunlight.

The light-tightness of the cap was also checked. The resistance across the photocell was measured with an unpainted white cap and a cap painted with black lacquer. With both caps the resistance was greater than $20M\Omega$ when the lid was fully screwed home. With the white cap the resistance varied from $2.5M\Omega$ with the lid sitting on the bottle to $8M\Omega$ with it screwed two turns, demonstrating that it was not sufficiently light-tight. With the black cap the resistance remained greater than $20M\Omega$ even with the lid not screwed down. At the other extreme even in low lighting conditions with the container filled with tablets an opening was recorded.

4.1.3.3 Electromagnetic interference.

The circuit contained several decoupling capacitors such that even when the spark produced from a car ignition coil was only a few centimetres away this did not create spurious records in the memory.

4.1.3.4 Condensation

For one of the medications used in the study of lymphoma patients (see chapter 5) it was necessary for the tablets to be stored in a refrigerator. The circuit functioned at 5-8°C, but there was concern that removal of the device from the cold to a warm room may cause water condensation on the circuit board causing malfunction. To prevent this the boards were sprayed with a silicone-based lacquer before they were fitted into the bottle. No problems arose when the device was kept in a refrigerator.

4.1.3.5 Testing the Device with Student Volunteers.

After the tests in section 4.1.3.1 had been carried out and the device was shown to be functioning properly, it was handed out to a post-graduate volunteer to test its robustness in normal use. It was filled with Skittles (Rowntrees Ltd) and the student was asked to open the container twice a day for a 7-10 day period and to record the times accurately on an accompanying printed sheet. The student was told exactly what the container did and it was stressed that if they forgot to record an opening it defeated the purpose of the test. When the student returned the device the memory was read and compared with the students written record.

One problem that came to light in this trial was occasionally it was found the record in the memory for a particular opening was in the location an hour ahead of

the written record. Studying the records further revealed this occurred when the device was opened less than 10 minutes before the memory was due to switch to the next hourly location. For example, if the container had been initiated at 16:45 an opening occurring at 20:37 would be recorded in the memory location for the hour 20:45-21:45 instead of 19:45-20-45. This was shown to be due to an extra pulse given by the reader device when the container was initiated, such that the time of initiation was approximately 10 minutes prior to the correct time. This problem was subsequently resolved.

4.1.3.6 Concealing the Electrical Socket.

When the device was issued to patients the hole in the base allowing access to the electrical socket was covered. A number of materials and adhesives were tried to find something that was strong, would show evidence of being tampered with and would be easy to fit and replace. Strip adhesives were less messy than liquid or sprays; a special type (N° 9413) of double-sided pressure sensitive tape (3M Products) was found to be suitable. The use of thin aluminium labels was investigated but white labels were considered less conspicuous. A square of the double-sided tape was put over the hole and this covered with a square of white adhesive label before another square of adhesive and finally another square of white label.

4.1.4 Use of the Device

The batteries were charged to full capacity at 3mA for 20 hours in the week the device was issued to a patient. In this way, after the container had been used for a 14 day course of treatment, it was demonstrated the memory was retained for at

least 17 weeks. On the day of issue the memory was erased, checked and initiated and the time recorded. The hole in the base was covered to conceal the electrical socket. When the container was issued to a patient the approximate time of dispensing the medication was also recorded. When it was returned after the treatment period the device was again opened and the time recorded. After the memory was read out the times for dispensing and return were compared with the bottle record to give a running control that the container had functioned properly.

4.1.5 Discussion

The device was found to be robust and reliable. In only 5 cases out of the 212 times the monitors have been issued to date have the records been unavailable for assessment due to some malfunction of the container. A disadvantage of the device was that it had to be initiated within a few days of being used to ensure there was enough memory available for the treatment period. It was time consuming to make and test the device, and relatively expensive which might limit it use on a larger scale.

Using a device which is light sensitive overcomes the problem of how to conceal a switch mechanism in the cap. This method was found to be reliable in the tests conducted; however, if a patient opened the container in the dark no record would be made. It was felt this was unlikely to occur, especially if the patient had more than one medication to take. However, the container would be unsuitable for use with a blind patient who might open it in the dark.

A general disadvantage of electronic monitors is that when an opening is recorded there is no record of the number of doses removed. In all the studies patients were asked to keep the medication in the container, but the possibility cannot

be excluded that on some occasions patients may have removed two or more doses at one time and transferred them to another container, which would result in an underestimation of compliance. On the whole, however, it was found it was just as likely that there were more openings than required for perfect compliance which would indicate that the patient may have opened the container on occasions to count the tablets and check they had taken a dose.

It is recommended that all solid oral dosage forms be dispensed in containers with child-resistant closures, but none were found that fitted the device. Patients were therefore told the container was not child resistant and given the option of not participating in the study if they objected. Patients were counselled to keep the container well out of reach of children with the lid securely on. This had the advantage of decreasing the likelihood that the container would be left with the lid off when it would fail to function properly.

In the studies conducted where patients were unaware of monitoring most patients accepted the device without apparent suspicion, showing it fulfilled the criterion of being unobtrusive. However, on a few occasions where the patient had received the same medication before in a different container they questioned the change in the container.

4.2 ANALYSIS OF DATA GENERATED

From the records obtained by using electronic monitors information is available on the number of doses taken daily, the number of missed or extra doses and the dosing interval. This data can be analyzed in a number of ways. It has been used in a purely descriptive way but more often it is related to some ideal compliance pattern.

In some cases there has been an attempt to match missed or excess doses with adverse effects. A number of measures were developed to describe compliance patterns generated by the electronic device.

4.2.1 Review of Methods of Analysis

Yee et al (1974), who developed the first electronic compliance monitor, reported its use in just two patients. They published the complete print-out from the monitor for the two patients and used it in a descriptive way. In studies involving larger numbers of patients this method is not practical.

Norell & Granstrom (1980b) used an electronic monitor in 82 patients for whom pilocarpine eye drops had been prescribed to be used three times a day. They assumed there would be no therapeutic effect for the drug if the interval between dosing exceeded eight hours so they calculated the proportion of time exceeding an 8 hour dose interval for each patient. The problem with this approach is that the 8 hour cut off is arbitrary being dependant on the dose, the patient and the length of the previous intervals before the interval exceeding eight hours. In a subsequent paper they published all the intervals and reported only four patients used the drops at eight hourly intervals and that the mean length of intervals for the 84 patients combined, for the morning, noon and night doses were 6.4, 6.5 and 11.1 hours respectively (Norell 1981). To prove whether a patient using the drops at the mean intervals had less therapeutic benefit than if they used them every eight hours would have to be studied in a clinical trial. Using the 8 hour cut off, a patient using the drops at the mean intervals of 6.4, 6.5 and 11.1 hours for a month would be classified as having 84 hours (12% of the time) with no therapeutic effect.

Kass et al (1986a) also looked at compliance with pilocarpine eye drops, but in their case prescribed to be used four times a day. They analyzed the number of prescribed doses used for each patient and looked at the number of days with no pilocarpine administration. They also used the same measure as Norell & Granstrom (1980b) to assess the number of hours without adequate treatment, calculating the number of hours for each patient when the intervals between doses exceeded eight hours. Again the eight hour interval seems to be arbitrary especially as the daily dosage frequency in this study was four rather than three.

Cheung et al (1988a) studied compliance with trimethoprin prescribed to be taken twice daily or cephalexin prescribed to be taken four times daily in patients with urinary tract infections. They reported the totality of compliance as the number of container openings divided by the number expected had compliance been perfect, expressing this as a percentage. They also looked at the length of intervals and devised an index of the consistency of dosage intervals. They took the ideal interval for a twice daily regimen to be 12 ± 1 hour and those of a four times a day regimen to be 6 ± 1 hour. Only 7% of the dosage intervals with cephalexin met the ideal of 6 hours and only 17% of those with trimethoprin were 12 hours. The problem with this consistency index is that it assumes that patients divide a 24 hour day by the daily dosage frequency and take the medication at these equally spaced intervals. As is shown by the small number of intervals that were of ideal length this is clearly not the case. The index is not able to differentiate those patients who take their tablets in a regular pattern that is not the "ideal" and those patients who are irregular in their pattern of tablet taking.

Cramer et al (1989) studied compliance in patients prescribed various anti-

epileptic medications. They calculated compliance as the number of days during which doses were taken the prescribed number of times expressing this as a percentage of the number of days. Again this is an unsatisfactory measure since a day classified as non-compliant with a three times a day regimen could have no doses taken, one dose taken, two doses taken or four or more doses taken. Clearly these would not be therapeutically equivalent. They did, however, try to relate the occurrence of breakthrough seizures with missed doses as recorded by the monitor.

Kruse et al (1990a) monitored compliance in patients on various medications for chronic conditions. They expressed compliance as the number of container openings divided by the prescribed number for the period. They also looked at the regularity of dosing calculating the percentage of days when the dosage regimen was adhered to; when no doses were taken; when partial doses were taken and when extra doses were taken.

As can be seen from the above studies compliance data can be misleading depending on how it is analyzed. If the data collected by Cramer et al (1989) was reanalysed using the method of Kruse et al (1990a) the results generated would be quite different. Dosage regimens are decided based on experience with use of the medication in its development stages in clinical trials. In clinical trials the compliance assessment is usually based on the total number of tablets taken over the period (return tablet count) with no data collected on dosage intervals. Compliance is obviously a moderator of therapeutic effect but for most medications the level of compliance necessary to gain full therapeutic benefit, either in terms of the total amount of medication taken in a given period or the dosage intervals, is not known. This needs to be taken into account when developing a compliance measure.

4.2.2 Compliance Measures

Separate measures were developed to represent different aspects of compliance. The total number of tablets taken over the period was examined, analogous to an accurate pill count. The number of openings each day was analyzed with respect to the prescribed daily number and also the regularity of the pattern of intervals.

4.2.2.1 Overall Compliance

This measure was devised to represent the percentage of medication that was used in a given time period. It was calculated by dividing the number of bottle openings by the number expected had compliance been perfect, and expressing this as a percentage. Since the patient can open the device more times than required to take all the medication the measure can have a figure over 100%

4.2.2.2 Daily Irregularity Index

Although the total number of openings may be correct (ie 100% overall compliance) there may be a deviation from the prescribed daily number, hence a measure was devised to represent the number of daily discrepancies in bottle openings averaged over the time period studied. Any extra or omitted openings from the daily prescribed number are scored 1 and the index is calculated as the sum of these scores divided by the expected number of openings over the time period. Thus a figure of 0 for the index indicates that there are no missed or extra daily openings. A figure of 0.2 would indicate there were 2 missed or extra openings for every 10 openings expected. For a once daily regimen therefore, this would indicate there were 2 missed or extra openings in a ten day period. For a twice daily regimen and a three times

daily regimen a figure of 0.2 would indicate 4 and 6 missed or extra openings, respectively, in a 10 day period.

4.2.2.3 Hourly Irregularity Index

Even with the correct number of openings per day there may be irregularity in the time of bottle opening and so an index was devised to represent this. As mentioned in the introduction although it is tempting to score deviations from some ideal pattern, for example , 8 hourly intervals for a three times a day regimen, this is unrealistic as even well motivated patients are unlikely to follow such an ideal pattern. The index devised, therefore, was based on the repeatability of the patients own hourly pattern of openings. In the calculation of the index, days with the incorrect number of openings were first excluded. For the remaining days the modal values of the intervals between openings were determined. There is one mode for a once a day regimen but for a twice a day regimen two modes are calculated, one corresponding to the night time intervals and one to the day time intervals, similarly three modes are calculated for a three times a day regimen corresponding to the morning, afternoon and night intervals. All the intervals were then scored in relation to the appropriate mode using the following system;

mode	score 0
mode ± 1 hour	score 0.1
mode ± 2 hours	score 0.4
mode ± 3 hours	score 0.6
mode ± 4 hours	score 0.8
mode ± 5 hours	score 0.9
mode ± ≥ 6 hours	score 1.0

The total score for all the intervals graded was divided by the total number of intervals for the course. This gives an irregularity index from 0-1 where 0 corresponds to an exactly repeatable hourly pattern of bottle openings.

4.2.3 Discussion

In the calculation of the daily irregularity index missed and extra openings are not distinguished from one another as comparison with the value of the overall compliance should enable one to assess this. It would, however, be possible to calculated two daily indexes, one for missed doses and one for extra doses if this was considered necessary in a particular situation. In a number of the studies it was also decided to use a measure similar to that of Kruse et al (1990a) to report the percentage of days with the correct, less than correct and more than correct number of openings for the study population as a whole.

The disadvantage of the hourly irregularity index is that although it is a measure of how regular a pattern of openings was it does not give any information on the actual hourly intervals used. For this reason the data was also analyzed to show the distribution of the length of intervals for the study population as a whole.

CHAPTER 5

THE ASSESSMENT OF PATIENT COMPLIANCE WITH

THE ORAL COMPONENT OF CANCER CHEMOTHERAPY

FOR LYMPHOMAS

5.1 INTRODUCTION

5.1.1 Classification and Treatment of Lymphomas

A malignant lymphoma is a tumour occurring in the lymphoreticular system. There are two main types, Hodgkins disease and non-Hodgkins lymphoma, both of which are divided into sub-groups.

Hodgkins disease is the most common manifestation of lymphoma. The disease is staged at diagnosis using the Ann Arbor classification which recognises 4 stages. These are based on the number of lymph nodes involved, whether sites involved are both sides of the diaphragm and whether there is disseminated disease. Stages are subclassified A or B according to the absence or presence of symptoms of fever, night sweats, or weight loss which carry a poorer prognosis. Treatment choice depends on the stage at diagnosis. Radiotherapy is the treatment of choice in stage 1A and IIA disease (Haybittle et al 1985) with a 5 year disease free survival of 80-90%. Chemotherapy is generally considered to be the treatment of choice in all other stages. The most commonly used treatment is combination chemotherapy with mustine, vincristine, procarbazine and prednisolone (MOPP). Mustine and vincristine are given intravenously on days 1 and 8 and procarbazine and prednisolone are taken orally on days 1 to 14. Courses are repeated every 28 days depending on the white blood cell count, usually for 6 courses. A number of MOPP variants exist which may be as effective and are less toxic. These include substitution of chlorambucil for mustine (LOPP), given orally on days 1 to 14. Chlorambucil causes less severe nausea. Vinblastine is sometimes substituted for vincristine (MVPP). Chemotherapy with MOPP has been reported to produce complete remission in 80% of patients with an overall 10 year disease free survival rate of 70% (Henry-Amar & Somers 1990).

In stage IV disease MOPP is often alternated with a non-cross resistant regimen in an attempt to improve remission rates. The regimen commonly used includes doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) which are all given intravenously.

Non-Hodgkins Lymphomas (NHL) are a diverse group of tumours and the histological classification varies. They are broadly divided into two groups, one of low-grade and one of high-grade malignancy. Patients with lymphomas that have a good prognosis may remain well despite extensive disease for years and require no treatment whilst asymptomatic. Most other patients require chemotherapy, which may range from very gentle to intensive, depending on the histological sub-type and clinical circumstances. The most effective single drugs are alkylating agents. Corticosteroids may be used alone for lymphomas with good prognosis. Patients treated for good prognosis groups survive a median of 5 years although some live for many years. Patients with poor prognosis lymphomas are usually treated with combination chemotherapy similar to that used for Hodgkins disease. Regimens used include cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP) or methotrexate, doxorubicin, cyclophosphamide, vincristine, dexamethasone and bleomycin (M-BACOD).

These diseases generally have a good prognosis when compared with other malignant diseases and in a portion of cases chemotherapy is given to effect a cure. The oral cytotoxic agents used are not particularly toxic.

5.1.2 Compliance Studies in Lymphoma Patients

The only study to date on the compliance with the oral component of

chemotherapy in patients including those with lymphomas was carried out by Levine et al (1987) (see chapter 3). Compliance was assessed from blood levels of the drugs allopurinol and prednisolone and Levine et al (1987) reported, in a control group, that patients were compliant only 17% of the time with allopurinol and 27% of the time with prednisolone. After intervention, compliance with allopurinol improved to 44% but that with prednisolone did not differ. These figures represent a concerning level of under-compliance and bring in to question the reported survival rates of regimens which include oral components (Cohen & Diamond 1986).

5.1.3 Aim of the Current Study

The aim of this study was to observe the intake of oral chemotherapy in a group of out-patients attending a lymphoma clinic using the electronic tablet monitor described in chapter 4. This enabled the dosage intervals to be assessed as well as the overall amount of drug taken. There was no intervention to change or improve compliance. Factors that might influence compliance such as symptoms of the disease and experience of side-effects were also investigated.

5.2 METHODS

5.2.1 Patients

Patients being treated at out-patient lymphoma clinics at University College Hospital and The Middlesex Hospital over an eighteen month period were recruited into the study. Participation in the study was limited to those patients being treated with regimens including oral anti-cancer drugs. The patients and clinic settings are

typical of urban medical practice in the UK. The drug doses and schedules are outlined in tables 5.1 and 5.2 on pages 110 and 111.

5.2.2 Compliance Assessment

Compliance with oral chemotherapy was monitored using the electronic tablet monitor described in chapter 4. Data from the monitor was processed to give three measures; the overall compliance, a measure of the total amount of drug taken, the daily irregularity index, representing the number of daily discrepancies in bottle openings averaged over the course and the hourly irregularity index, an index of the repeatability of the patients own hourly pattern of openings. For details of how these measures were calculated see chapter 4 section 4.2.2.

5.2.3 Quality of Life Assessment

Patients experience of side-effects and quality of life was assessed by a previously validated diary card which has been shown to reflect day to day variation in symptoms during chemotherapy (Geddes et al 1990). Daily records were scored, using a 4 point scale of eight questions (see figure 5.1) . The questions cover three categories: (a) symptoms related mainly to treatment- sickness, vomiting and appetite; (b) symptoms related to disease- pain; and (c) a general assessment- mood, sleep, activity and general wellbeing. Patients were asked to fill in the card for the days they were taking their oral medication. The mean score for each question was calculated for the treatment period.

PLEASE ANSWER THE FOLLOWING QUESTIONS.   WEEK 1
WRITE DOWN THE NUMBER OF YOUR ANSWER
IN THE APPROPRIATE BOX OPPOSITE THIS PAGE.

	Mon	Tues	Wed	Thur	
DID YOU FEEL SICK TODAY? 1. Not at all 2. Occasionally 3. A lot 4. All the time					
DID YOU VOMIT TODAY? 1. Not at all 2. Once 3. Twice 4. More than twice					
HOW GOOD HAS YOUR APPETITE BEEN TODAY? 1. Good 2. Fair 3. Poor 4. Bad					
HOW MUCH PAIN HAVE YOU HAD TODAY? 1. None 2. A little 3. Quite a lot 4. A lot					
HOW DID YOU SLEEP LAST NIGHT? 1. Very well 2. Quite well 3. Badly 4. Not at all					
HOW HAPPY HAVE YOU BEEN TODAY? 1. Happy 2. Fairly happy 3. Unhappy 4. Very unhappy					
HOW ARE YOU FEELING GENERALLY? 1. Well 2. Fair 3. Poor 4. Very poor					
WHAT DID YOU DO TODAY? 1. Stayed in bed 2. Got up — did nothing 3. Light work/House work 4. Fully active					

Figure 5.1 A portion of the Diary Card for Assessment of Quality of Life.

5.2.4 Study Design

Patients were recruited regardless of whether they had received chemotherapy or radiotherapy before. Where possible patients were monitored for two or more courses not necessarily consecutively. Informed consent for monitoring the effects of the treatment was sought but patients were not told the recording nature of the bottle. Patients were told that the intention was to make a detailed assessment of symptoms using a diary card; if they asked what the bottle was they were told that it had a light-

proof construction. Where patients were not satisfied with this explanation the nature of the device was revealed. This occurred with 4 patients out of the 25 (2 male and 2 female) and data from these patients were treated separately.

The diary card was given out by the research pharmacist and the patient was shown how to complete it at the end of each day. The patient's prescription and a separate tablet bottle for each drug item were taken to the hospital pharmacy department. The prescription was dispensed in the normal manner, clearly labelled as to the contents and treatment regimen with the exact number of tablets or capsules required. A label was also affixed asking for the bottle to be returned to the clinic. Because of the current recommendation that all oral solid dosage forms be dispensed with child resistant closures patients consent to having non-child resistant closures was obtained and it was emphasised that the bottle should be kept with the cap securely on, well out of the reach of children. Patients were asked not to transfer the tablets to any other container and to return the containers and completed diary card next time they attend the clinic. An information sheet covering these points was given to the patient and is shown in Appendix 1.

On returning the containers any remaining tablets were counted. A record of patients' attendance at the clinic was kept.

5.2.5 Statistical Methods

Due to the unbalanced nature of the data a linear modelling approach was adopted (Armitage & Berry 1987) using the statistical package GLIM[1]. This

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1 *GLIM: Numerical Algorithms Group Ltd, 256 Banbury Rd, Oxford, 1987*

approach allows for the testing of the effects of independent variables both within patients and between patients. The following three attributes were regarded as within-patient factors: prescribed daily frequency, monitoring period sequence and drug type. The eight mean scores on physical and mental well-being from the diary cards were also treated as within-patient variables. The number of relapses and the number of years since initial diagnosis were regarded as between-patient variables. The strategy employed was in essence a stepwise approach as used in conventional multiple linear regression (Draper & Smith 1981). Each variable or factor was alternately entered into the equation and its effect within-patients or between-patients, as appropriate, tested for significance. If the level of significance reached the P=0.05 level it was retained in the equation and the process repeated with all the other variables or factors. After the inclusion of a new variable in the equation all variables in the equation were re-examined for significance and any that fell below the P=0.05 level were eliminated.

Residuals were tested for normal distribution by the Shapiro-Francia W' test (Royston 1983) and by chi squared test. In the case of the overall compliance the residuals were initially found to depart from normality and this essentially stemmed from the high proportion of values near 100%. To correct this the overall compliance, C, was transformed by the expression

$$\sinh^{-1}\left(\frac{C-100}{5}\right)$$

This transformation acts symmetrically on values of C lying on either side of the 100% value. Apart from a scaling factor and shift of origin, values of C lying near the 100% value are affected negligibly, but increasingly outlying values of C are shifted so as to progressively limit their deviation from the 100% value.

A similar transformation was required for the daily irregularity index, D, and was given by

$$\sinh^{-1}\left(\frac{D}{0.05}\right)$$

5.3 RESULTS

No patients refused to participate in the study and no patients failed to return their tablet bottles although two forgot at one appointment and brought them to a following appointment. 2 patients failed to return the diary card and one of these consistently failed to turn up to appointments. His mean "overall compliance" for the course of LOPP monitored was 89% with a mean "daily irregularity index" of 0.32 and an "hourly irregularity index" of 0.70 . The "hourly irregularity index" is much higher than that for the group overall but the "overall compliance" is not significantly different (p<0.01). One patient dropped out of the study during his second course of LOPP as the treatment was discontinued due to relapse. On one occasion one of the monitors failed to function. This was for a patients receiving chlorambucil and prednisolone; the data for prednisolone was lost but that for chlorambucil was available.

Patients received the exact number of tablets required for their course of treatment so none should be returned. On only 3 occasions were any tablets remaining when the bottles were returned. One of these was the patient who had his treatment discontinued so these data were disregarded. One patient receiving LOPP, who was aware of the recording nature of the bottles, on one occasion returned 3 chlorambucil tablets out of a course of 28, giving a compliance by pill count of 89%. This patient's "overall compliance" by bottle openings was 93%. One patient

receiving chlorambucil and prednisolone, who did not know the nature of the bottles, returned 1 prednisolone tablet out of a course of 56, giving a compliance by pill count of 98%. This patient's "overall compliance" by number of bottle openings was 86%.

5.3.1 Analysis of Monitor Records

A total of 65 records were analyzed from patients who were unaware that monitoring was taking place. This "unaware" group consisted of 21 patients monitored for 1 to 4 (mean 1.76) treatment cycles. Of the 65 records, 28 were for chlorambucil, 24 for prednisolone, 5 for procarbazine, 4 for dexamethasone and 3 for cyclophosphamide, (for a summary see table 5.1). For the overall compliance, daily irregularity index and hourly irregularity index, respectively the grand means (SD) were 100.6% (20.6%), 0.15 (0.16) and 0.32 (0.20). Figure 5.2 shows the distribution of overall compliance.
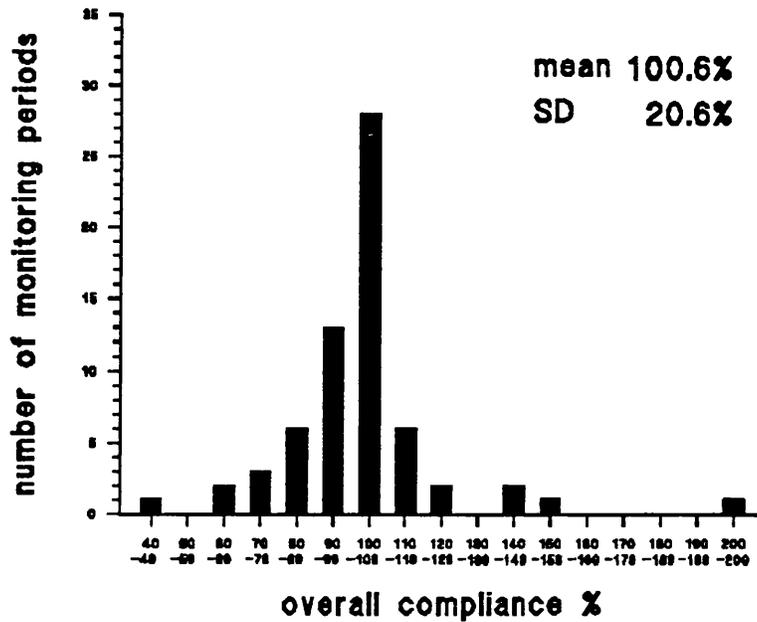
Figure 5.2 Distribution of the values for the Overall Compliance for lymphoma patients unaware of monitoring.

Clearly some patients opened the bottle more than the prescribed number of times, however since patients receive the exact number of tablets required for the course, they cannot actually be over-compliant in amount of medication taken. If all values of overall compliance over 100% were adjusted to 100% the grand mean (SD) became 94.3% (10.6%). Figure 5.3 shows the distribution of the daily irregularity index. The mean of 0.15 shows that on average there were two extra or omitted openings in a 14 day treatment period of a once daily regimen, four extra or omitted openings for a twice daily regimen and six for a three times daily regimen.
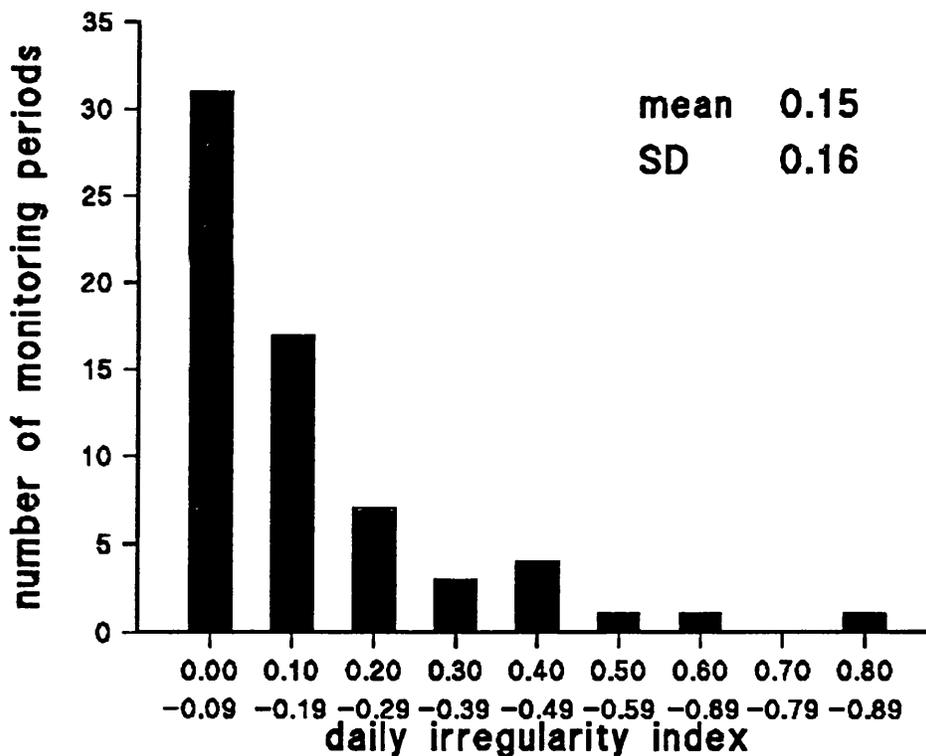
Figure 5.3 Distribution of Values of the Daily Irregularity Index
for lymphoma patients unaware of monitoring.

Another way of expressing the daily regularity is to look at the number of days

with the correct number of openings for the prescribed daily frequency. Of the 850

days monitored 80.9% fell into this category. Figure 5.4 shows the distribution of the

daily monitor openings in relation to the prescribed daily number.
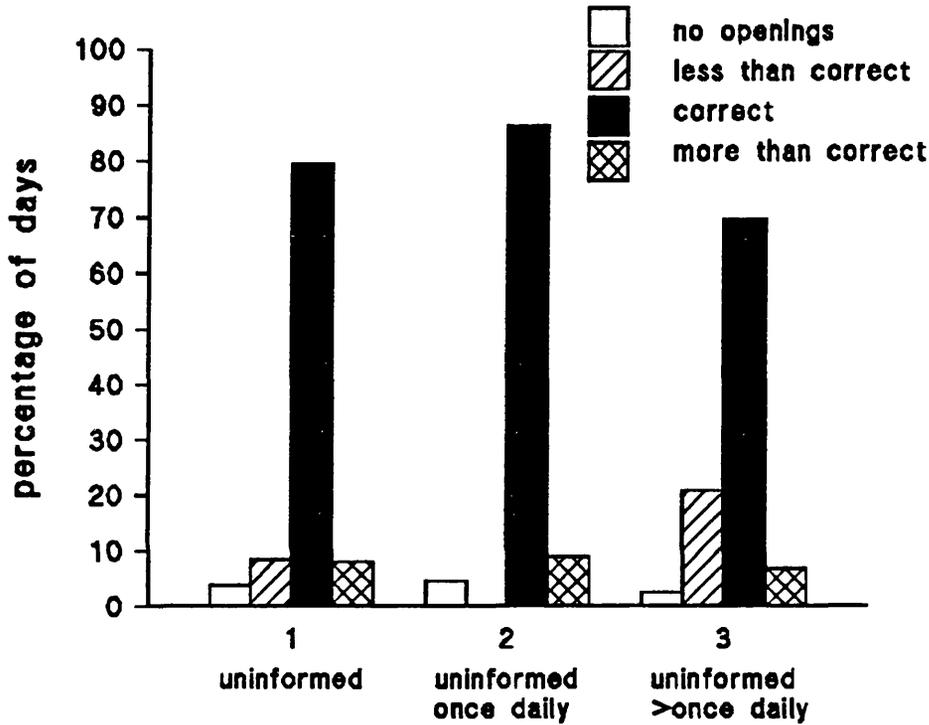
*Figure 5.4 Distribution of the number of daily monitor openings
in relation to the prescribed daily number*

1. Patients unaware of monitoring, all regimens.
2. Sub-group of 1: regimens taken once daily.
3. Sub-group of 1: regimens taken twice or three times daily.

As can be seen, when the prescribed daily frequency was more than once daily

the percentage of days with the correct number of openings fell from 85% to 70%.

For regimens that were more than once daily the data was analyzed to show which

time of day doses were missed. For twice a day regimens, taking 3.00-15.00 as the

morning dose and 15.00-3.00 as the evening dose, 32% of doses missed were the

morning dose and 68% were the evening dose. For a three times a day regimen,

taking 3.00-11.00, 11.00-18.00 and 18.00-3.00 as the morning, afternoon and evening

doses respectively, 31.6% of doses missed were the morning dose, 43.4% the

afternoon dose and 25% the evening dose. Figure 5.5 shows the distribution of the

hourly irregularity index.
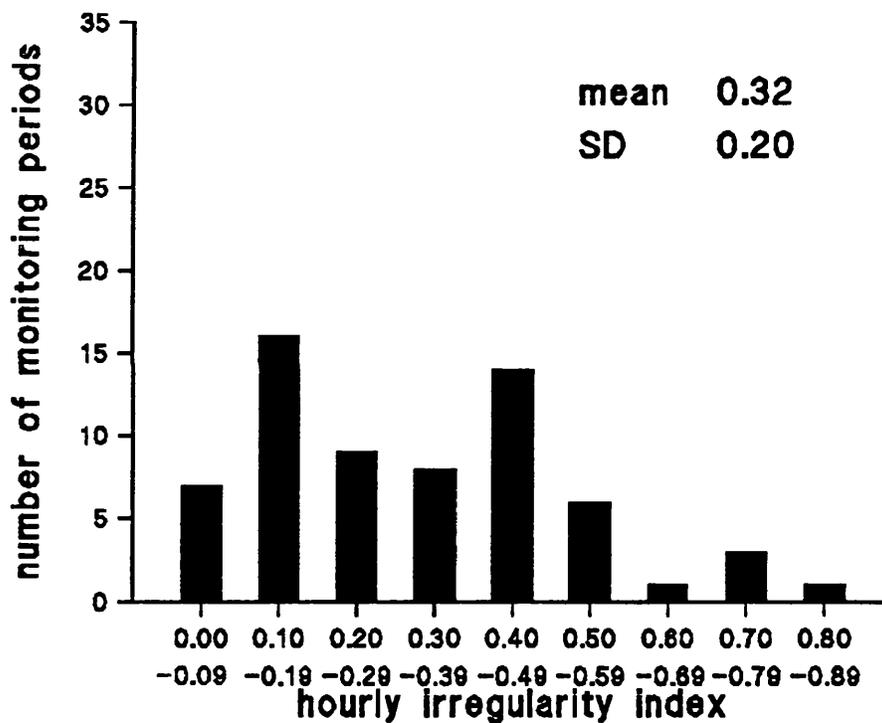
Figure 5.5 Distribution of values of the Hourly Irregularity Index
for lymphoma patients unaware of monitoring.

When compared with the daily irregularity index (see figure 5.3), it can be

seen that patients are more consistent at complying with the prescribed daily frequency

than with an hourly pattern of intervals between doses.

A further 13 records were collected from 4 patients who, for various reasons, had been informed that the bottle recorded the time when it was opened (for a summary of the doses and schedules see table 5.2). For this group the grand mean (SD) for the overall compliance, daily irregularity index, and hourly irregularity index was, respectively, 99.7% (7.7%), 0.07 (0.05), 0.30 (0.13). The grand mean for the overall compliance and for the hourly irregularity index were not significantly different from the "unaware" group. However, unpaired t tests showed that the grand mean for the daily irregularity index was significantly less (P<0.005) in the "informed" group than in the "unaware" group. In addition the SD's for the overall compliance and the daily irregularity index were significantly less in the "informed" group than in the "unaware" group (F test, P<0.001 for both). Thus the consequence of informing the patients appears to be better day to day regularity and, rather obscurely,   less variability between records for the overall compliance.

The following analysis was confined to the "unaware" group of patients. The data for overall compliance was used in the "raw" state, that is no adjustment of figures over 100% was made. The data were used in this way because if adjustments of figures over 100% were made it would be hard to justify not adjusting the figures below 100% as well and there is no suitable way of doing this. Using the linear modelling strategy (see statistical methods) with overall compliance as dependent variate, the final equation contained two explanatory variables, the prescribed daily frequency significant at the P<0.025 level, and the mean nausea score (P<0.05). The magnitude of the effect of the first of these corresponded to a reduction in overall compliance of 4% and 10% as the number of prescribed daily doses increases from

1 to 2 and from 2 to 3 respectively. Figure 5.6 shows a scatter plot of the overall compliance versus the prescribed daily frequency which demonstrates this reduction. The second effect corresponded to a reduction in overall compliance of approximately 2.5% with an increase in mean nausea score of 0.1.
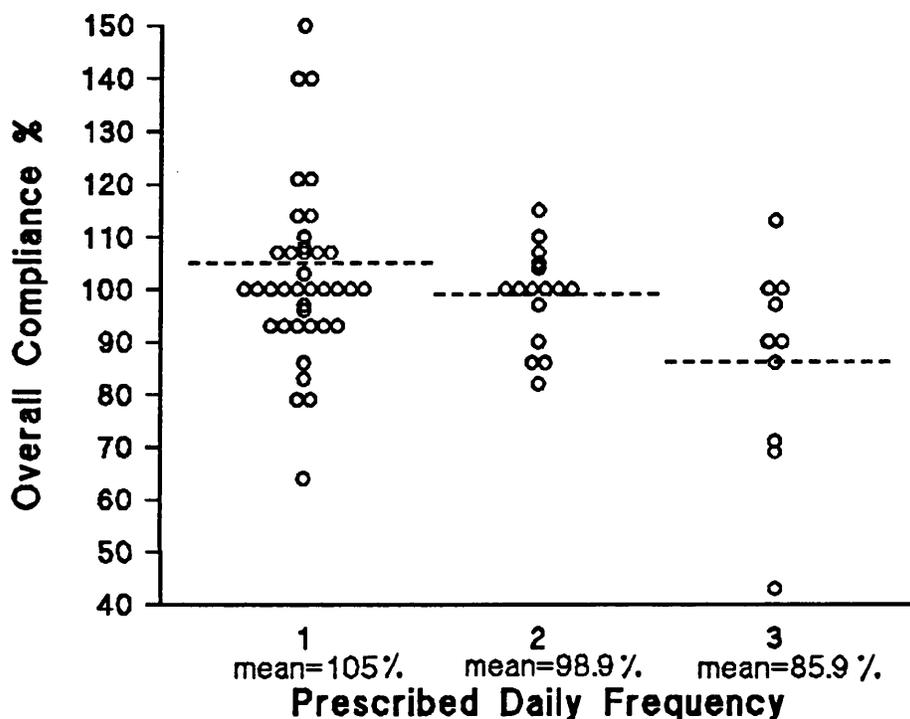
Figure 5.6   Scatter Plot of the Overall Compliance Versus the Prescribed Daily Frequency.

With the daily irregularity index as dependent variate none of the explanatory variables examined showed a significant effect.

With the hourly irregularity index as dependent variate the final equation contained only the mean nausea score as explanatory variable (P<0.05). However the direction of the effect was of a decrease in hourly irregularity index of 0.1 with an increase in mean nausea score of 0.1 which was unexpected.

Regimen	Diagnosis	No Patients	No Courses	No Bottle Records
Chlorambucil 6mg/m^2 po days 1-14	Low grade follicular NHL	2	7	7
Prednisolone 20-40mg po & Chlorambucil 6mg/m^2 po days 1-14	Low grade follicular NHL	7	15	29
Prednisolone 20-40mg po & Cyclophosphamide 100mg po days 1-14	Low grade follicular NHL	2	3	6
Prednisolone 60mg po in three divided doses (as part of CHOP) days 1-5	Intermediate grade NHL	2	2	2
Chlorambucil 6mg/m^2 po, Prednisolone 40mg po in two divided doses & Procarbazine 100mg/m^2 po in three divided doses(as part of LOPP) days 1-14	Hodgkins disease	4	6	17
Dexamethasone 6mg/m^2 po (as part of M-BACOD) days 1-5	High grade NHL	4	4	4
		21	37	65

NHL = Non Hodgkin's lymphoma

Table 5.1   Summary of schedules prescribed in lymphoma patients

unaware of monitoring.

Regimen	Diagnosis	No Patients	No Courses	No Bottle Records
Prednisolone 20-40mg po & Chlorambucil 6mg/m^2 po days 1-14	Low grade follicular NHL	1	2	4
Chlorambucil 6mg/m^2 po, Prednisolone 40mg po in two divided doses & Procarbazine 100mg/m^2 po in three divided doses(as part of LOPP) days 1-14	Hodgkins disease	2	3	8
Dexamethasone 6mg/m^2 po (as part of M-BACOD) days 1-5	High grade NHL	1	1	1
		4	6	13

Table 5.2 Summary of schedules prescribed in lymphoma patients aware of monitoring. NHL = Non Hodgkin's lymphoma

The hourly irregularity index, although a measure of the consistency of a patients pattern of tablet taking does not give information on the actual hourly intervals used. For this reason data was also analyzed to show the distribution of the length of intervals for the study population as a whole. Figure 5.7 shows the distribution of the length of all the intervals in hours for once daily regimens in patients unaware of monitoring. 78.4% of the intervals were between 22 and 26 hours in length. Figure 5.8 shows a subset of the same data as in figure 5.7. This shows the distribution of the length of the intervals for days when there was the correct number of openings, that is days with only one opening. This included 84% of the data. 96% of the intervals were between 22 and 26 hours and the mean (SD) was 24.0 (1.5) hours.
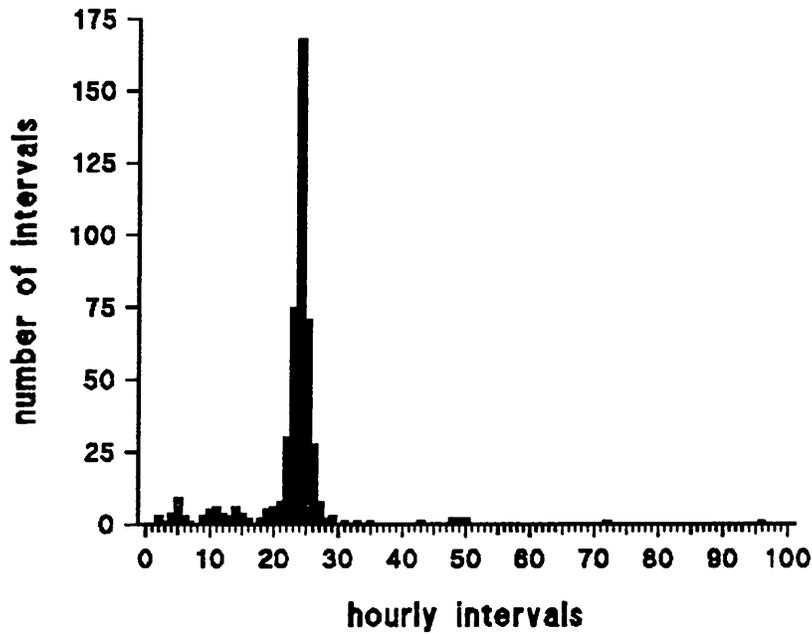
Figure 5.7   Distribution of the length of intervals between doses for once daily regimens in lymphoma patients unaware of monitoring.
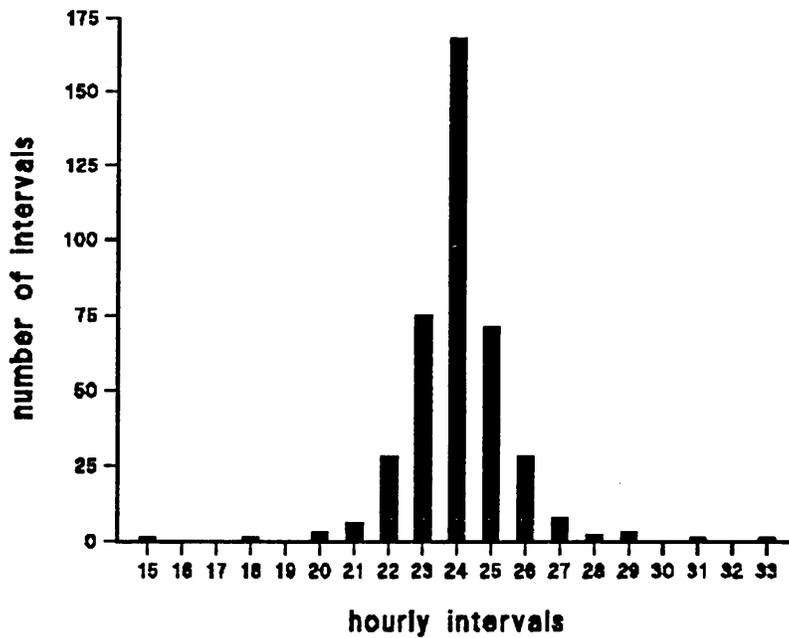
Figure 5.8   Subset of the data in figure 5.7:   distribution of length of intervals between doses for days with one interval in once daily regimens.

Figure 5.9 shows the distribution of the length of all the intervals, in hours, for the twice daily regimens in patients unaware of monitoring. Figure 5.10 shows a subset of 90% of the data from figure 5.9. This is the distribution of the intervals for days when there were two bottle openings, the correct number for a twice daily regimen. The data has been subdivided to show the length of the day time intervals and the length of the night time intervals. The mean (SD) day time interval was 8.5 (3.1) hours and the mean (SD) night time interval was 15.3 (3.2) hours. The distribution is bimodal with a proportion of the day time intervals at 4-6 hours and a proportion of the night time intervals at 18-20 hours. These probably correspond to some patients who found that, if they took prednisolone in the evening, they were unable to sleep because of a stimulant effect from the drug. These patients were subsequently advised to take both the doses in the morning at approximately 4 hours apart.

Figure 5.11 shows the distribution of the length of all the intervals, in hours, for the thrice daily regimens in patients unaware of monitoring. Figure 5.12 shows a subset of 72% of this data. This is the distribution of the intervals for days when there were three openings. The data has been subdivided to show the length of the morning, afternoon and night dosing intervals. The means (SD) for these intervals were 4.7 (1.6) hours, 6.7 (2.1) hours and 12.4 (2.4) hours respectively.
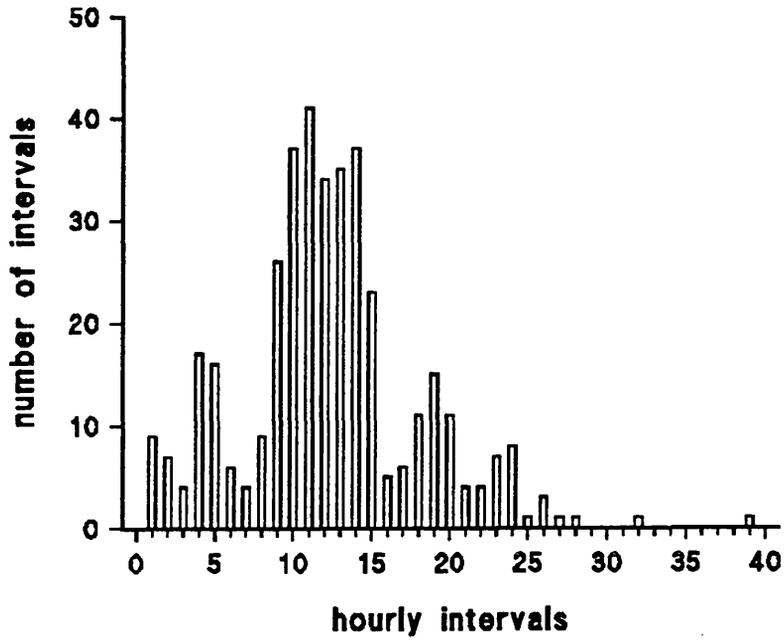
Figure 5.9   Distribution of the length of intervals between doses for twice daily regimens in lymphoma patients unaware of monitoring.
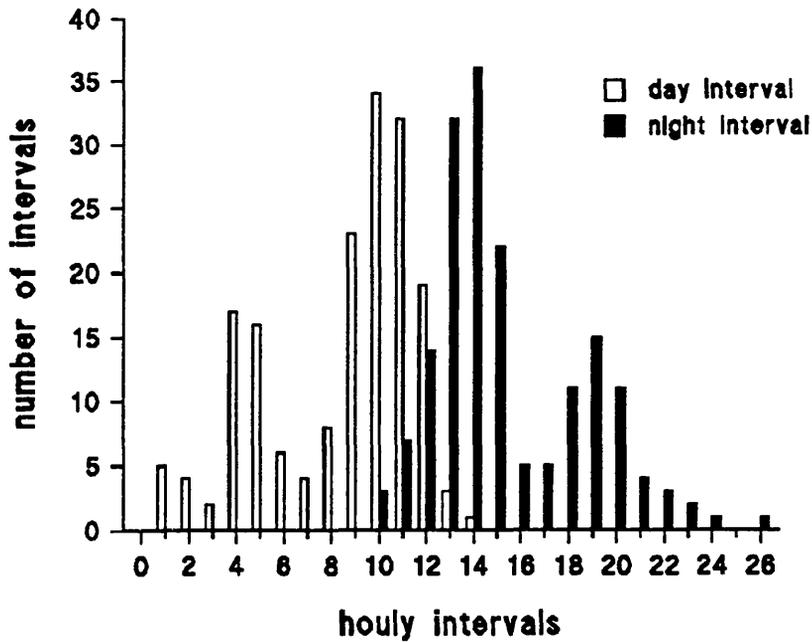
Figure 5.10   Subset of the data in figure 5.9:   distribution of length of intervals between doses for days with two intervals.
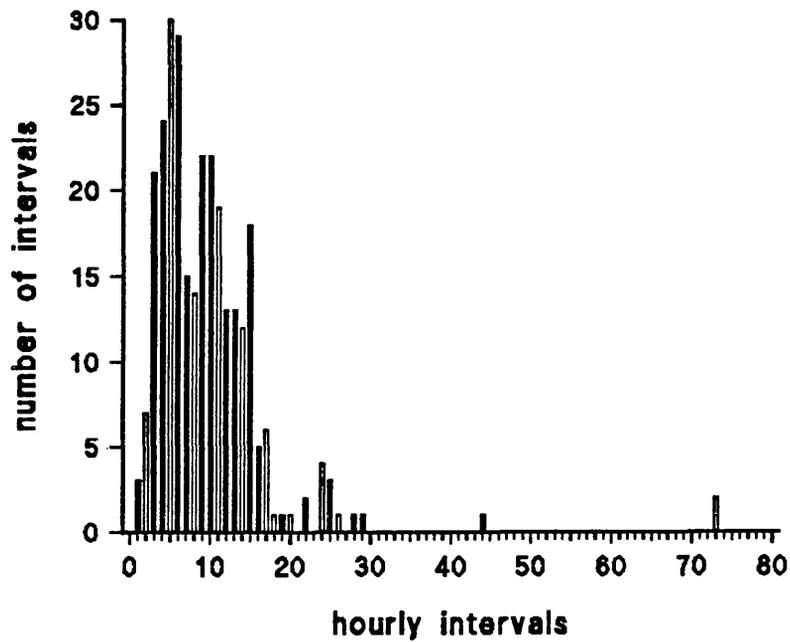
Figure 5.11 Distribution of the length of intervals between doses for thrice daily regimens in lymphoma patients unaware of monitoring.
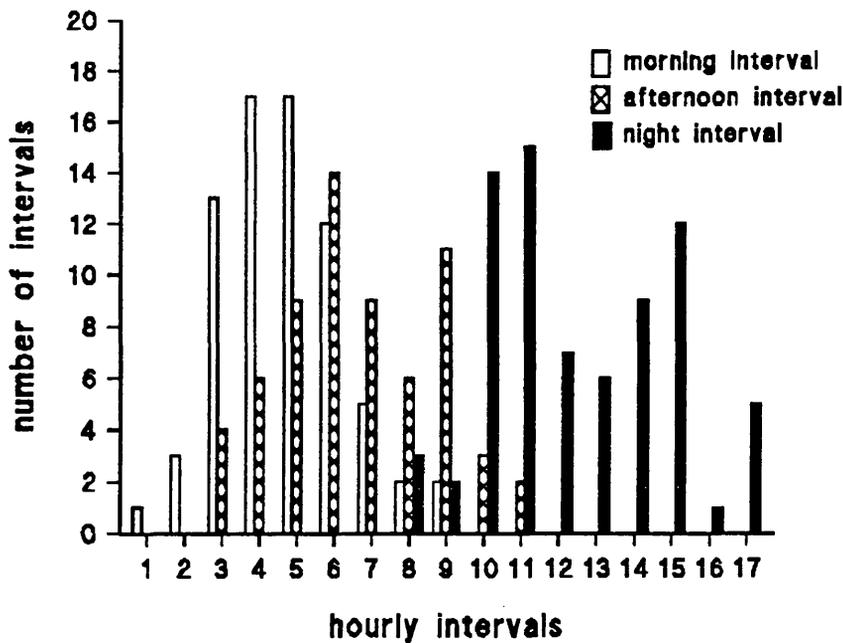
Figure 5.12 Subset of the data in figure 5.11: distribution of length of intervals between doses for days with three intervals.

5.4 DISCUSSION

The electronic tablet monitor is not a perfect method to assess compliance since the opening of the bottle by the patient does not guarantee ingestion of the medication. However, where a regular pattern of openings is seen, as was the case in most of our patients, it would be unlikely that these openings do not correspond to tablet taking. This would seem equally true for the minority of patients who were aware of the recording nature of the device. The method has a considerable advantage over previous methods in that it provides a continuous measure with which to analyze tablet taking habits.

Compliance in this study is much higher than has been reported previously (Levine et al 1987, Lebovitis 1990). This may, in part, be due to the different methods used to measure and score compliance. In the study by Levine et al (1987) another difference lies in the patients' attendance at monthly clinic appointments, quoted as occurring on average only 66.4% of the time. In the present study all the patients except one kept all their clinic appointments. If medication compliance could be shown to be generally related to appointment keeping, the latter may provide a simple indication of populations at risk from poor compliance.

No attempt has been made to define a level of overall compliance below which patients are considered non-compliant. It is not easy with these drugs to define a level of overall compliance and level of deviation from the prescribed schedule below which patients are putting the success of their treatment at risk. Anti-cancer drugs have been shown to have a steep dose response curve in animals (Schabel et al 1984). It has been reported that breast cancer patients who had received 85% or less of their adjuvant chemotherapy had lower relapse free periods and total survival time

(Bonadonna et al 1981) although the retrospective analysis of received dose in relation to survival has many obvious biases. Nevertheless the dose received must be an important factor in response and survival especially in chemosensitive tumours like lymphoma (Hryniuk 1987). In the present study, of the 35 treatment cycles monitored only 2 cycles had a mean overall compliance (ie, the mean of the overall compliance of each medication in the cycle) of less than 85% (74% and 75%) These 2 cycles where from different patients who were both monitored for more than one cycle and in subsequent cycles their mean overall compliance was greater than 85% in both cases. These results are reassuring in that they suggest for this group of out-patients systematic under-dosing with oral chemotherapy is unlikely.

The group of patients who were aware that the time they took their tablets was being recorded did show a small but significant increase in their regularity of tablet taking. Although the group studied was small this does seem to imply that the outcome may be different when compliance is assessed by a method, such as a questionnaire, where the patient is aware of monitoring. For ethical reasons some physicians may consider it necessary to reveal to the patient that monitoring is taking place and this may therefore affect the outcome.

A total of 13 explanatory variables were examined for effect on the three compliance variates. This would be expected to generate several spurious effects nominally "significant" at $P<0.05$. For this reason the apparent effects of the nausea score should be interpreted cautiously. The effect of the prescribed daily dosage frequency, nominally significant at $P<0.025$ may represent a genuine effect. This would accord with the findings of Pullar et al (1988) who, in a study designed to look specifically at daily dosage frequency, concluded that the compliance with once daily

was best, and that twice daily was similar but that both were superior to three times

a day. It is a commonly held view that twice or thrice daily dosage is better because

if the patient misses a dose the loss is less important than if a dose were missed on

a once a day regimen (Cramer et al 1990). However, our results for overall

compliance, which is a measure of the total amount of drug taken over the course,

indicate that this is poorer for a thrice a day regimen with a mean reduction of 10%

in overall compliance as compared to a once a day regimen.

The mean lengths of the three intervals for the thrice daily regimens of 4.7, 6.7

and 12.4 hours demonstrate that patients do not normally interpret three times a day

as every eight hours. Interestingly these figures are similar to those reported by

Alfredsson et al (1981) in a study using an electronic eye-dropper bottle to look at the

timing of doses by patients on pilocarpine prescribed to be used three times a day.

They found the means of the first, second and third intervals to be 6.4, 6.5 and 11.1

hours respectively. These figures suggest if it is considered important that medication

is taken eight hourly then this should be explained to the patient.

Compliance was apparently unrelated to the quality of life or the experience

of side-effects. Similarly Richardson et el (1988) found the presence and frequency

of adverse physical effects did not correlate with any aspect of compliance in a group

of patients with haematologic malignancy. This is in agreement with studies done in

other diseases which have shown no difference in frequency of side-effects for

compliers and non-compliers (Haynes 1979). That compliance was unrelated to any

factor we assessed supports the view that there may not actually be a reliable way to

predict compliance from quality of life assessment.

It could be argued that compliance is good in these patients because they have

a good prognosis and the drugs are not particularly toxic hence a comparable study

was carried out in small cell lung cancer patients being treated with oral etoposide;

a disease with a poor prognosis and a drug with a worse side-effect profile than those

used in this study (see Chapter 6).

CHAPTER 6

PATIENT COMPLIANCE WITH

ORAL ETOPOSIDE FOR SMALL-CELL LUNG CANCER

6.1 INTRODUCTION

6.1.1 Classification and Treatment of Lung Cancer

Lung cancer is the leading cause of cancer deaths in males and in 1985, 40,000 people in the UK died of the disease (Thatcher 1990). 80-90% of lung cancer patients die within the first year of registration.

Lung cancers are classified into small-cell cancer, SCLC, which accounts for 19 to 25% of lung cancers and those which are non-small cell in nature which account for the remaining cases and may be further classified into four sub-types. SCLC differs from the others in that it grows more rapidly and metastases earlier. Because of this SCLC is typically disseminated at presentation and radiotherapy or surgery are not usually useful. It is, however generally more sensitive to chemotherapy than non-small cell lung cancers. On presentation it is subdivided into limited or extensive disease. Untreated, it is rapidly fatal with the median survival being 3 months in limited disease and 1.5 months in extensive disease (Spiro 1985). Combination chemotherapy is usually the treatment of choice and this involves moderately intensive combinations of cytotoxic agents such as doxorubicin, cisplatin, etoposide, vincristine and methotrexate. Such combinations have lead to a four-five fold improvement in median survival compared with untreated patients. In limited disease the median survival is increased to 12-15 months with 10-15% of patients surviving 2 years. In extensive disease the median survival is increased to 6-10 months with less than 5% of patients surviving 2 years.

6.1.2 The Use of Etoposide in the Treatment of Cancer

Etoposide, a semi-synthetic derivative of podophyllotoxin, was introduced in

1971 and has become established in the treatment of malignant disease. Used as a single agent it has a response rate of approximately 20% in a variety of tumours. Consequently, it has been added to standard chemotherapy regimens shown to be active in these tumours in an attempt to improve response rates. It has proved to be very active in combination with cisplatin and the synergy of the two drugs is clinically relevant in a number of tumours. The use of this combination in the initial treatment of SCLC has been extensively studied. Non-randomised studies of intravenous etoposide containing regimens for primary treatment of limited disease SCLC showed the more active combinations to be etoposide with cyclophosphamide, doxorubicin and vincristine (CAVE) or etoposide and cisplatin alternating with CAV (Henwood & Brogden 1990).

The efficacy of etoposide is dose-schedule dependent in vitro against various malignant cell lines and as a result of this and early work it was usually given as part of combination chemotherapy over 3 to 5 days. Further clinical evidence of the schedule dependency of etoposide came from a recent study which demonstrated that the same IV dose of etoposide when given divided over 5 days as opposed to over 24 hours produced a response rate of 89% as opposed to 10% (Slevin et al 1989). This has lead to the hypothesis that prolonged maintenance of low plasma concentrations of etoposide are more important than peak concentrations for the cytotoxic action of the drug (Slevin 1990a). As a result of this work a number of studies have been carried out taking this hypothesis to its logical conclusion in giving low-dose etoposide over longer periods using the oral formulation (Johnson et al 1990, Clark et al 1990, Einhorn 1991). The results of these studies have been promising with the data suggesting that etoposide may be a "new" drug when given in these schedules

(Greco et al 1991). The high response rates with oral etoposide suggest that oral administration may be substituted for IV. This substitution may allow for greater flexibility in chemotherapy administration, less hospitalization and more acceptable toxicity (Carney 1991). One of the main questions in transferring from IV therapy to out-patient oral therapy is whether or not the patients take the medication as prescribed.

6.1.3 Aim of the Current Study

Having previously shown a high rate of compliance with oral chemotherapy for lymphoma, the aim of this study was to use the same methodology to assess compliance with oral etoposide in SCLC. No work had hitherto been published on compliance with this therapy and this study is of particular interest due to the new low-dose oral etoposide schedules currently being investigated.

6.2 METHODS

6.2.1 Patients

The patients were being treated at the oncology out-patient clinic at the Homerton Hospital, a London teaching hospital. Participation in the study was limited to those patients receiving low-dose oral etoposide for SCLC. Of the 14 patients, (11 male 3 female) mean (SD) age 62.4 (11.0) years, 9 had received no prior treatment and were given single-agent etoposide. One patient had received previous radiotherapy and IV chemotherapy with etoposide and cisplatin with a complete response and had subsequently relapsed. One patient had received radiotherapy immediately prior to starting single-agent etoposide and two patients were receiving

low-dose etoposide as part of a combination chemotherapy regimen including IV cyclophosphamide and vincristine. The low-dose oral etoposide schedule used at the Homerton was 50mg (one capsule) twice daily for 14 days of a 21 day cycle, although this was modified and/or reduced in some patients.

6.2.2 Compliance Assessment

Compliance with oral chemotherapy was monitored using the novel electronic tablet monitor described in chapter 4. There was no intervention to change or improve compliance but factors that might influence compliance such as side-effects of medication and symptoms of disease were also investigated. Data from the monitor for each treatment period was processed to give three measures; the overall compliance, a measure of the total amount of drug taken, the daily irregularity index, representing the number of daily discrepancies in bottle openings averaged over the course and the hourly irregularity index, an index of the repeatability of the patients own hourly pattern of openings. For details of how these measures were calculated chapter 4 section 4.2.2 should be consulted.

6.2.3 Quality of Life Assessment

Patients' experience of side-effects of the etoposide treatment and of symptoms relating to the disease were self-assessed using the diary card described in chapter 5, section 5.2.3. Patients were asked to fill in the diary card for the days they were taking their oral medication. The mean score for each of the eight questions was calculated for each treatment period.

6.2.4 Study Design

Where possible patients were monitored for two or more cycles of etoposide, not necessarily consecutively. Informed consent for monitoring the effects of the treatment was sought but patients were not told the recording nature of the bottle. Patients were told that the intention was to make a detailed assessment of symptoms using a diary card; if they asked what the bottle was they were told as before (chapter 5 section 5.2.4) that it had a light-proof construction. If more details about the device were requested consent was obtained to reveal this at the end of the study; this occurred with two patients.

The diary card was given out by the research pharmacist and the patient was shown how to complete it at the end of each day. The patient's prescription and the electronic tablet bottle were taken to the hospital pharmacy department. The prescription was dispensed in the normal manner, clearly labelled as to the contents and treatment regimen with the exact number of capsules required. A label was also affixed asking for the bottle to be returned to the clinic. Because of the current recommendation that all oral solid dosage forms be dispensed with child-resistant closures patients consent to having non-child resistant closures was sought and it was emphasised that the bottle should be kept with the cap securely on, well out of the reach of children. Patients were asked not to transfer the capsules to any other container and to return the containers and completed diary card next time they attend the clinic. Patients were given the information sheet shown in Appendix 1. On returning the containers any remaining capsules were counted. A record of patients attendance at the clinic was kept.

6.2.5 Statistical Methods

A linear modelling approach was used to analyze the compliance data to look for any relationship between reported symptoms, course number, months since diagnosis and the compliance measures, see chapter 5 section 5.2.5. The monitoring period sequence and the eight mean scores from the diary cards were regarded as within-patient factors. The number of months since initial diagnosis was regarded as a between-patient variable.

Residuals were tested for normal distribution by the Shapiro-Francia W' test (Royston 1983) and by chi squared test. In the case of the overall compliance the residuals were found to depart from normality. To correct this the overall compliance was transformed using in the same way as in chapter 5 section 5.2.5. No transformation was required for values of the daily irregularity index or the hourly irregularity index.

6.3 RESULTS

No patients refused to participate in the study. Two patients failed to return their tablet bottles at their next appointment and due to rapid deterioration of their disease had no subsequent out-patient appointments so no data is available from them.

Patients received the exact number of capsules required for their course of treatment so none should be returned. On no occasion were any capsules found remaining. No patients failed to attend for scheduled clinic appointments except when they became progressively ill, when alternative arrangements were made.

6.3.1 Analysis of Records

A total of 25 treatment periods were analyzed from 12 patients who were all unaware that monitoring was taking place. These patients were monitored for 1 to 3 cycles (mean 2.1). Of the 25 treatment periods 20 were for 50mg etoposide twice daily, 3 were for 50mg twice daily alternating with 50mg once daily and 2 were for 50mg once daily.

The grand mean (SD) of the overall compliance for the 25 treatment periods was 93.2% (12%) and figure 6.1 shows the distribution of the values.
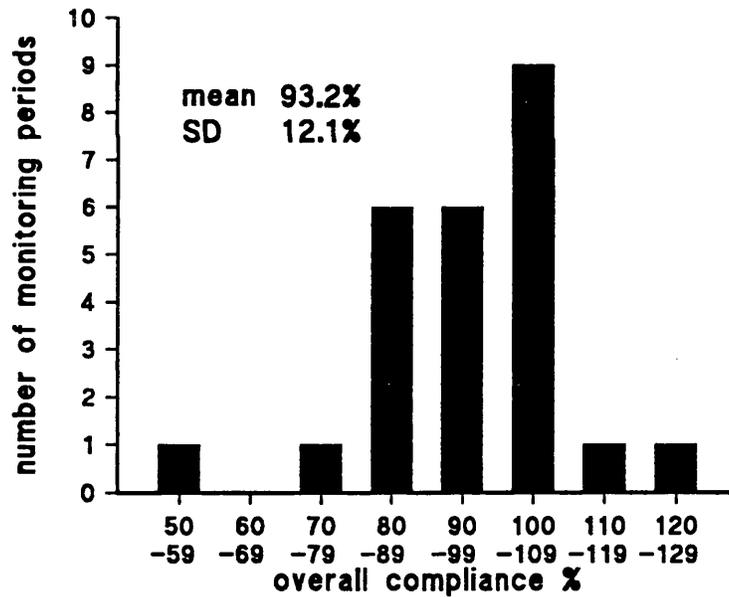
Figure 6.1 Distribution of the values of Overall Compliance for patients with SCLC.

Figure 6.2 shows the distribution of the daily irregularity index. The mean of

0.19 shows that on average there were 5.3 extra or omitted openings in a 14 day

treatment period of a twice daily regimen.
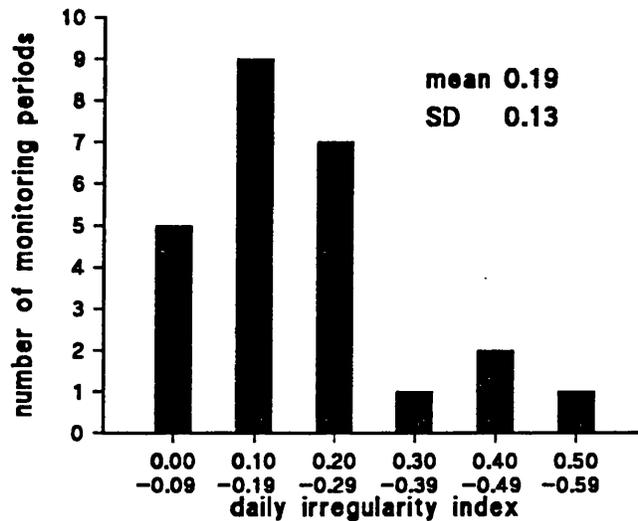
*Figure 6.2   Distribution of values of the Daily Irregularity Index
for SCLC patients.*

Another way of expressing the daily irregularity is to look at the number of

days with the correct number of openings in relation to the prescribed daily number.

Of the 307 days monitored 68.4% fell into this category. 10% of days had extra

openings, 17.6% of days had less than correct openings and 3.9% of days had no

openings.

Figure 6.3 shows the distribution of the hourly irregularity index. When

compared with the daily irregularity index in figure 6.2, it can be seen that patients

are more consistent at complying with the prescribed daily frequency than with an

hourly pattern of intervals between doses.
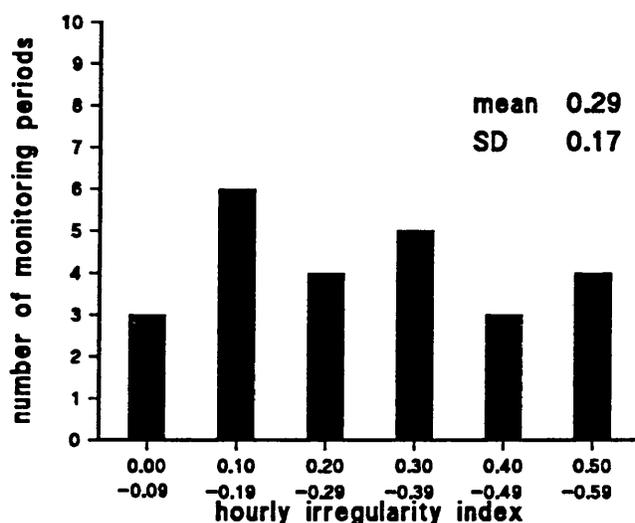
Figure 6.3 Distribution of values of the Hourly Irregularity Index for SCLC patients.

The hourly irregularity index, although a measure of the consistency of a patient's pattern of dose taking does not provide information on the actual hourly intervals used. Therefore, the data was also analyzed to show the distribution of the length of the intervals for the study population as a whole. Figure 6.4 shows the distribution of the length of all the intervals in hours for twice daily regimens, 20 of the 25 treatment periods. Figure 6.5 shows a subset of the data from figure 6.4. This is the distribution of the intervals for days when there were two bottle openings, the correct number for a twice daily regimen. The data has been subdivided to show the length of the day time intervals and the length of the night time intervals. The mean (SD) day time interval was 10.6 (2.4) hours and the mean night time interval was 13.2 (2.1) hours which are close to the "ideal" for a twice a day regimen of every 12 hours.
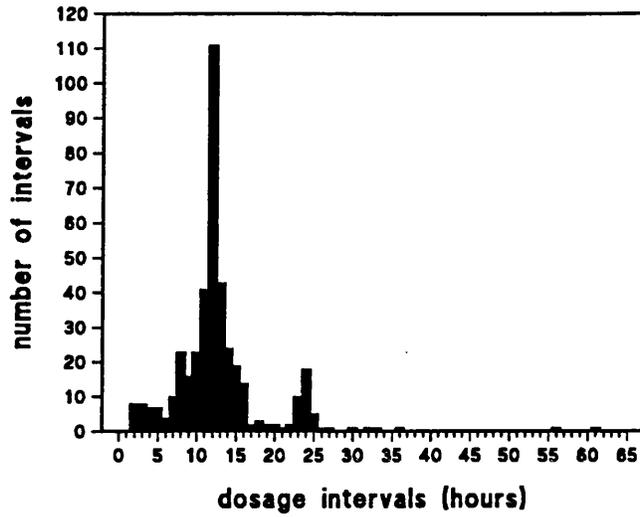
Figure 6.4 Distribution of the length of intervals for twice daily regimens in SCLC patients
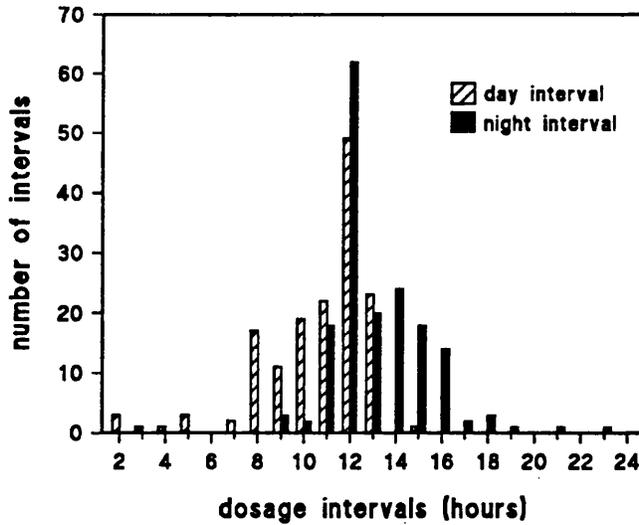
Figure 6.5 Subset of the data in Figure 6.4: distribution of the length of intervals for days with two openings.

Using the generalised linear modelling procedure, see section 6.2.5, the relationship between each of the three compliance measures and the various explanatory variables was examined. The treatment period sequence was regarded as a factor variable whereas the 8 diary card scores and number of months since initial diagnosis were regarded as continuous variables.

No significant (ie $P<0.05$) effect of course number was found for any of the three compliance measures. For the overall compliance a significant within-patient effect of the diary card scores for sickness was found for vomiting, appetite , pain and activity when each was entered into the equation one at a time, the most variance being explained by the activity score ($P<0.005$). However, it was apparent that these explanatory variables were inter-related, because if the activity score were already entered into the equation, the addition of any of the other three scores did not make a significant contribution. The magnitude of the effect of the activity score corresponded to a decrease in the overall compliance of about 3% with a decrease in the activity score of 1 so although this is a significant effect it is small in magnitude. Between the two extremes of activity, fully active and staying in bed, compliance would decrease by 9%.

On the daily irregularity index none of the diary card variables showed a significant effect. There was a between patient ($P<0.025$) effect on the daily irregularity index of the time since diagnosis, and this corresponded to a minimal decrease in the daily irregularity index of 0.005 per month.

On the hourly irregularity index there was a between patient effect ($P<0.025$) on the score for vomiting, and this corresponded to an increase in the hourly irregularity index of 0.23 for an increase in the vomiting score of 1. This is worthy

of comment since between the two extremes of not being sick and vomiting more than twice in a day a patient could go from a regular hourly pattern of openings to a totally irregular hourly pattern.

6.3.2 Comparison with the Lymphoma Patients

It is of interest to compare compliance with that previously observed in lymphoma patients (see chapter 5). The latter group of patients differed in that they were prescribed daily dosage frequencies between 1 and 3 as against predominantly 2 in the present group. As dosage frequency was previously found to affect compliance only data relating to drugs prescribed twice daily in the lymphoma group will be used for the purpose of comparison. Of the 16 treatment periods in the lymphoma group that were prescribed to be taken twice daily 13 were for prednisolone, 2 were for cyclophosphamide and one was for dexamethasone. Because, in both groups, individual patients were followed for differing numbers of treatment periods the mean value for overall compliance, daily irregularity index and hourly irregularity index over all treatment periods for each patient were first calculated. The mean (SD) values for the three compliance measures for the two groups are shown in table 6.1. Comparison of these values for significant differences by unpaired t test showed only the daily irregularity index in the present group was larger than in the lymphoma group (t=2.25, df=21, P<0.05). Another way of expressing the daily irregularity is to look at the percentage of days with the correct number of openings, more than the correct number and less than the correct number. This data for the two groups is represented in figure 6.6.

	SCLC Group: 10 patients 20 treatment periods	Lymphoma group: 11 patients 16 treatment periods
Overall Compliance %	94.7 (6.7)	96.4 (8.9)
Daily Irregularity Index	0.22 (0.11)*	0.11 (0.09)*
Hourly Irregularity Index	0.31 (0.14)	0.31 (0.18)

* *Difference significant P<0.05*

Table 6.1 Mean (SD) values for the three compliance measures for patients in the etoposide group and in the lymphoma group prescribed twice daily regimens.
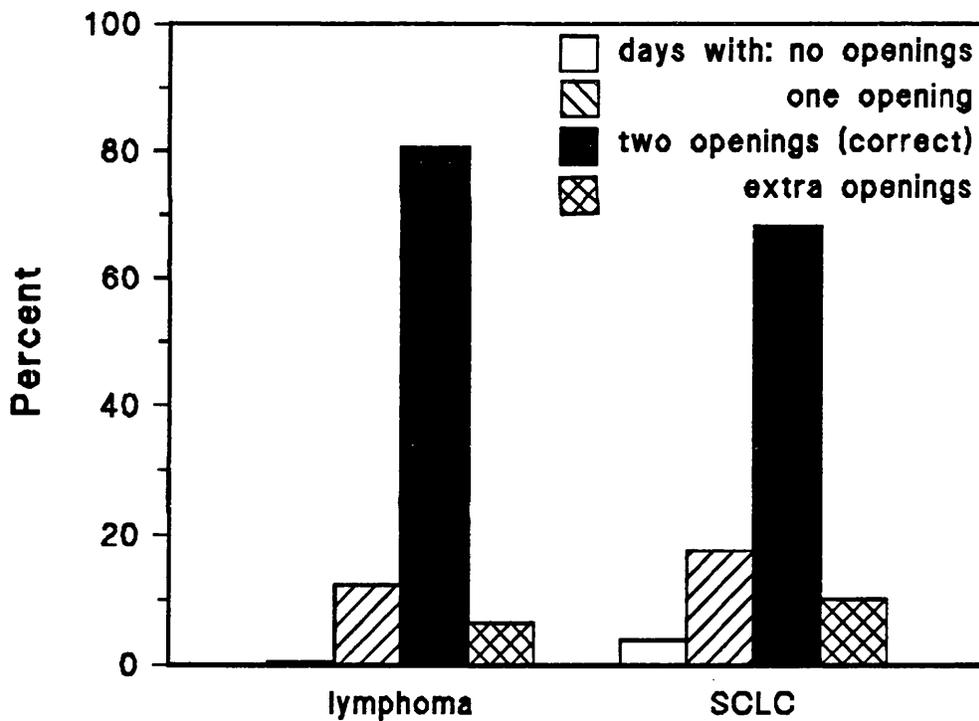
Figure 6.6 Distribution of the number of daily openings with respect to the prescribed daily number in lymphoma patients and SCLC patients.

lymphoma: the subset of lymphoma patients on twice daily regimens
SCLC: the subset of SCLC patients on twice daily etoposide

Because the 8 scores for physical and mental state of the patients in the present group and in the lymphoma group were assessed in the same way a direct comparison is possible. Because the patients were followed for differing numbers of treatment periods the mean value over all the treatment periods for each patient was calculated. For the lymphoma group all the patients who completed diary cards were included regardless of treatment. The mean values ± SD between patient for the present group (12 patients) and the lymphoma group (18 patients) are given in table 6.2. Comparison of the means by unpaired t test showed that the score for activity was significantly lower in the present group (t=2.8, df=28, P<0.01).

| | Etoposide 12 patients | | Lymphoma 18 patients | |
	mean	SD	mean	SD
Sickness	1.35	0.35	1.25	0.44
Vomiting	1.18	0.30	1.17	0.41
Appetite	1.75	0.58	1.49	0.52
Pain	1.30	0.35	1.46	0.56
Sleep	1.75	0.46	2.04	0.56
Activity	2.44*	0.53	3.07*	0.70
Mood	1.71	0.50	1.55	0.51
General Well Being	1.72	0.55	1.76	0.55

difference significant P<0.01

Table 6.2   Mean values of the diary card scores for lymphoma patients and SCLC patients.

6.4 DISCUSSION

Using the same methodology as in lymphoma patients, (chapter 5), the results for compliance in SCLC patients were very encouraging. It had been suggested that the compliance behaviour might be poorer in patients with less optimistic clinical outcome and/or a treatment with more unpleasant side-effects. However, we did not find this to be significantly so.

The diary card method of self assessment of mental and physical wellbeing affords a basis for other comparisons between the two groups. The only significant difference we could uncover was between the scores for activity, these being lower in the SCLC group. Etoposide has the reputation of causing more unpleasant side-effects than the drugs used in the lymphoma group and this is certainly the case for alopecia. However we saw no evidence of increased sickness and vomiting. The most likely explanation for this is that giving low-dose oral etoposide over 14 days does in fact cause less emesis than when the drug is used by the more conventional intravenous route in higher doses over 3 to 5 days. These results are encouraging in that they suggest low-dose oral etoposide is a well tolerated regimen and patients generally take it as prescribed.

In the relationship of the compliance measures to the various explanatory variables, a decrease in overall compliance with a decrease in activity score was seen ($P< 0.001$), an increase in the daily irregularity index with increase in time since diagnosis ($P<0.025$) and an increase in the hourly irregularity index with the vomiting score ($P<0.025$). All these effects were small in magnitude and seem likely to have little practical consequences. It is interesting however that the activity score, as well as being the only distinguishing feature between the SCLC group and the lymphoma

group, has also a highly significant effect (even if small in magnitude) on overall compliance in the present group. This accords with the use of, for example, Karnovsky performance index as a useful correlate of disease severity and prognosis in SCLC (Souhami et al, 1985).

The high levels of compliance observed in the SCLC and lymphoma studies imply that inadequate compliance is unlikely to be a significant factor affecting treatment outcome in these groups of patients. The high compliance may be seen as in line with the readiness of cancer patients to opt for radical treatment with minimal chance of benefit, as documented by Slevin et al (1990b). This inspires confidence in the use of the self-administered oral medication having, as it does, advantages in the cost of treatment and convenience for the patient.

CHAPTER 7

PATIENT COMPLIANCE WITH

ALTRETAMINE (HEXALEN®)

FOR ADVANCED OVARIAN CANCER

7.1 INTRODUCTION

7.1.1 Background to Ovarian Cancer and its Treatment

3700 women died of cancer of the ovary in 1983 (Lambert & Soutter, 1990) and the incidence of the condition is increasing. It is rare before the menarche and occurs most commonly between the ages of 50 and 70 years. The early signs and symptoms are of an insidious nature so that it is generally at an advanced stage on presentation. Treatment usually consists of surgery then chemotherapy and only in less extensive disease is radiotherapy used. Treatment with single-agent alkylating agents gives an initial response of 35-65% however the duration of the response is only 10-14 months. Combination chemotherapy with the platinum analogues, for example cisplatin, gives a better response rate but the long term survival is poor with most patients eventually relapsing. On relapse chemotherapy is usually given again using single-agents or combinations but cures are not achieved. There is interest in monitoring a tumour marker, antigen CA 125, which was derived from a human ovarian cancer line. An increase in this marker may indicate relapse before clinical detection so enabling chemotherapy to be started earlier with an improved response rate.

7.1.2 The use of Altretamine (Hexalen®) in the Treatment of Ovarian Cancer

Altretamine (formerly hexamethylmelamine) is a synthetic compound derived from melamine and possibly acts as an alkylating agent although it does not show cross-resistance with classical alkylating agents. It is licensed in some European countries and the USA (as Hexalen®, U.S. Bioscience) for use as a single agent in the palliative treatment of patients with persistent or recurrent ovarian cancer following

first-line therapy with a cisplatin and/or alkylating agent based combination. In early studies neurotoxicity and severe gastrointestinal toxicity limited its use, however, using intermittent dosage schedules and with the more effective antiemetics available these toxicities may not now be so much of a problem (Rosen et al 1985, Manetta et al 1990). Hexalen® is currently undergoing a phase II clinical trial in the UK in patients with advanced ovarian carcinoma in relapse and this study formed an addition to the trial. Hexalen® has the advantage of being active when given orally and thus can be used on an out-patient basis avoiding the need for hospitalization. Hexalen® is administered at a dose of 260mg/m²/day for a period of 14 days in a 28 day cycle. It is available as 50mg capsules and the total daily dose, rounded to the nearest 50mg, is given as four divided doses at meal times and at bedtime, although pharmacokinetic data to support this is not available.

7.1.3 Aims of the Present Study

When compliance is assessed in clinical trials it is most commonly assessed by return tablet count. This method may overestimate compliance since it is subject to patient manipulation as discussed in chapter 1 section 1.2.1.5. In addition to this it only gives information on the totality of compliance with no information on dosing intervals. The use of electronic compliance monitors in trials reduces ambiguity about compliance and helps in the interpretation of the outcome data (Rudd et al 1990).

In the previous study involving a group of lymphoma patients, overall compliance was significantly lower with medications to be taken three times a day compared with those to be taken once daily, see Chapter 5 section 5.3.1. Oral Hexalen® is prescribed to be taken four times a day and antiemetics are routinely

prescribed to be taken with Hexalen® in contrast to the treatments that were monitored in the lymphoma and small-cell lung cancer groups (chapter 5 and 6). The aim of this study was to demonstrate the use of the monitor in a phase II trial, in this case of Hexalen®, and to compare the findings with those from the two oncology groups already studied. The data from the monitor was also compared with the return tablet count and patients reporting of symptoms using a daily diary card.

7.2 METHODS

7.2.1 Patients

Patients recruited into the phase II study of oral Hexalen® in advanced ovarian cancer were eligible for entry into the study. The aim was to recruit 25 patients over a six month period covering three centres, Mount Vernon Centre for Cancer Treatment and the Departments of Oncology at University College Hospital and The Hammersmith Hospital.

7.2.2 Study Plan

Patients received medication as outlined in the study protocol except that it was dispensed in the electronic tablet bottle. Where possible they received the containers for two or more cycles of treatment not necessarily consecutively. On returning the containers any remaining capsules were counted and the data retrieved from the monitor.

7.2.3 Patient Information

Verbal consent was sought for the study. Patients were informed a diary card

would be used to record and assess their symptoms. They were told that they would receive their capsules in light-proof containers that had been made specially for the study and that these needed to be returned with any remaining capsules at the next visit. The recording nature of the monitor was not revealed. The patients were given the information sheet shown in Appendix 1 and where they were not satisfied with the explanation about the container consent was obtained to give them further information at the end of the study. The diary card was handed out and the researcher explained how to fill it in. The capsules were dispensed in the monitors by the pharmacy department and labelled as to the contents with full dosage instructions. An additional label was affixed with the wording "Important: please return bottle with any remaining capsules to oncology out-patients".

7.2.4 Statistics

A linear modelling approach was used to analyze the compliance data to look for any relationship between reported symptoms, course number and compliance, see chapter 5 section 5.2.5. The compliance data was compared with that obtained in the lymphoma and small-cell lung cancer studies using the t-test.

7.3 RESULTS

Although patients were recruited form three centres, the number of patients who were suitable for treatment with this particular therapy was less than initially expected. Over the course of one year data was only available from 6 patients followed in total for 13 courses. However, even from this small group it is possible to see that there is little difference between compliance in this group and the previous

two oncology groups studied.

Six patients, mean (SD) age 59.7 (11.9) yrs, were entered into the study. No

patients were told the recording nature of the monitor although one patient asked to

be told at the end of the study. No patients failed to return the containers and no

containers malfunctioned. One patient did not fill in the diary card for one course of

treatment.

7.3.1 Analysis of Monitor Records

The records from the monitor were analyzed as described in chapter 4 section

4.2.2 to give three compliance measures, the overall compliance, the daily irregularity

index and the hourly irregularity index.

The mean (SD) overall compliance for the 13 courses was 97.3% (8.0%) and

the distribution is shown in figure 7.1.
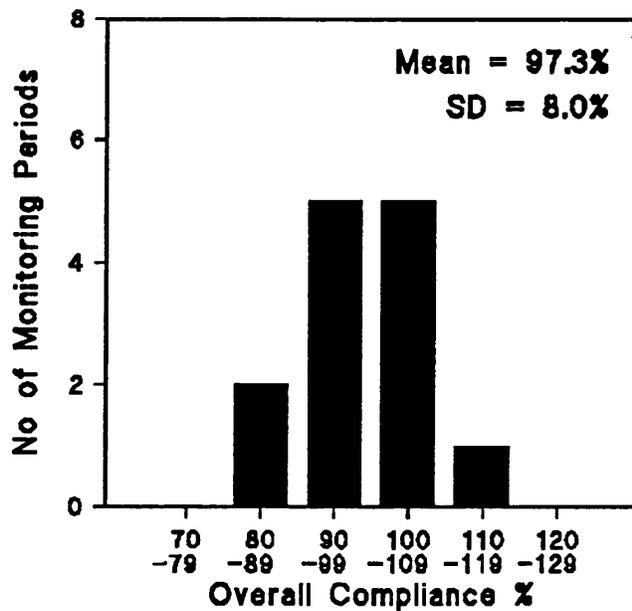
Figure 7.1   Distribution of values of the Overall Compliance
for patients with ovarian cancer.

The mean (SD) of the daily irregularity index for the 13 courses was 0.10 (0.06). This means that on average there were 5.6 missed or extra openings per 14 day monitoring period for this four times daily regimen. The distribution of values for the Daily Irregularity Index is shown in figure 7.2.
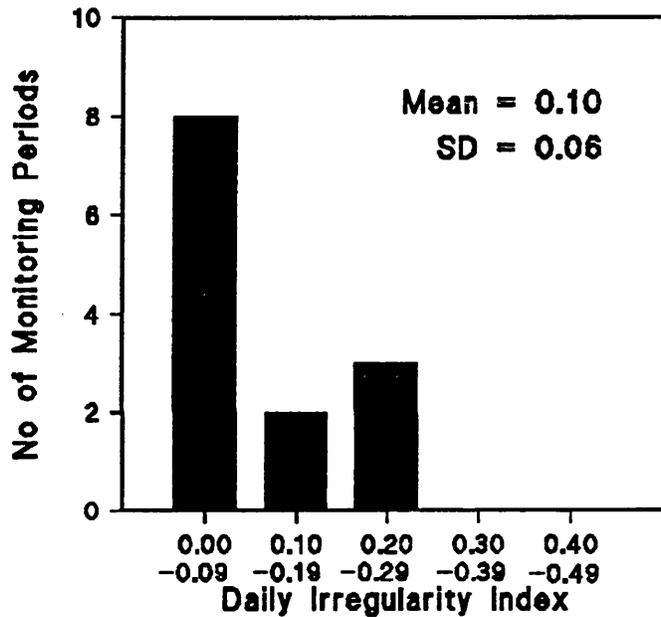
Figure 7.2 Distribution of values of the Daily Irregularity Index for patients with ovarian cancer

The number of openings per day for all the courses combined were also classified as being correct, less than and more than correct compared to the prescribed daily number, and these were 67%, 21% and 11%, respectively.

The mean (SD) of the hourly irregularity index was 0.23 (0.12) and the

distribution of values is shown in figure 7.3
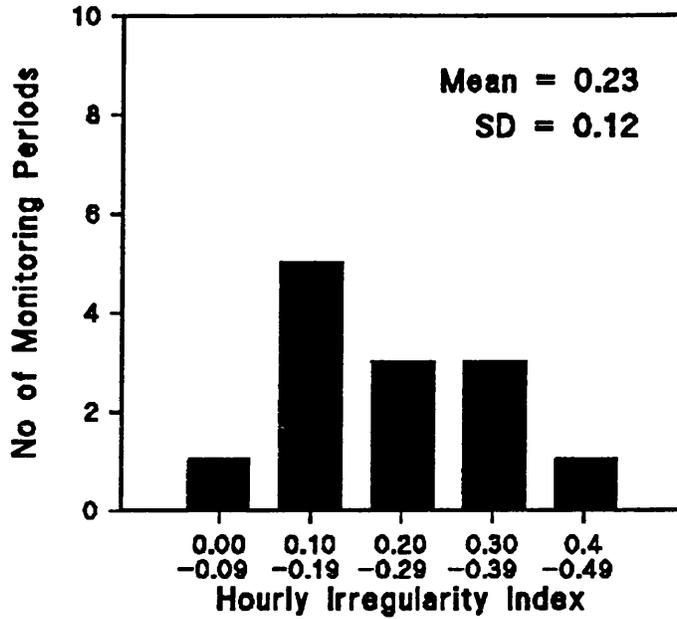
Figure 7.3   Distribution of values of the Hourly Irregularity Index
for patients with ovarian cancer

The length of all the intervals between monitor openings was analyzed and the

distribution of these is shown in figure 7.4.
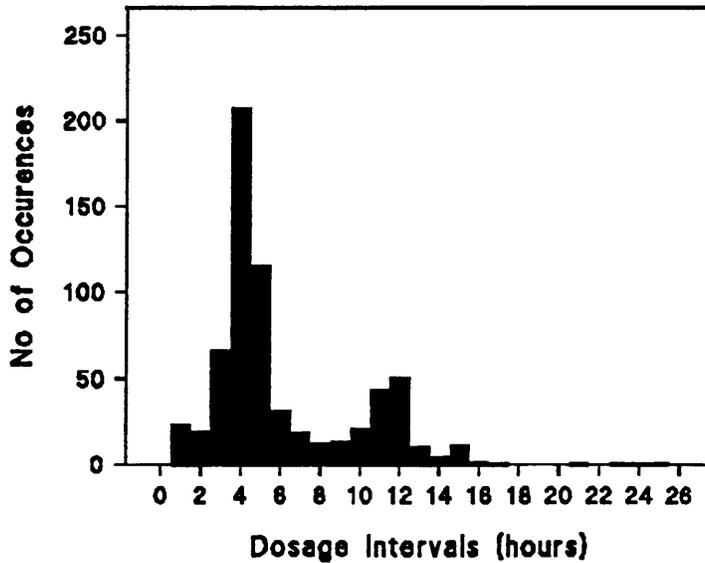
Figure 7.4   Distribution of the length of dosage intervals
for patients with ovarian cancer

A subset of the data in figure 7.4 is shown in figure 7.5 and includes the length of intervals between opening on days when there were the correct number of openings in relation to the prescribed daily number, that is four. These are divided into the morning, afternoon, evening and night intervals and the means (SD) for these were 4.4 (1.2), 4.5 (1.0), 4.2 (1.0) and 11.0 (1.5) respectively.
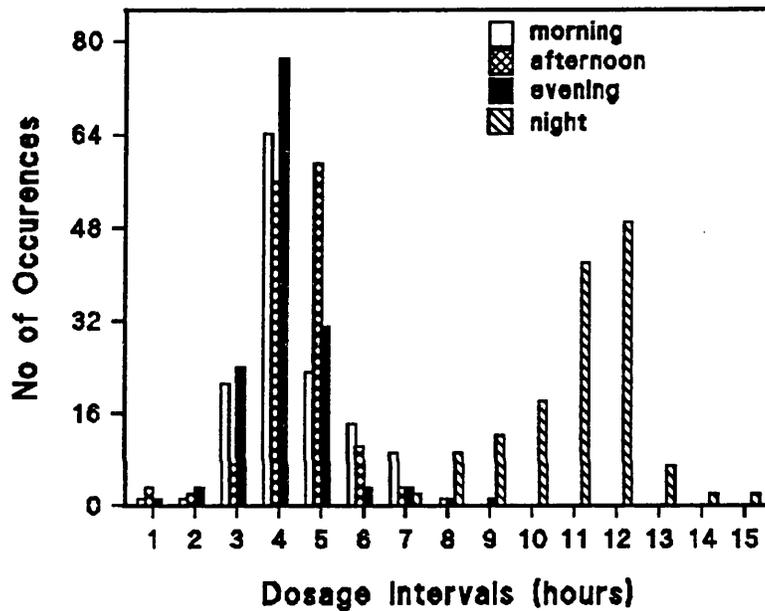
Figure 7.5 A subset of the data shown in figure 7.4, distribution of the length of intervals in days with four openings

For those patients monitored for more than one course no difference in the compliance measures could be demonstrated between the courses. Using the score from the diary card it was possible, for those patients monitored for more than one course, to analyze the data within patients to see if compliance was related to the score. This was not demonstrated. The diary card data were also analyzed to show between patients whether those with higher diary card scores for nausea and sickness had different values for the compliance measures. Again this effect was not demonstrated. The only statistically significant effect between the diary card scores

and compliance measures was between the daily irregularity index and sleep (p<0.05). As the daily irregularity increased sleep was poorer. However, this is unlikely to be a genuine effect but due to the large number of statistical tests carried out.

7.3.2 Comparison with the Lymphoma and Small-Cell Lung Cancer Groups

The lymphoma patients and small-cell lung cancer groups differed in that they were prescribed daily dosage frequencies between 1 and 3, and predominantly 2, respectively, as against 4 in the present group; moreover dosage frequency had previously been found to affect compliance. Thus, for the purpose of comparison with this data, data relating to drugs prescribed three times daily in the lymphoma group and twice daily in the small-cell lung cancer group were used. Drugs prescribed in the lymphoma group were prednisolone and procarbazine and in the SCLC group, etoposide. Because in each group individual patients were followed for differing numbers of treatment periods the mean value for each of the three compliance measures over all treatment periods for each patient was first calculated. The mean (SD) for the three compliance measures for the groups are shown in table 7.1.

	Ovarian Cancer 6 patients 13 courses	Lymphoma 5 patients 10 courses	SCLC 10 patients 21 courses
Overall Compliance (%)	95.5 (7.5)	90.9 (6.5)	94.7 (6.7)
Daily Irregularity Index	0.11* (0.05)	0.16 (0.09)	0.22* (0.11)
Hourly Irregularity Index	0.24# (0.09)	0.45# (0.11)	0.31 (0.14)

*Table 7.1 Means (SD) for the three compliance measures for each of the three oncology patient groups, Differences significant; * p<0.05, # p<0.01*

Comparison of the means by unpaired t-test revealed that the hourly irregularity index was significantly lower in the ovarian cancer group than in the lymphoma group, p<0.01. The differences between the overall compliances were not significant although it is interesting to note that the mean overall compliance in the ovarian cancer group was higher. The only significant difference between the ovarian cancer group and the SCLC group was that the daily irregularity index was significantly better in the ovarian cancer group, p<0.05.

The percentage of days with less than, more than and the correct number of monitor openings with respect to the prescribed daily number for the three oncology groups are shown in figure 7.6.
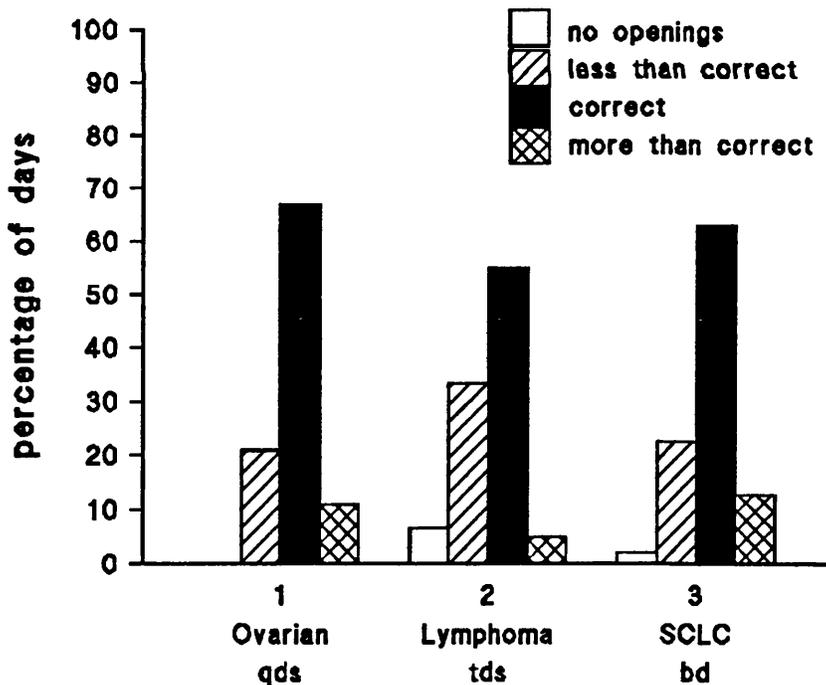
Figure 7.6 Percentage of days with less than, more than and the correct number of openings with respect to the prescribed daily number

Lymphoma is the subset of patients on three times daily regimens and SCLC is the subset of patients on twice daily regimens.

Since the method of evaluating symptoms by diary card in the three oncology studies was the same it is possible to compare the data. Table 7.3 shows the mean (SD) diary card scores for the three treatment groups. Where a patient was monitored for more than one course the mean of the diary card scores were first calculated for all the courses. The only significant difference between the present group and the lymphoma and small cell lung cancer was that the ovarian group scored significantly higher for activity than the SCLC group, $P< 0.05$.

	Ovarian Cancer 6 patients	Lymphoma 18 patients	SCLC 12 patients
Sickness	1.54 (0.42)	1.25 (0.44)	1.35 (0.35)
Vomiting	1.06 (0.11)	1.17 (0.41)	1.18 (0.30)
Appetite	1.67 (0.49)	1.49 (0.52)	1.75 (0.58)
Pain	1.59 (0.57)	1.46 (0.56)	1.30 (0.35)
Sleep	2.08 (0.35)	2.04 (0.56)	1.75 (0.46)
Activity	2.88* (0.42)	3.07# (0.70)	2.44*# (0.53)
Mood	1.83 (0.47)	1.55 (0.51)	1.71 (0.50)
General Wellbeing	1.76 (0.55)	1.76 (0.55)	1.72 (0.55)

difference significant; * $P< 0.05$, # $p<0.01$
Table 7.3 mean (SD) of the diary card values for each of the oncology patient groups

7.3.2 Return Tablet Count

On none of the occasions when the monitors were returned were any capsules remaining so compliance by return tablet count for all courses was 100%. The overall compliance was exactly 100% on two occasions only. For 7 of the courses the compliance by return tablet count was higher than the overall compliance; for 5 of

these the difference was less than 10% and for 2 it was 16%. For the remaining 4

courses the overall compliance was greater than 100%. Since patients received the

correct number of capsules for the course they cannot actually be over-compliant so

it seems likely in these four cases that on some occasions the patients opened the

monitor for reasons other than to take a dose. The discrepancy between the return

tablet count (RTC) and the overall compliance is shown in figure 7.7.
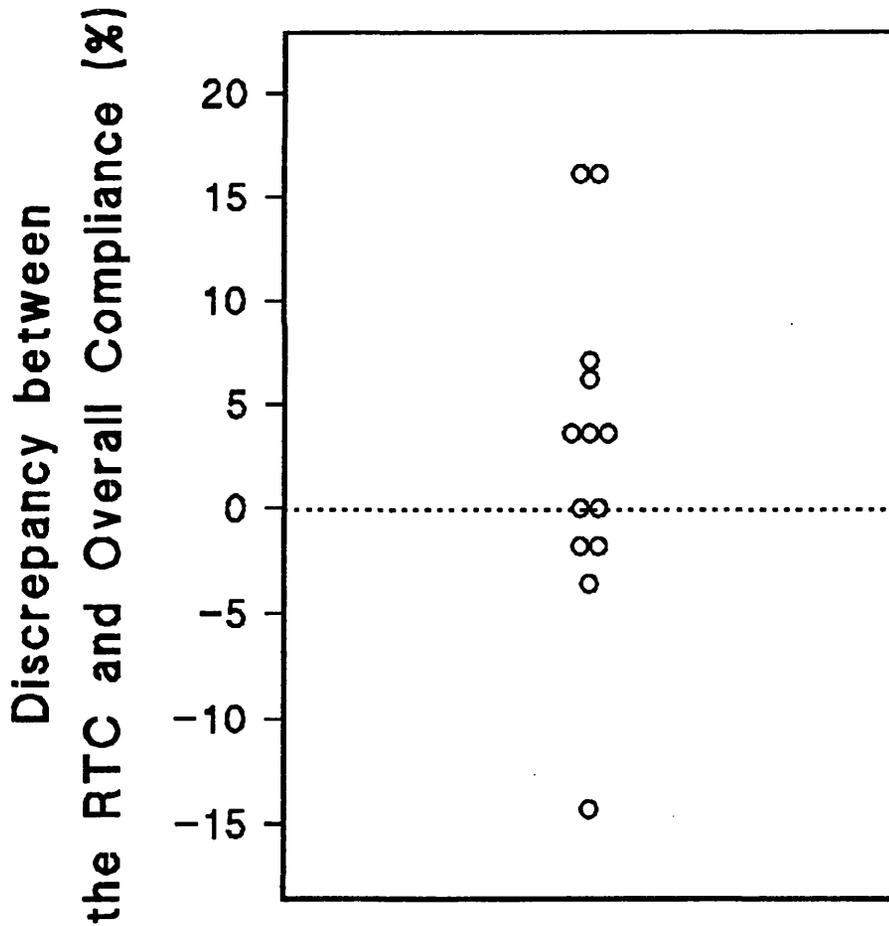
Figure 7.7 Difference between the Return Tablet Count and the Overall Compliance for Ovarian Cancer Patients.

7.4 DISCUSSION

Although there were only a small number of patients studied there was little variation in the compliance measures and overall compliance was very good. In the trial protocol for Hexalen® it is stated that if patients return capsules such that their compliance by this measure is less than 80% they should be withdrawn from the study. Examining the data from the electronic monitor revealed that no patients had an overall compliance of less than 80%. On only two occasions was the overall compliance less than 85% and these were both 83%. One of these was for a patient monitored for 3 courses, her overall compliance for the other two courses was 100% and 96%.

In the lymphoma group it was found that the overall compliance for medications prescribed three times a daily was in the order of 10% lower than those prescribed once daily. Other researchers have also found that compliance decreased as the prescribed daily frequency increased, see chapter 2 section 2.2.1.1. This suggested that overall compliance in the Hexalen® regimen, which was prescribed four times a day, may have been lower than that for the lymphoma patients prescribed medication three times a day. However, there was no significant difference between the overall compliance for these two groups and the direction of difference was that the mean overall compliance in the four times daily Hexalen® regimen was 4.6% higher than the lymphoma group on a three times daily medication. The overall compliance in the present group did not differ significantly from the lymphoma group prescribed medication to be taken twice daily but was significantly lower than the lymphoma group prescribed medication once daily, $p < 0.05$.

The return tablet count overestimated compliance in 54% of courses. Although

this overestimation was less than 10% for 39% of these courses in the remaining 15%

the return tablet count overestimated compliance by 16%. In addition, the return

tablet count gives no information on dosing intervals. It is interesting that when

prescribed a four times a day medication patients tended to compress the intervals

having a long interval at night; previously this has been shown with eye drop

medication with an electronic monitor (Kass et al 1986a).

Despite the reputation that hexamethylmelamine causes severe gastrointestinal

toxicity (Hahn 1983) none of the patients in this study had dose reductions due to this

effect and the mean diary card sores for sickness and vomiting were not significantly

different to those for the lymphoma and SCLC groups. Patients were prescribed

antiemetics and these included domperidone, prochlorperazine, metoclopramide,

dexamethasone and domperidone, prochlorperazine and dexamethasone and

metoclopramide and domperidone. One very anxious patient asked to be prescribed

ondansetron because she had heard of it and had felt sick on her first course. Out of

183 days monitored patients reported actually vomiting on only 13 days.

It is reassuring that patients were so compliant and this could, in part, be

explained by the increased motivation likely to occur when participating in a clinical

trial, however, it could also be due to the disease. Patients in the trial had relapsed

advanced ovarian cancer that had been previously successfully treated with cisplatin

based chemotherapy. Hexalen® represents a new option as salvage chemotherapy and

patients are therefore likely to be keen to try it.

CHAPTER 8

PATIENT COMPLIANCE WITH

THE ORAL HYPOGLYCAEMIC AGENT GLIBENCLAMIDE

IN NON-INSULIN DEPENDENT DIABETES

8.1 INTRODUCTION

Non-compliance with oral hypoglycaemic agents is a potential cause of poor diabetic control. General reports on diabetes compliance suggest compliance with medication in this chronic condition is probably around 50%, based on the much quoted phrase from Sackett and Haynes (1976) that "across a wide range of diseases and therapies approximately 50% of patients are non-compliant". In one study looking at compliance with oral hypoglycaemic agents approximately half of the patients admitted to some degree of non-compliance (Chan & MacFarlane 1988). However, other studies that have measured compliance report compliance with medication in the range 72% to 96% (Peterson et al 1984, Diehl et al 1985, Ary et al 1986, Davis & Strong 1988). These studies relied on "subjective" interview techniques or single point measures such as "pill-counting" and are therefore subject to the disadvantages previously outlined.

The aim of this study was to assess the compliance of non-insulin diabetic patients with their oral hypoglycaemic agent using the electronic monitor, which allows compliance to be measured in a continuous and objective manner. This was compared with compliance assessed by return tablet count and the physicians' estimation. Patients were aware of the recording nature of the monitor and for this reason compliance was also assessed by measuring the level of the drug in patients serum. The patients diabetic control was monitored and related to compliance with therapy. Using previously validated scales the relationship between compliance and patients health beliefs was investigated.

8.2 METHODS

8.2.1 Patients

Non-insulin dependent diabetics under the care of their general practitioner at two surgeries, Well Street and Steels Lane, in the east end of London were recruited into the study. Patients were eligible to enter the study if they were being treated with an established regimen of the oral-hypoglycaemic agent glibenclamide. When patients were seen for their annual diabetes review they were invited to participate. Measures of diabetes control were also recorded for patients who declined to participate in the study.

8.2.2 Compliance Assessment

8.2.2.1 Electronic Monitor

Compliance was assessed using the electronic monitor described in chapter 4. Data from the monitor were processed to give three measures; the overall compliance - a measure of the total amount of drug taken, the daily irregularity index - representing the number of daily discrepancies in openings of the device averaged over the course and the hourly irregularity index - an index of the repeatability of the patients own hourly pattern of openings. For details of how these measures were calculated see chapter 4 section 4.2.2. The monitor data were also analyzed to show the distribution of the length of intervals between openings.

8.2.2.2 Return Tablet Count

Compliance over the course of the study was assessed by return tablet count. On each of 4 occasions over the 12 week period of assessment patients were given an

excess supply of tablets in the monitor. When patients returned the monitor at their next visit, unknown to them, any remaining tablets were counted. The number returned was then related to the number expected had compliance been perfect.

8.2.2.3 Physicians' Assessment

The patient's physician was asked to rate how well they estimated their patient adhered to their tablet regimen using the following scale; almost all the time, three-quarters of the time, half of the time, quarter of the time, and never, see appendix 2. At the time they rated their patient's compliance the physician was unaware of the results from the monitor.

8.2.2.4 Blood Levels of the Drug.

The main method of assessing compliance in this study was the electronic medication monitor. However, as mentioned in chapter 1, section 1.2.4, the opening of the container does not ensure the tablets have been taken. If a regular pattern of openings is seen when a patient is unaware of the purpose of the monitor it would be very unlikely that these did not correspond to tablet ingestion. In this study, because of the clinicians wishes, the patients were told that the container recorded when it was opened. It is therefore possible that patients may open the container and not take the tablets, although, to do this over the 12 weeks of monitoring would seem unlikely. To demonstrate that patients were actually taking the tablets it was decided, unknown to the patients, to assay their serum for glibenclamide. For this purpose, any serum in excess to that required for the biochemical measures of diabetes control was used, see section 8.2.5.

8.2.2.4.1 HPLC method for the Detection of Glibenclamide in Serum

Glibenclamide has been assayed in serum using radioimmunoassay (Glogner et al 1977), gas-liquid chromatography (Castoldi & Tofanetti 1979) and high-performance liquid chromatography (HPLC). In this work, an HPLC method which used a simple extraction procedure was employed (Abdel-Hamid et al 1989).

8.2.2.4.1.1 Equipment

The HPLC system consisted of a Gilson (model 303) pump and a Rheodyne (model 7125) injection port fitted with a 20μl loop. Glibenclamide was detected by ultraviolet radiation using a Waters (model 481) variable wavelength detector set at 230nm which was near the maximum for glibenclamide in the mobile phase. The flow rate was set at 1.8ml/min. Separation was effected using a Spherisorb 5μ C8 reverse phase column (4.6 x 100mm Hichrom Ltd). A 50mm guard column of the same packing material was used. A model C-R5A Shimadzu integrator was employed to evaluate the peak height of the chromatograms.

8.2.2.4.1.2 Materials and Reagents

Glibenclamide (donated by Hoechst Pharmaceuticals) and flufenamic acid (Sigma F-9005) were used to prepare the standards. The mobile phase was prepared by mixing acetonitrile (BDH HiPerSolv for HPLC) and deionized water and adjusting the pH to 3.8-3.9 using glacial acetic acid (BDH analytical grade) then degassing with helium. Vacutainers which were sterile and silicone coated but otherwise additive-free were obtained from Becton-Dickinson.

8.2.2.4.1.3 Development of the HPLC Assay

The analysis of glibenclamide used flufenamic acid as internal standard and was based upon that described by Abdel-Hamid et al (1989). However, a number of problems had to be solved before serum containing in the order of 100ng/ml could be monitored in a reproducible way.

8.2.2.4.1.3.1 Mobile Phase

In the published work satisfactory resolution of drug and internal standard were obtained using a mobile phase with an acetonitrile/water ratio of 45/55. In this work, it was found that with the above composition of mobile phase, the retention time of glibenclamide was 6.9 minutes and was associated with peaks derived from constituents in the serum. Decreasing the proportion of acetonitrile to 0.40 increased the retention times of glibenclamide and flufenamic acid to 10.9 and 14.9 minutes respectively. However, the retention time of flufenamic then interfered with other peaks from the serum constituents arising at later times. It was therefore decided to use a mixture of acetonitrile/water 42.5/57.5 at pH 3.8-3.9 which allowed clear identification of glibenclamide and flufenamic acid from other serum constituents with retention times of 9 and 12 minutes respectively.

8.2.2.4.1.3.2 Extraction from serum

In the initial experiments to work up the extraction procedure bovine serum was obtained from Sigma Ltd (B-2771). The HPLC chromatograph for blank bovine serum gave a peak at 12 minutes which would completely obscure the internal standard, see figure 8.1(a). A batch of human serum was therefore purchased from

Sigma Ltd (S-7023) to make up the standards. Unfortunately extraction of this serum

produced traces which were totally unusable, see figure 8.1 (c). The suppliers

subsequently informed me that their source material was expired donor serum, so it

is highly likely that it had degraded before they received it. Ultimately it was

necessary to obtain fresh plasma from three volunteers and this was used in all future

experiments. A blank sample of this serum gave the trace shown in figure 8.1(b).
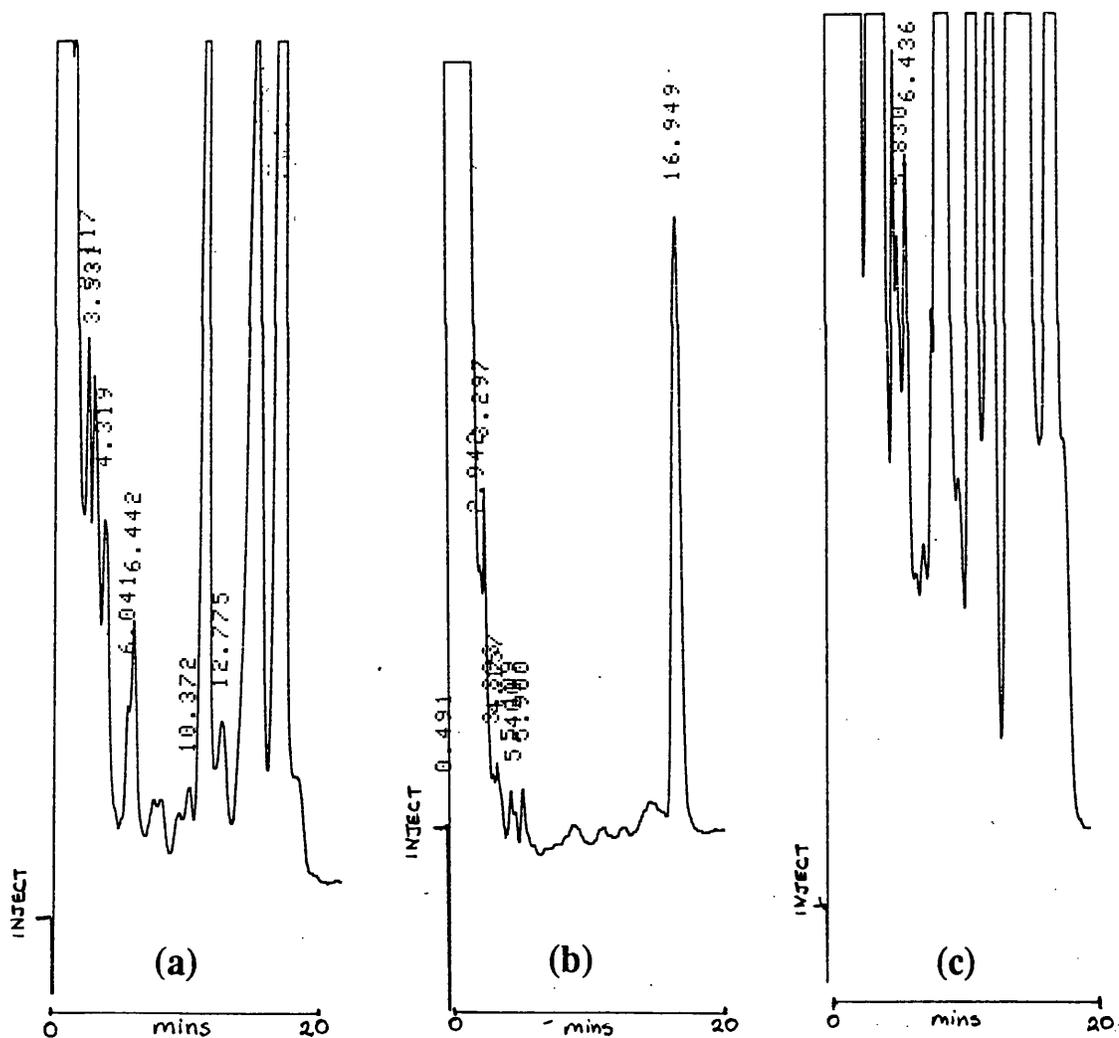
Figure 8.1   HPLC chromatographs for blank samples of serum
at the same attenuation.
(a) Bovine serum, Sigma (b) Human serum,volunteer (c) Human serum, Sigma

In the published work, Abdel-Hamid et al (1989) did not report acidifying the serum before extraction although other published HPLC methods for the detection of glibenclamide or flufenamic acid report this (Emilsson et al 1986, Lin et al 1980). It was found that flufenamic acid was extracted better when the serum was acidified before extraction.

8.2.2.4.1.3.3 Extraction Tubes

Prior to extraction, samples of serum were pipetted into Vacutainers. The resulting chromatographs had many stray peaks and this was initially ascribed to the breakdown of plasma. However, when 0.5mls of acetonitrile was put into the Vacutainer and extracted in the same way as a serum sample, the trace in figure 8.2 was obtained. This problem was resolved by washing the Vacutainers thoroughly with detergent prior to use.
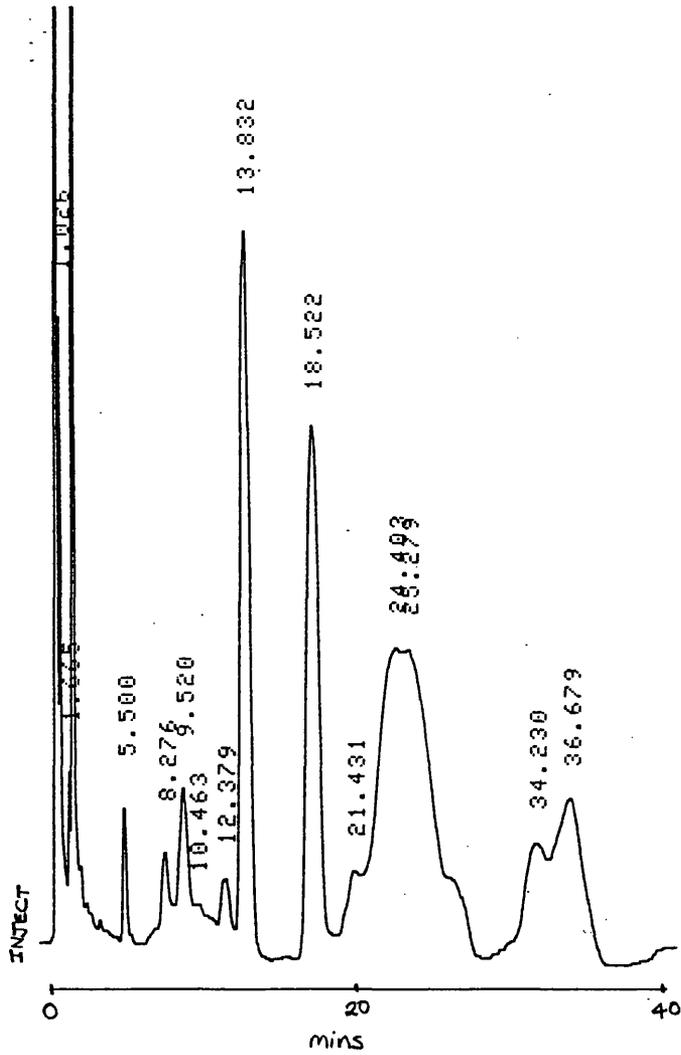
Figure 8.2 HPLC chromatograph for a blank unwashed Becton-Dickinson Vacutainer.

8.2.2.4.1.4 Final Procedure for Analysis of Glibenclamide

8.2.2.4.1.4.1 Standards

An accurate weight of ~50mg of glibenclamide was dissolved in 50ml acetonitrile. 0.5ml of this was diluted to 50ml with the mobile phase to give the stock solution of 10µg/ml. A stock solution of 10µg/ml of flufenamic acid was prepared in the same way. Five standards were prepared from these stock solutions each containing 2.5µg/ml of the internal standard flufenamic acid and 0, 0.25, 0.5, 1 and 2µg/ml of glibenclamide in mobile phase. These solutions were used to determine the detector linearity and to construct the standard curve. They were stored at ~4°C and were stable over a 4 week period, (CV = 2.1-7.1%, 2 samples of each standard analyzed one month apart). Standard serum solutions were prepared from the stock solution to contain 0, 0.1, 0.2 and 0.4µg/ml of glibenclamide in serum. These were stored frozen at approximately -20°C and were stable over a 14 day period, (CV = 2.0-6.5%, 2 samples of each standard analyzed 2 weeks apart).

8.2.2.4.1.4.2 Analytical Procedure

0.5ml of each of the 4 serum standards were pipetted into washed and dried 8ml Vacutainers. To each sample, 25µl of the stock solution of internal standard was added and the mixture vortexed for 30s. The sample was then acidified by adding ~25µl of a solution containing 10% glacial acetic acid in mobile phase and vortexed for a further 20s. 2ml of acetonitrile was then added as a protein precipitant and the sample vortexed again for 1min, then centrifuged for 10mins at speed 6 in a MSE (model minor "S") centrifuge. The supernatant was transferred to a 3ml glass test tube and evaporated to dryness in a water-bath at 45°C in a fume cupboard under a stream

of nitrogen. The residue was taken up in 100μl of mobile phase and transferred to an Eppendorf 1.5ml micro test tube (type 3810) and centrifuged for 2min in a Wifug centrifuge (model Haemicrofuge). The supernatant was then loaded onto the loop and injected onto the column. The concentrations of glibenclamide used provided a calibration curve over the range 0-400ng/ml after final dilution. Serum samples collected from patients were treated in the same way as the glibenclamide standards.

8.2.2.4.1.4.3 Quantification

Glibenclamide concentrations were determined by using the peak height ratio of glibenclamide to flufenamic acid. Both peak height ratios and peak area ratios gave a linear relationship with glibenclamide concentration using the solvent standards over the range studied. However, with the serum standards the peak height ratio was found to be more accurate since occasionally there was a broad peak that interfered with the internal standard peak and peak heights are less affected by the presence of interfering peaks than are peak areas (Pryde & Gilbert 1979). Figure 8.3 (a) shows a typical HPLC chromatograph of the serum standard containing 100ng/ml glibenclamide. Figure 8.3 (b) shows the chromatograph of a typical patient sample. The baseline for this trace is not very stable and this is due in part to the nanogram levels of drug being detected and in part to the fact that there was no control over how soon the blood samples were frozen after being taken from the patient. However, the integrator was able to take account of changes in the baseline and was able accurately to determine the height of a peak on the tail of another peak. The coefficients of variation for duplicate samples of the patient samples were acceptable, ranging from 3.6 - 12.5%. Moreover, the results from the HPLC were being used qualitatively, that

is to detect the presence or absence of the drug.
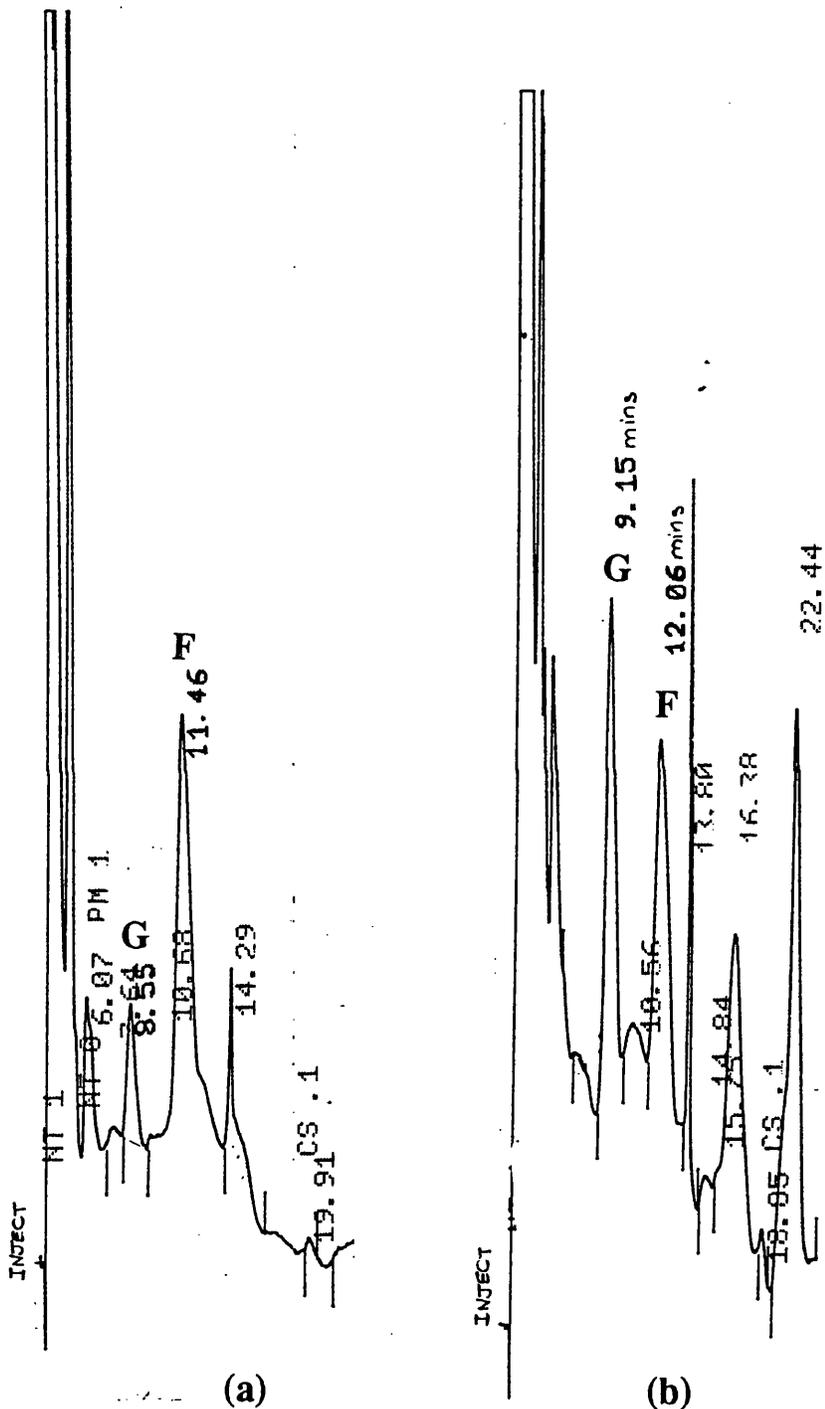
G = glibenclamide, F = internal standard

Figure 8.3   HPLC chromatographs for (a) Serum standard, 100ng/ml glibenclamide (b) Patient sample, 445ng/ml glibenclamide.

Figure 8.4 shows the standard curve for the solvent standards with the concentration of glibenclamide represented as the equivalent ng/ml of serum to allow comparison with the standard curve for the serum standards, see figure 8.5.
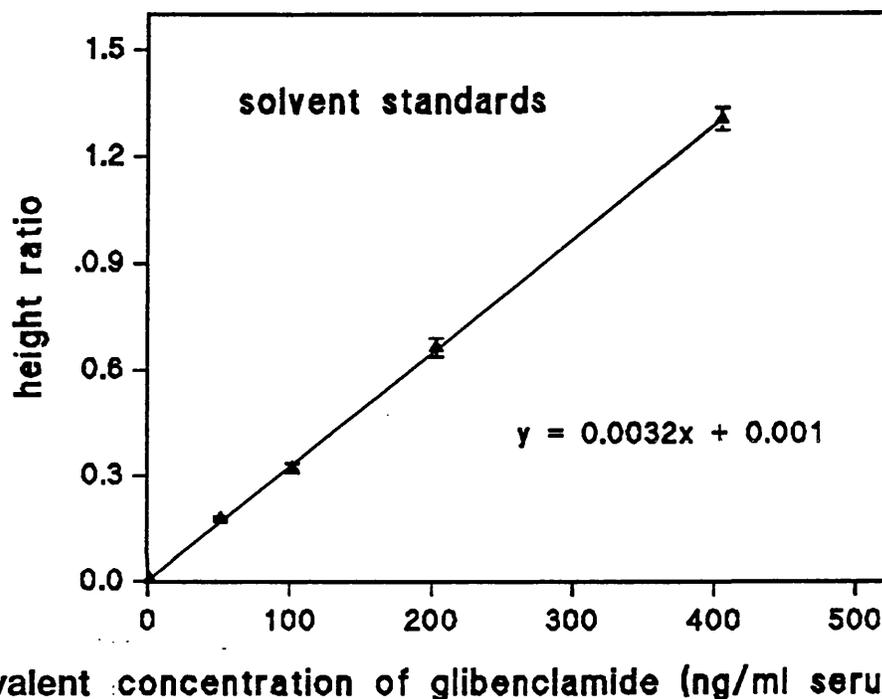
Figure 8.4 Standard curve for the detection of glibenclamide by HPLC;
solvent standards

The linear regression equation for the solvent standards was y = 0.0032x + 0.001 (r=0.9999) demonstrating the detector linearity over the concentrations used. The within-day precision of the solvent standards was 0.9-2.2% (n=6). The coefficient of variation between-day for these standards over six days was 2.4-4.3%.

Figure 8.5 shows the standard curve for serum standards which gave the linear regression equation y = 0.0031x + 0.004 (r = 0.9993). This is essentially the same as that for the solvent standards, see figure 8.4, demonstrating that the recovery from serum was approximately 100%. The within-day precision of the serum standards was

7.0-8.0% (n=3) and the coefficient of variation between day for these standards was

5.8-7.6% (n=6). The regression line obtained is similar to that quoted by Abdel-

Hamid et al (1989), y = 0.0035x + 0.015.
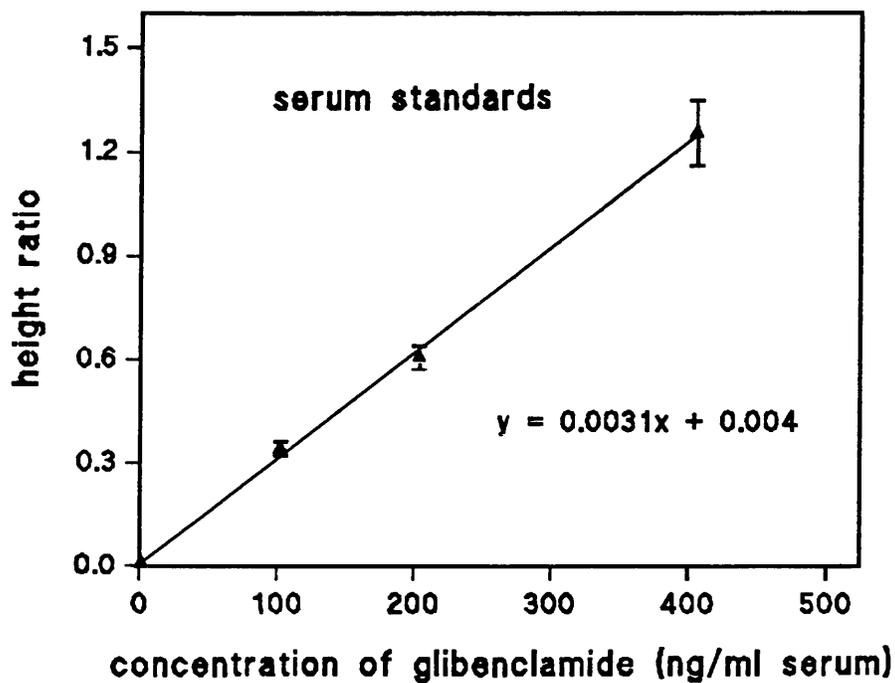
*Figure 8.5 Standard curve for the detection of glibenclamide
by HPLC; serum standards.*

8.2.3 Patients' Health Beliefs and Health Locus of Control

Using scales supplied by Dr Clare Bradley[1] that had been developed specifically for tablet treated diabetics (Lewis et al 1989, Bradley & Lewis 1990a, Bradley et al 1990b) patients' health beliefs, health locus of control and wellbeing and treatment satisfaction were measured (see chapter 3 section 3.2.3). Patients were given the questionnaires (see Appendices 3-6) at the end of the study with a self-addressed envelope and asked to post them when completed. It was felt that patients might be more honest if they knew that their doctor would not see the completed questionnaire so patients were informed that it would be see only by the researcher. Patients were told the questionnaires were quite lengthy but to make every effort to complete them. They were also asked to be as honest as possible in their answers. If the questionnaire was not returned after a month a reminder was sent.

8.2.4 Study Design

At the patient's annual review the physician told them a study was being carried out and asked them if they would like further information. They were then referred to the research pharmacist. Written informed consent for monitoring the outcome of the patient's treatment was sought, see appendix 7. The physicians were not happy for the study to be conducted without the patients' knowledge of the recording nature of the device. For this reason patients were told that the time of day they took their tablets was being monitored, see information sheet Appendix 8. Patients were asked only to use the tablets from the monitor and not to transfer them

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[1] *Royal Holloway & Bedford New College, Egham Hill, Surrey.*

to anything else. As the container has not got a child-resistant closure patients were asked to keep the container well out of the reach of children and to keep the cap screwed on. Patients were encouraged to take their tablets as they normally do.

On the first day of the study patients were provided with the monitor containing an excess supply of glibenclamide over that required until the next visit. The glibenclamide tablets, 2.5mg and 5mg, were supplied by Hoechst Pharmaceuticals and were dispensed by the research pharmacist. The container was labelled according to the requirements of the Medicines Act 1968, labelling of dispensed medicines, with the contents and the directions for use clearly stated. A record of the supply was made in the patients' medical notes. Patients returned to the surgery every 3 weeks for a period of 12 weeks for an appointment with the research pharmacist and the surgery nurse. The research pharmacist collected the monitor from the patient and dispensed them a further supply of glibenclamide in another monitor. The surgery nurse took a blood sample which was sent to the local hospital biochemistry department for the analysis of various indicators of diabetic control, see section 8.2.5. At the final visit the research pharmacist handed out the questionnaires which patients returned by post when they had completed them, see section 8.2.3.

8.2.5 Analysis of Blood Samples to Assess Diabetic Control

Patient samples from the surgery at Well Street were analyzed at the Homerton Hospital Biochemistry Department and those from Steels Lane at the London Hospital Clinical Biochemistry Department. Samples were analyzed for cholesterol and triglycerides, glucose and glycated haemoglobin. Samples analyzed at the Homerton

were also assayed for fructosamine. Any serum remaining after that required for the analysis of cholesterol and triglycerides or fructosamine was stored and collected by the researcher for the analysis of glibenclamide. Samples collected for the analysis of glucose or glycated haemoglobin were not suitable for this since the tubes contained other additives which could potentially interfere with the assay.

8.2.6 Statistical Methods

The relationship between each of the three compliance measures and the various possible explanatory measures was examined by a linear modelling approach using the statistical package GLIM[2] as described previously in chapter 5 section 5.2.5. This allows for the testing of possible effects both within patients and between patients. Of the explanatory measures the monitoring period sequence was regarded as a four level factor and the biochemical values regarded as continuous variables. The residuals were tested for normal distribution by the Shapiro-Francia W' test (Royston 1983). The residuals from the overall compliance measure did depart marginally from normality so were transformed in the same way as for the overall compliance in chapter 5, section 5.2.5. The residuals for the other two compliance measures were on the edge of normality so were not transformed. T-tests were used to compare the measures of diabetic control between participants and non-participants.

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[2] *GLIM: Numerical Algorithms Group Ltd, 256 Banbury Rd, Oxford, 1987*

8.3 RESULTS

Patients were recruited from the Well Street practice over the course of a year. Of the 25 non-insulin dependent diabetic patients on the practice list on glibenclamide 20 attended for their annual diabetes review and 11 of these were recruited into the study. Of the 9 patients who were not recruited 3 were housebound so would not have been able to join the study, 3 had their therapy changed from glibenclamide to another hypoglycaemic agent or to diet alone and 3 did not wish to participate. The reasons given for non-participation were employment and travel. Measures of diabetes control were available for all 25 patients.

Additional patients were recruited from the Steels Lane practice over the course of 6 months. Of the 10 patients on glibenclamide scheduled to be seen for their annual diabetes review in that time, 2 were recruited into the study, 2 did not attend and 6 did not wish to participate. Reasons given for non-participation included employment, dislike of blood tests, and travel abroad. Measures of diabetes control were not available for 1 of the patients who did not attend and 2 of the patients who did not wish to participate.

The 13 study participants (8 male, 5 female, mean age 64 yrs, range 44 - 86yrs) had been diabetic for a mean of 5.7yrs (range 2-13yrs) and were taking a mean of 3.2 prescribed medications daily inclusive of glibenclamide. 6 patients were also taking the oral hypoglycaemic agent metformin. The 19 non-participants (5 male, 14 female, mean age 66yrs, range 48 - 93yrs) had been diabetic for a mean of 7.7yrs (range 3-18yrs) and were taking a mean of 3.2 medications daily inclusive of glibenclamide. 7 patients were also taking the oral hypoglycaemic agent metformin.

Of the 13 participants 11 were followed for the full period of the study. One

patient was followed for 9 weeks because he was then leaving for a 3 month trip abroad. One patient dropped out of the study after 6 weeks because of an emergency admission to hospital. 3 patients were followed for an additional week owing to holidays. Table 8.1 gives a summary of the doses of glibenclamide prescribed and the number of patients and monitoring periods.

Glibenclamide regimen	N° Patients	N° Monitoring Periods
2.5 mg in the morning	3	9
5 mg in the morning	4	15
10 mg in the morning	2	6
15mg in the morning	1	4
20mg in the morning	2	7
10mg in the morning and 5 mg at night	1	4

Table 8.1   Summary of dosage regimens in non-insulin dependent diabetics

8.3.1 Analysis of Monitor Records

On 4 occasions out of the 49 times the monitors were issued no data were available due to malfunction. The mean (SD) overall compliance for the 45 monitoring periods analyzed was 95.4% (12.9%) and the distribution is shown in figure 8.6.
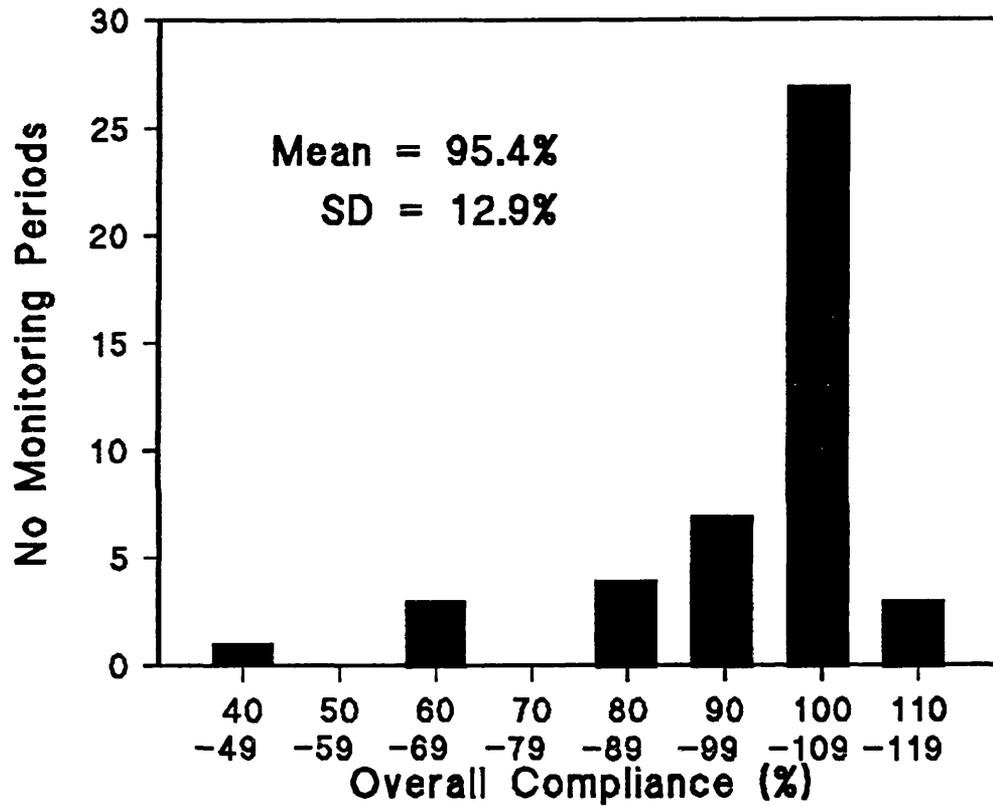
Figure 8.6 Distribution of the Overall Compliance for non-insulin dependent diabetics.

Figure 8.7 shows the data for the overall compliance subdivided into each of the 4 monitoring periods each consisting of 3 weeks. The mean (SD) overall compliance for the monitoring periods was 97% (10%), 95.3% (17.8%), 94.5% (12%), and 94.9% (12.3%), respectively. The difference between the means was not statistically significant, (t-test).
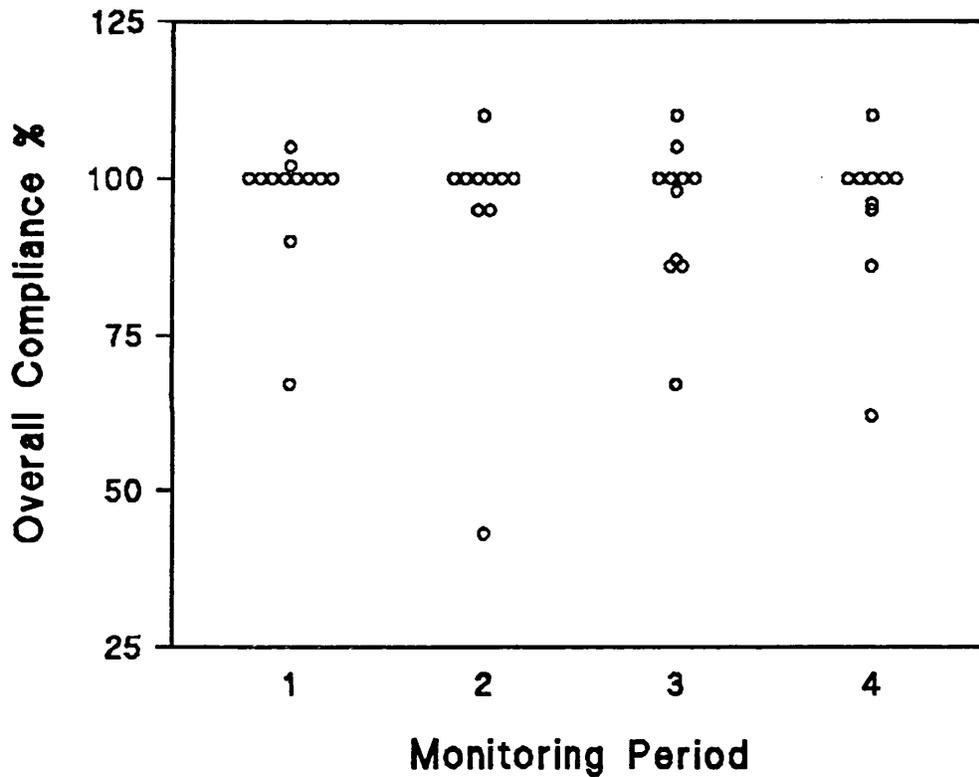
Figure 8.7 Scatter plot of the Overall Compliance for 4 monitoring periods over 3 months for non-insulin dependent diabetics.

The mean (SD) of the daily irregularity index for the 45 monitoring periods was 0.08 (0.13) showing that on average there were 1.7 extra or omitted openings in a 3 week period of monitoring. Another way of expressing the daily regularity is to look at the number of days with the correct number of openings for the prescribed daily frequency. Of the 972 days monitored 92.3% fell into this category. Figure 8.8 shows the distribution of the daily irregularity index for the 45 monitoring periods.
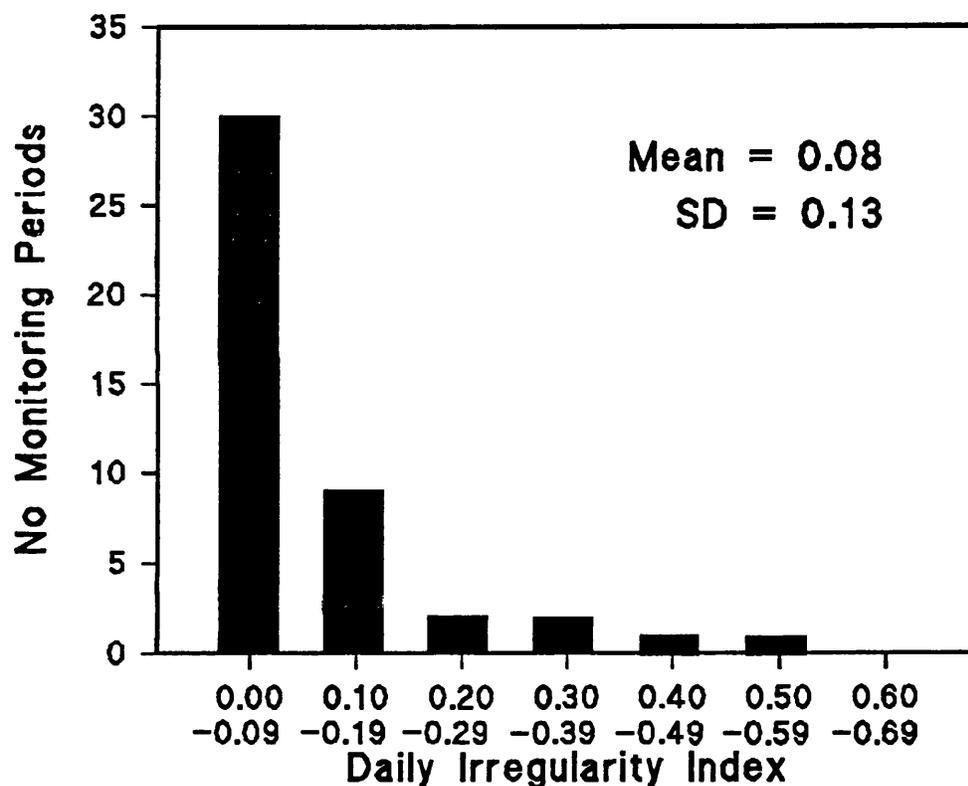
Figure 8.8 Distribution of the daily irregularity index in non-insulin dependent diabetics.

The means (SD) of the daily irregularity index for the four monitoring periods were 0.05 (0.14), 0.09 (0.17), 0.10 (0.11) and 0.09 (0.12). The differences between these means were not statistically significant (t-test).

The mean (SD) of the hourly irregularity index for the 45 monitoring periods

was 0.22 (0.17). Subdividing these data into the four monitoring periods gave means

(SD) of 0.18 (0.18), 0.21 (0.15), 0.25 (0.16) and 0.27 (0.19). The differences between

these means were not statistically significant (t-test). Figure 8.9 shows the distribution

of the hourly irregularity index for the 45 monitoring periods.
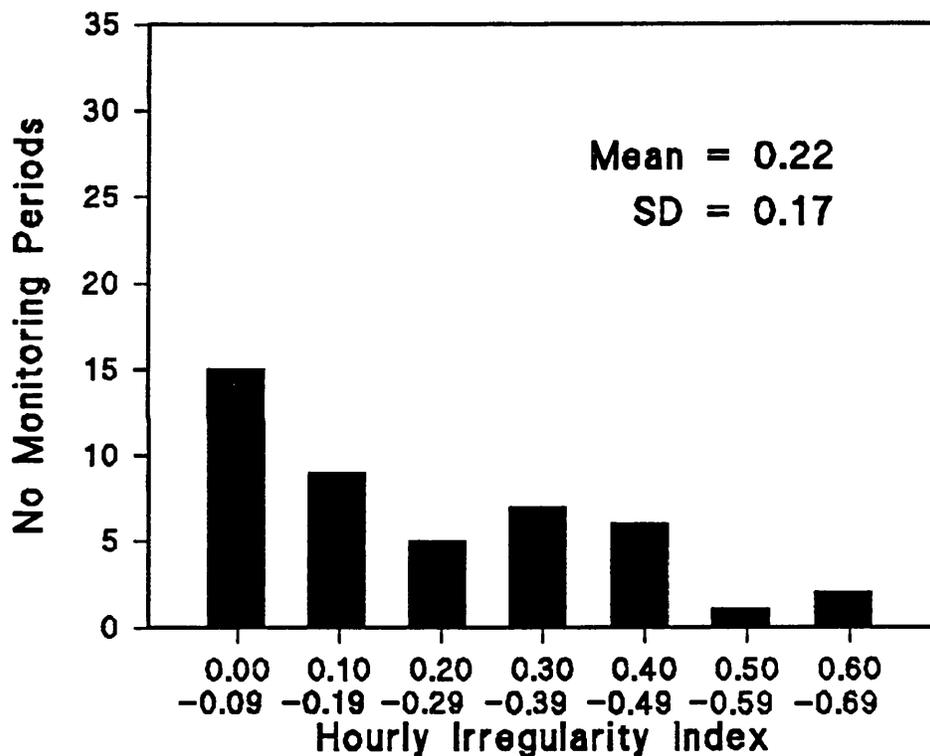
Figure 8.9   Distribution of the hourly irregularity index
for non-insulin dependent diabetics

The length of the intervals between openings of the monitor were analyzed for

the 45 monitoring periods as a whole. Figure 8.10 shows the distribution of this data

excluding the 4 monitoring periods from the patient who was taking a twice daily

regimen of glibenclamide. 84.9% of the intervals were between 22 and 26 hours long.
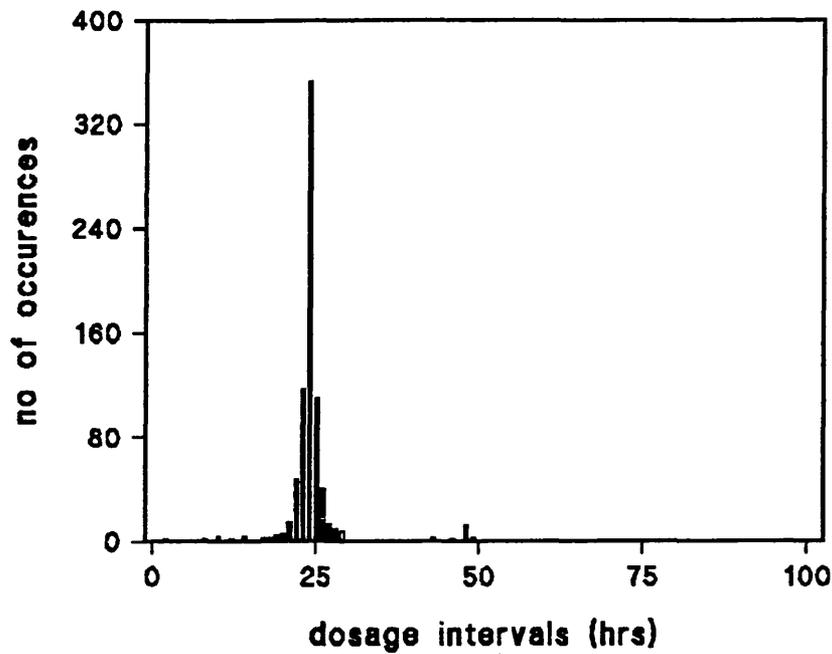
Figure 8.10 Distribution of the length of dosage intervals in hours for once daily regimens in non-insulin dependent diabetics.
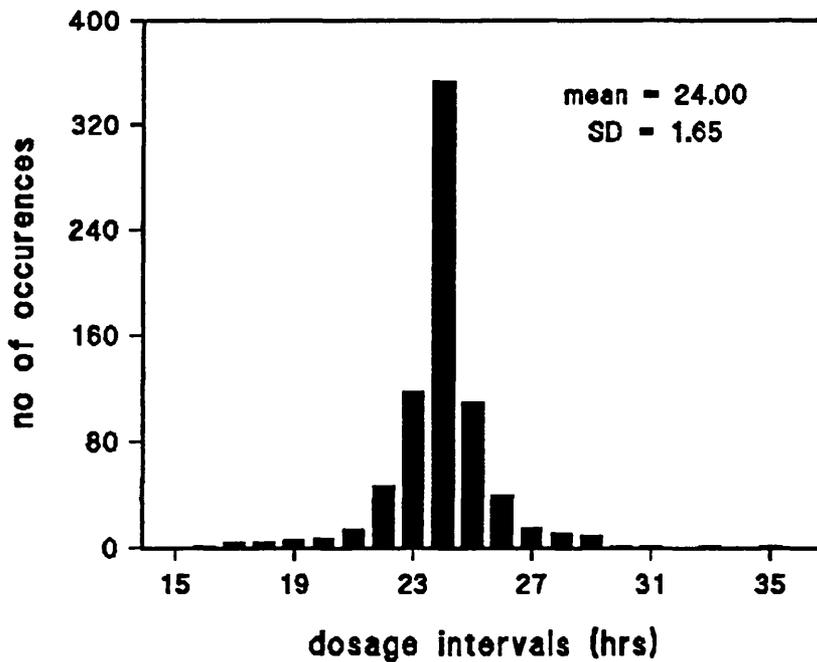
Figure 8.11 Subset of the data shown in figure 8.10, distribution of the length of dosage intervals for days with only one monitor opening

Figure 8.11 shows a subset of the data in figure 8.10. This shows the distribution of the length of the intervals for days when there was the correct number of openings, that is days with only one opening. The mean (SD) of these openings was 24.0 hrs (1.7hrs). The mean (SD) length of the day-time and night-time intervals for the patient on a twice daily regimen were 11.2 (1.5) and 12.9 (1.3), respectively.

8.3.2 Compliance by Return Tablet Count.

The return tablet count was available from 44 monitoring periods. Figure 8.12 shows the scatter-graph of the discrepancy between the return tablet count and the overall compliance from the electronic monitor.

For 25 of the monitoring periods the compliance by return tablet count was in complete agreement with the overall compliance. For 22 of these monitoring periods, compliance by both the return tablet count and the monitor was 100%. For the remaining 3 the compliance by return tablet count and the overall compliance were 86, 95 and 105%; these were all from the same patient.

In 14 monitoring periods the return tablet count was higher than the overall compliance and in 5 of these the difference was greater than 15%. In the remaining 5 monitoring periods the compliance by return tablet count was less than the overall compliance. In 4 of these cases the overall compliance was greater than 100% and compliance by return tablet count was 100%, which probably indicates that the patient opened the monitor on occasions to check whether they had taken a dose. In one case the compliance by return tablet count was 95% and that from the monitor 110%.
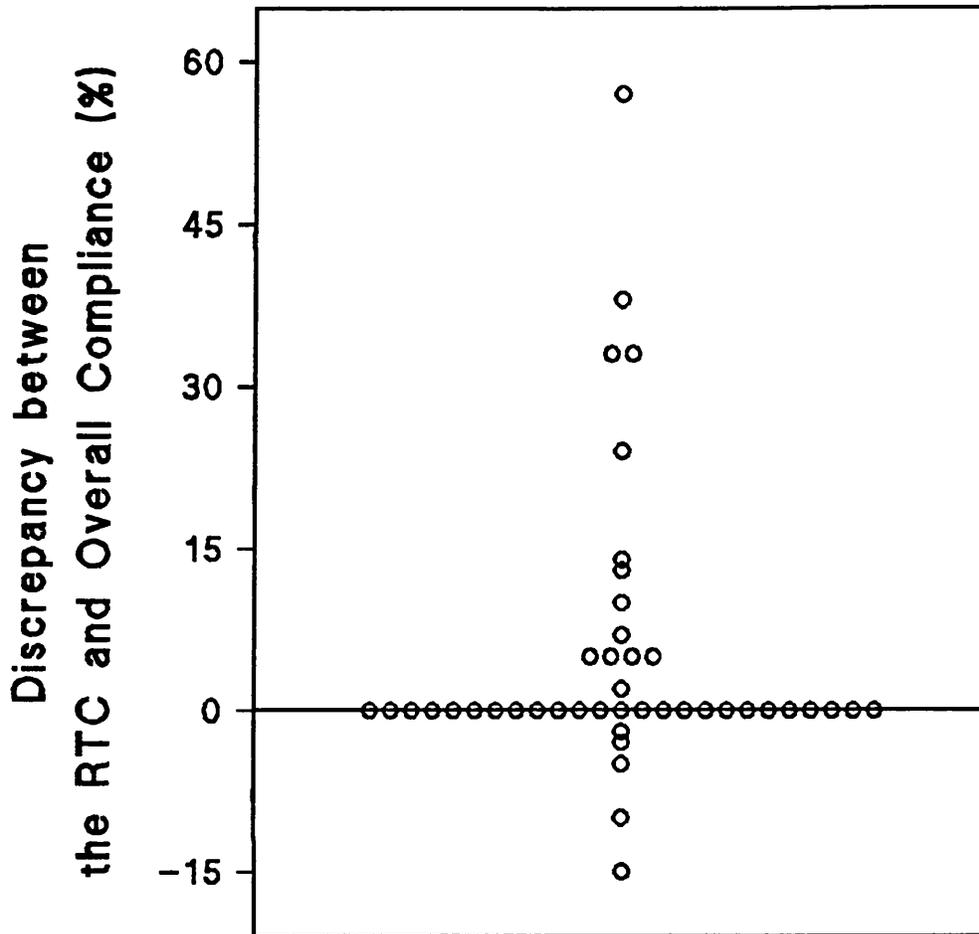
*Figure 8.12   Scatter-graph of the discrepancy between compliance
as assessed by return tablet count and by the monitor.*

8.3.3   Compliance by Physicians' Assessment.

For the purpose of the comparison between the compliance as assessed by the

monitor and the physicians' assessment the mean overall compliance was calculated

for each patient. Figure 8.13 shows the scatter-plot of the overall compliance and the

physicians' assessment. Only 5 of the 12 patients with a mean overall compliance

greater than 91% were rated by their physician as adhering to their tablet regimen

almost all of the time. Of the remainder, 5 were rated as adhering to their tablet

regimen three-quarters of the time and 2, half of the time. The patient with a mean

overall compliance of 60% was rated as adhering to her tablet regimen three-quarters

of the time.
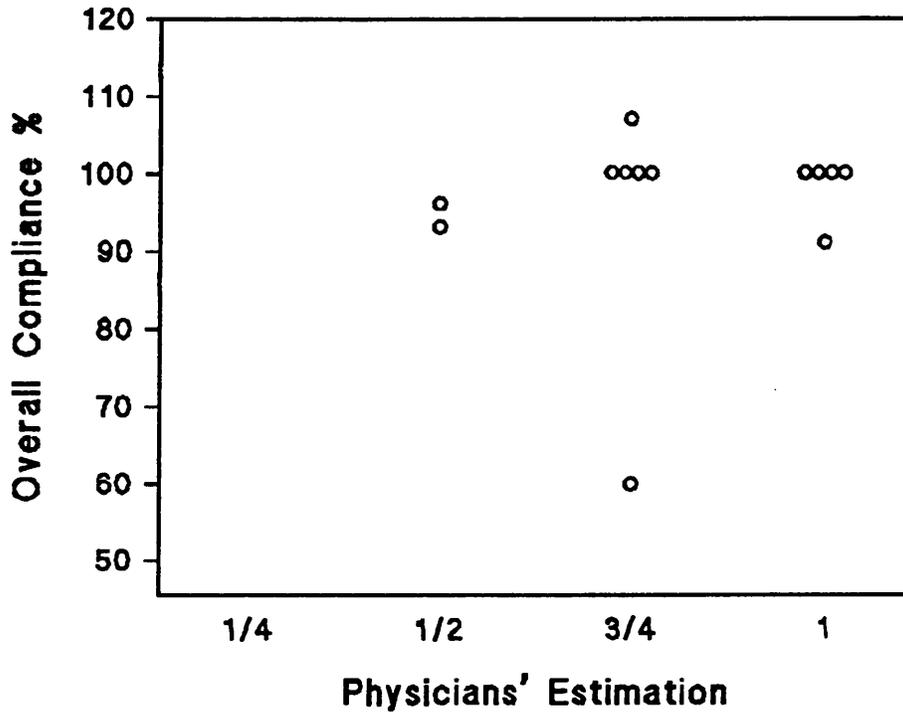
Figure 8.13   Comparison between the overall compliance
and the physicians' assessment for non-insulin dependent diabetics

8.3.4. Compliance by Blood Levels of Glibenclamide

Patient samples were analyzed for the measures of diabetic control by the

Clinical Biochemistry labs at the London and the Homerton hospitals. Any residual

serum left after these tests were completed was collected and analyzed for

glibenclamide. Wherever there was sufficient volume of sample levels were analyzed

in duplicate and a mean value calculated. Not all duplicates were analyzed on the

same day. The mean coefficient of variation between the duplicates for 11 patient

samples was 7.5% ± 2.9%. Table 8.2 gives the concentrations of glibenclamide in the

patient samples for the monitoring periods where it was available together with the

dose prescribed and the overall compliance. In all cases patients opened the electronic

monitor 1 to 4 hours prior to giving a blood sample. Glibenclamide was present in

all samples analyzed.

Patient	monitoring period			
	1	2	3	4
5 2.5mg morning		138 (N/A)	39 (86%)	110 (95%)
6 5mg morning	71 (100%)	91 (100%)	32 (100%)	41 (100%)
7 10mg morning	277 (100%)			
8 20mg morning		235 (43%)	470 (67%)	
9 10mg morning			484 (100%)	635 (100%)
10 5mg morning	148 (90%)			
11 2.5mg morning	86 (105%)			
12 5mg morning	93 (100%)	147 (100%)		
13 10mg morning & 5mg night			113 (98%)	

Table 8.2 Concentrations of glibenclamide in ng/ml by monitoring period with the corresponding overall compliance value in brackets for 9 of the patients.

These results suggest that opening of the monitor did correspond to ingestion

of the medication even though patients were aware of the recording nature.

8.3.5 Measures of Diabetes Control

Biochemical measures of diabetes control were collected for each participant for their annual review and for the subsequent 4 monitoring periods and for each non-participant for their last annual review. A measure of obesity, the body mass index (B.M.I.) was calculated for each participant and non-participant. This was obtained by dividing the persons weight in kilograms by their height in metres squared, a value of 20-25 being acceptable, 26-30 overweight, 31-40 seriously overweight and 41+ dangerously overweight.

During the study the Biochemistry department of the Homerton Hospital changed its method of analyzing glycated haemoglobin from measuring HbA_{1c} to HbA_1 with a change in reference values from 3.4-6.1 to 4.5-8.5. In addition, the London Hospital Biochemistry Dept changed from measuring HbA_1 to HbA_{1c} with references ranges from their assay of 4-6 and 2.8-4.9. Because of this it was not possible to make direct comparisons between patients for this measure. Values for fructosamine were available for all patients from the Well street surgery making comparisons possible. The reference values for cholesterol, triglycerides and glucose for the two departments were the same so comparisons were made for these measures.

Table 8.3 gives the mean values from the patients' annual reviews for the participant and two sets of non-participants, A and B. The subset of non-participants, B, include all those patients who did not wish to participate or failed to attend the clinic; it excludes those patients who had their therapy changed or were housebound.

Group	HbA$_{1c}$ reference range 3.4 - 6.1%	Fructosamine reference range up to 4.2%	Cholesterol reference range 3.5 - 6.7mmol/l	Triglycerides reference range 0.5 - 2.0mmol/l	Random Blood Glucose mmol/l	B.M.I.
Participants n=13	6.7 (1.2) n=10	3.9 (0.7) n=11	6.3 (1.0) n=13	2.94 (2.1) n=13	11.8 (4.2) n=13	28.3 (6.1) n=13
Non-participants, A n=19		4.2 (1.2) n=14	7.1 (1.4) n=16	2.67 (1.6) n=16	11.6 (3.5) n=13	30.3 (6.3) n=18
Non-participants, B n=13		4.6 (1.2) n=8	6.9 (1.2) n=12	2.80 (1.5) n=12	11.7 (3.9) n=9	31.8 (7.1) n=12

Table 8.3 Measures of diabetes control: group means (SD) for participants and non-participants.

T-tests were used to compare the means from the participants and the non-participant groups. None of the t-values was significant at the p=0.05 level. Two of the t-values were significant at the 0.1<p>0.05 level; these were for fructosamine between the participants and non-participants group B, and for cholesterol between the participants and non-participants group A.

For each of the 13 participants, in addition to the values of diabetes control from the annual review, values were also available for each monitoring period. Table 8.5 shows the mean (SD) of the first and the last value for each of the measures. These means were compared by paired t-test and none of them were significant at the p=0.05 level.

	HbA$_{1c}$ (%)	Fruct (%)	Cholesterol (mmol/l)	Trigs (mmol/l)	RBG (mmol/l)
Participants First value	6.7 (1.2) n=6	3.9 (0.7) n=11	6.3 (1.0) n=13	2.94 (2.10) n=13	11.7 (4.2) n=13
Participants Last value	5.9 (0.9) n=6	4.0 (0.7) n=11	6.1 (1.1) n=13	3.01 (1.66) n=13	10.4 (2.1) n=13

Fruct= fructosamine, Trigs= triglycerides, RBG= random blood glucose

Table 8.4   Measures of diabetes control for participants
at the beginning and end of monitoring

Using an analysis of variance within participants the effect of monitoring period on the measures of glycated haemoglobin, fructosamine and glucose was studied. None of these measured varied significantly between monitoring periods.

Of the 11 patients for whom fructosamine values were available, 4 had a mean value above 4.2 % for the study period, these were 4.4, 4.5, 4.8 & 4.8%. 6 out of 13 had a mean glycated haemoglobin value above the reference range; of these 4 had fructosamine values above 4.2%, 1 had a fructosamine value of 3.6% and 1 did not have fructosamine measured. 5 patients had a mean cholesterol above 6.7mmol/l, excepting 1 these all had normal fructosamine values. 3 patients had a mean triglyceride above 4.0mmol/l which, even accepting they were not fasting, is high; none of these had raised cholesterol. A random blood glucose (RBG) above 15mmol/l is indicative of poor control (Holman & Turner 1988). One patient had a mean RBG of 17.2mmol/l with a fasting blood glucose value of 9.3mmol/l. This patient also had mean HbA_{1c} of 8.0% (reference range 3.4-6.1%) and fructosamine of 4.4% and was the only patient with a mean overall compliance of less than 90%, namely 60%.

8.3.6 Questionnaires relating to Health Beliefs, Wellbeing and Locus of Control.

One participant was not given the questionnaires because she was hospitalised half-way through the study. Of the 12 sets of questionnaires handed out 9 were returned. One patient who did not return the set replied when sent a reminder to say that he did not wish to fill it in because he did not want to be "psychoanalysed". The other two patients sent reminders did not reply. Of the 9 sets returned one was not able to be analyzed. This was from an 86yr old lady who, from the parts of the questionnaires she had attempted to fill in, clearly did not understand the questions. There was no statistically significant difference between the overall compliance, the hourly irregularity index, and fructosamine between those patients who returned the

questionnaires and those who did not. However, the daily irregularity index was lower in the three patients who did not complete the questionnaires (p<0.05).

8.3.6.1 Health Beliefs

The Benefits and Barriers scale consisted of 10 statements (see Appendix 4), 5 relating to perceived benefits (1,3,7,8 &10) and 5 relating to perceived barriers (2,4,5,6, &9). Patients rated their agreement or disagreement with each statement on a 7-point scale. Ratings for the benefits statements were summed separately from ratings for the barriers statements. A measure of the treatment cost-effectiveness was obtained by subtracting the sum of the barriers statements from the sum of the benefits statements.

For the Beliefs about Severity scale (see Appendix 4) there were 16 disorders, 8 of which were disorders unrelated to diabetes (disorders 2,4,7,8,9,10,13, & 15) and 8 which were diabetic complications (disorders 1,3,5,6,11,12,14, & 16). Patients were asked to rate on a 5 point scale how serious they thought a problem would be if they developed it. Ratings for the conditions unrelated to diabetes were summed separately. In addition there were two further items about the patients' diabetes.

The list of problems in the Perceived Vulnerability scale (see Appendix 4) was the same as that in the Beliefs about Severity scale. Patients rated on a 5 point scale how likely they felt it was that they would develop the problems listed. They were also asked to rate the vulnerability of an "average person with their kind of diabetes" of the same age, sex and being treated with the same medication. Ratings for conditions unrelated to diabetes were summed separately from complications of diabetes.

Table 8.5 gives the means (SD) for the 8 Health Beliefs questionnaires analyzed. In addition it gives the means published by Dr Bradley's group (Lewis et al 1990) from 187 non-insulin dependent diabetics on oral hypoglycaemic agents treated at a hospital out-patient clinic.

	Mean (SD) A	Range	Possible range	Mean (SD) B
Perceived Benefits Barriers Cost-effectiveness	23.3 (5.5) 14.3 (6.8) 8.6 (4.0)	12 - 30 7 - 26 1 - 13	0 - 30 0 - 30 0 - 30	27.2 (3.4) 13.5 (8.2) N/A
Perceived Severity Diabetic Complications General Disorders Diabetes (2 items)	24.9 (5.5) 19.9 (7.1) 4.1 (2.0)	15 - 32 11 - 32 2 - 8	0 - 32 0 - 32 0 - 8	28.3 (3.5) 23.8 (5.8) 4.9 (1.9)
Perceived Vulnerability Diabetic Complications Complications (averaged) General Disorders Diabetes (1 item)	15.0 (6.7) 2.2 (1.0) 13.0 (7.7) 2.9 (0.9)	7 - 26 1 - 4 7 - 30 2 - 4	0 - 32 0 - 4 0 - 32 0 - 4	13.5 (7.6) 1.9 (1.0) 9.3 (6.6) 2.3 (1.2)
Perceived Vulnerability of the "Average Person" Diabetic Complications Complications (averaged) General Disorders Diabetes (1 item)	19.4 (8.6) 2.4 (1.1) 14.5 (8.1) 3.1* (1.0)	8 - 32 1 - 4 6 - 32 2 - 4	0 - 32 0 - 4 0 - 32 0 - 4	16.6 (6.8) N/A 10.8 (6.9) 2.3* (1.2)

* *difference significant, p<0.05*

Table 8.5   Mean (SD) and minimum and maximum scores
for Health Belief Questionnaires
Group A is the present study and Group B published data (Lewis et al, 1990)

Using the paired t-test to compare differences between the ranks assigned for the treatment benefits to those for the treatment barriers it was demonstrated that patients gave higher ratings to benefits than to barriers, p<0.01.

Patients rated the perceived severity of diabetic complications higher than those for general disorders, p<0.05. For the perceived vulnerability patients rated that they and the "average person" were more vulnerable to diabetic complications than general disorders, p<0.05. However, in contrast to the published data, the difference in ratings for the vulnerability of the average person to diabetic complications in comparison to the patient did not reach significance.

The means for the different scales for the present group (A) were compared with those from group B (published data Lewis et al 1990) using the unpaired t-test. The only significant difference was that the mean rating for the vulnerability to diabetes (1 item) for the "average person" was significantly higher than for published data, p<0.05.

8.3.6.2 Wellbeing and Treatment Satisfaction

The Wellbeing scale consisted of 6 depression (statements 1 - 6), 6 anxiety (statements 7 - 12) and six positive wellbeing statements (statements 13 - 18), see Appendix 5. Patients rated each statement on a 4-point scale to indicate how often they felt each applied to them in the past few weeks. Ratings for each of the three sub scales were summed separately after reversing the scores where necessary. A general wellbeing score was calculated by subtracting the depression rating from 18 and the anxiety rating from 18 then summing these with the positive wellbeing rating.

The Treatment Satisfaction scale consisted of 8 items rated on a 7-point scale. Two items relating to blood sugars were summed separately and were not used further in the analysis in this study since the patients did not test their blood sugars.

The means (SD) for the Wellbeing and Treatment Satisfaction scales are shown

in Table 8.6 for the present group (A) and for Group B which is published data

(Bradley & Lewis 1990a).

Scale	mean (SD) A	range A	possible range	mean (SD) B	range B
Depression	6.4 (5.2)	0 - 15	0 - 18	3.2 (2.9)	0 - 13
Anxiety	7.8 (5.4)	0 - 16	0 - 18	4.5 (3.9)	0 - 15
Positive Wellbeing	8.4* (6.3)	0 - 18	0 - 18	13.2* (3.8)	2 - 18
General Wellbeing	30.3 (16.3)	5 - 53	0 - 54	41.4 (9.3)	13 - 54
Treatment Satisfaction	26.3 (6.7)	14 - 33	0 - 36	29.4 (5.9)	6 - 36

difference significant at p<0.05

*Table 8.6 Means (SD), range and possible range for Wellbeing
and Treatment Satisfaction Scales.*

Group A is the present study and group B is published data (Bradley & Lewis 1990a)

In contrast to the published data, in the present group, the ratings for the positive wellbeing scale were not significantly higher than either that of the anxiety or the depression scale, paired t-test.

Using the unpaired t-test the means for present group (group A) were compared with the published data (group B). The means for the anxiety and depression ratings were not significantly greater than for group B, however the mean for the positive wellbeing scale was significantly lower than that for group B, p<0.05. It is interesting that, in this group of 8 patients, the maximum rating found for both the depression and anxiety scales was higher, and the minimum positive wellbeing score was lower, than

that found in 187 patients (group B). The mean of the general wellbeing score in the present study was not significantly lower than that for group B, neither was there any difference detected between the means for the treatment satisfaction scales.

8.3.6.3 Perceived Control

The Perceived Control scale describes 5 hypothetical events which are commonly experienced by, or particularly relevant to non-insulin dependent diabetics, see Appendix 6. 2 are negative outcomes (1 & 2) and three are positive outcomes (3,4 & 5). For each hypothetical event patients are asked to imagine that they have recently experienced the particular outcome and to write down its single most likely cause. They then rate this cause on seven separate 7 point scales which may be labelled internality, treatment, externality, chance, personal control, medical control and foreseeability respectively. Three composite scales are then obtained from these: Personal Control is calculated as the sum of internality, personal control and foreseeability, Medical Control is calculated as the sum of treatment and medical control and Situational Control is calculated as the sum of externality and chance. These are then summed across the 5 scenarios to produce composite scale totals. They were also summed separately for the 2 negative scenarios and the 3 positive scenarios. The composite scores were corrected so that they all had a possible range of 0 - 30 to allow for comparison between them. Table 8.6 shows the mean (SD) of the present study (group A) and published data (group B, Bradley et al 1990b).

For the negative outcome of becoming unacceptably overweight reasons given were lack of exercise, too much food and boredom. For that of testing high urine sugars reasons given were eating the wrong food, too much beer, eating too many

tinned foods which don't state the sugar content and having a disturbance in a daily food routine. One patient wrote that he couldn't understand why his urine sugar varied when he seemed to be eating the same things and sticking to his diet. For the positive outcome of feeling well and being the correct weight over a number of weeks reasons given were exercise, diet and willpower. For that of the avoidance of diabetic complications such as foot problems, reasons given were diet and exercise, regular treatment, comfortable shoes and foot care. Reasons given for a recent reduction in weight from being overweight were attention to diet and daily exercise.

Scale	Mean (SD) A	Range	Mean (SD) B
Composite scales: Personal Control Medical Control Situational Control	18.5* (5.8) 12.3 (6.5) 7.9 (5.1)	10.0 - 28.7 2.5 - 22.5 0.0 - 14.0	23.3* (4.8) 12.6 (6.4) 6.9 (5.9)
Composite scales for positive outcomes: Personal Control Medical Control Situational Control	19.4* (6.1) 14.3 (8.1) 5.9 (5.6)	9.4 - 27.8 4.2 - 30.0 0.0 - 14.2	24.2* (3.1) 17.4 (5.1) 6.0 (3.9)
Composite scales for negative outcomes: Personal Control Medical Control Situational Control	16.8 (7.9) 6.4 (6.1) 11.0 (6.6)	5.0 - 30.0 0.0 - 15.0 0.0 - 20.0	21.8 (2.9) 5.1 (2.7) 8.3 (2.8)

* *differences significant, p<0.05*
Table 8.6 means (SD) and range for the Perceived Control Scales
Group A is the present group and Group B published data (Bradley et al 1990b)

The paired t-test was used to compare the ranks between the composite scales for personal control, medical control and situational control for all outcomes together.

Personal control was significantly higher than medical control, p<0.05, which was significantly higher than situational control, p<0.05. This is in agreement with the findings of Bradley et al (1990b) for group B and demonstrates that, for all outcomes together, this group of patients is more likely to view management of their diabetes as under their personal control than medical or situational control. They are least likely to attribute outcomes to chance factors (situational control). Patients tended to see the positive outcomes as due more to medical control than the negative outcomes, p<0.05, and to see the negative outcomes as more due to situational control than the positive outcomes, p<0.05. For negative outcomes the tendency for medical control to be rated as more important than situational control was reversed and medical control was lower than situational control, p<0.05. The difference between positive and negative outcome ratings for personal control did not reach significance.

The unpaired t-test was used to compare the means between the two groups. The mean rating for personal control for all outcomes together and for positive outcomes was significantly lower in the present group than in published data, p<0.05.

8.3.6.4 Comparison of Questionnaire data, the Compliance Measures and Measures of Diabetes Control.

Using linear regression and correlation tests for the 8 patients with questionnaire data available the questionnaire data were compared with the three compliance measures, the body mass index and the mean random blood glucose. Correlations were also made for the six patients with questionnaire data who also had fructosamine values.

Not surprisingly depression and anxiety were significantly negatively correlated

with general wellbeing (r=-0.933, p<0.05). The only other significant correlation within the questionnaire data was between barriers and perceived vulnerability (r=0.801, p<0.02). Patients who had higher scores for barriers to their diabetes treatment also perceived themselves to be more vulnerable to diabetic complications.

There were two significant correlations between the questionnaire data and the compliance measures. Both perceived severity and perceived vulnerability were significantly correlated with the hourly irregularity index (r=0.789, r=0.756, p<0.05). Patients who had higher scores for perceived severity of diabetes and perceived vulnerability to diabetic complications also had higher values for the hourly irregularity index.

There was one significant correlation between the measures of diabetes control and the questionnaire data. Fructosamine was significantly negatively correlated with situational control (r=-0.866, p<0.05). Patients who attributed outcomes more to chance had better diabetic control! This is the opposite to that expected and is the opposite to that found by Bradley et al (1990b) in their study.

8.3.7 Comparison with Oncology Data

It is of interest to compare diabetic compliance with that already observed in oncology patients. The oncology patients differed in that they were prescribed daily dosage frequencies between 1 and 4 as against predominantly 1 in the present group. As dosage frequency was previously found to affect compliance, for the purpose of comparison therefore only data relating to drugs prescribed once daily were used. This limited the comparison to patients in the lymphoma group; 16 of these had 41 courses prescribed once daily. The lymphoma patients differed in that they were

unaware of monitoring, although there was a small subset of the lymphoma group who

were aware of monitoring so these were also used in the comparison. Because in each

group individual patients were followed for differing numbers of treatment periods the

mean value for overall compliance, daily irregularity index and hourly irregularity

index over all treatment periods for each patient were first calculated. The mean (SD)

values for the three compliance measures for the groups are shown in table 8.7 which

also shows the percentage of days with the correct number of monitor openings in

relation to the prescribed daily number and the percentage of dosage intervals between

22 and 26 hours. Comparison of the mean values of the three compliance measures

by unpaired t-test failed to reveal any significant differences. Using the variance ratio

test it was found that the variation in overall compliance for the diabetes group was

lower than for the unaware lymphoma group, $p < 0.05$.

	Diabetes group Aware 12 patients 38 periods	Lymphoma Group Unaware 16 patients 41 periods	Lymphoma Group Aware 3 patients 5 courses
overall compliance (%)	95.5 (12.0)	111.5 (27.5)	102.3 (2.0)
daily irregularity index	0.07 (0.13)	0.20 (0.21)	0.06 (0.07)
hourly irregularity index	0.22 (0.16)	0.35 (0.22)	0.31 (0.14)
Days with one opening (%)	93.1	86.2	93.7
Intervals between 22-26 hrs (%)	84.9	78.8	N/A

Table 8.7 Means (SD) for compliance data for lymphoma and diabetes groups

8.4 DISCUSSION

Compliance monitored by the electronic monitor was excellent in this study, the overall compliance being in the order of 96% which is higher than some previous studies and equivalent to others, see chapter 3 section 3.2.2.1. Because of the method of compliance assessment used it was also possible to look at the daily and hourly pattern of openings. 93% of the days had the correct number of openings in relation to the prescribed daily number and 85% of the intervals were between 22 and 26 hours long representing a very high level of consistency. The level of overall compliance necessary to achieve the desired therapeutic effect is not known but if we were to take it as greater than or equal to 85% 41 of the 45 monitoring periods fell into this category. The four monitoring periods less than 85% were for the same patient who had an overall compliance for the study period of 60%.

Patients were aware that the time of day they took their tablets was being monitored. From the findings of the lymphoma study this may be expected to alter compliance. In the lymphoma study patients who were aware that the time of day they took the tablets was being recorded showed an increase in daily regularity but no increase in the overall compliance which was high for all the patients anyway. The finding that the overall compliance was so good and the consistency data was excellent in the diabetic patients could therefore,in part, be explained by the fact they were aware of monitoring. However, if patients' compliance improved considerably on entering the study because they knew they were being monitored, we might have expected to see that compliance decreased again by the end of the study since it may be difficult to keep up an improved compliance for 3 months when the novelty of the study wore off. None of the three compliance measures decreased over the course of

the study, so this effect was not seen. If patient compliance improved considerably on entering the study and remained that way for the duration of the study we would have expected to see an improvement in the measures of diabetic control over the course of the study. Neither fructosamine, which reflects glucose control over the preceding 3 weeks or glycated haemoglobin which reflects control over a period of 8-10 weeks showed any variation over the course of the study. Because neither the compliance measures or the measures of diabetic control changed over the study it seems likely that the overall compliance during the study was not much different to that previous to the study.

Another explanation for the excellent compliance in this study is that the 38% of potential participants that took part in the study were good compliers in contrast to the patients who did not participate. However, some reasons for non-participation were quite "legitimate" such as employment making it impossible to visit the surgery the number of times required for the study. In addition, there was no difference detected in diabetic control between those patients who participated and those who did not.

To confirm that opening of the monitor was actually related to ingestion of the medication, especially as patients were aware of monitoring, a number of serum samples available from three-quarters of the patients were analyzed for glibenclamide. All the samples contained the medication proving that patients were actually taking it.

In just over half of the patients the return tablet count was in complete agreement with the overall compliance for all monitoring periods but only one of these patients for three monitoring periods had overall compliance different to 100%. In

just under half of the patients there were monitoring periods with the overall compliance of less than 100% which was not revealed by the return tablet count. The return tablet count overestimated compliance by more than 15% in 11% of monitoring periods which were all from the same patient.

The physicians' assessment did not correlate with overall compliance. Physicians underestimated compliance in just over a half of patients and overestimated it in 1 patient. This is in contrast to one study of compliance with antacids where physicians tended to overestimate their patients compliance (Roth & Caron 1978). In another study of compliance, with eye drops in glaucoma, physicians under and overestimated compliance (Kass et al 1986).

Not all the patients who took part in the study had well controlled diabetes. 36% had a mean fructosamine higher than the reference value and 46% had a mean glycated haemoglobin outside of the reference value. 31% of the patients were seriously overweight from their body mass index. None of the compliance measures were related to the measures of diabetes control using analysis of variance.

75% of the patients responded to the questionnaire and 8 were available for analysis. The main significant differences between this group and the 187 out-patients studied by Bradley et al (1990) was that the present group had a lower mean rating for general wellbeing and a lower mean rating for personal control of their diabetes. Similar to the findings of Bradley et al (1990), patients had higher perceived benefits than barriers to the treatment and perceived diabetic complications to be more serious and themselves to be more vulnerable to diabetic complications than general disorders. They also rated outcomes of their diabetes to be more under their personal control than under medical control and rated this higher than chance factors. Perceived

severity of and vulnerability to diabetic complications were significantly correlated with the hourly irregularity index which was the compliance measure with the most variation. It is difficult to know how to interpret this finding. In contrast to the findings of Bradley et al (1990) situational control was negatively correlated with fructosamine so that patients who had a higher rating for chance had better diabetic control. This may be a spurious finding because of the small sample size and the large number of statistical tests carried out.

Comparing the compliance measures with the oncology group also taking once daily medication revealed no significant differences except that there was less variability in the overall compliance in the diabetes group. This can be explained, in part, by the fact that the diabetes group were aware of monitoring.

The finding of this study that medication compliance was unrelated to diabetic control is supported by Peterson et al (1984) who monitored compliance in NIDDM patients by prescription refill. They found that compliance with medication was unrelated to control but that compliance with diet was related to control. Other studies using subjective methods of compliance assessment have found that patients reported less difficulty with medication compliance than with diet or exercise. In our study when patients were asked in the questionnaire the reasons for possible outcomes in their diabetes management the most common factors given that affected this were diet and exercise.

Compliance in this study may be higher than would be found on average in this population since patients knew they were in a study and were aware of monitoring and they may have been better compliers than the non-participants. However, the generally very high level of compliance does suggest that diet and exercise are more

significant factors in diabetes control than medication. Patients may feel that if they comply with their tablets perfectly they can cheat a little on their diet. More emphasis should perhaps be placed on helping these patients to tailor a suitable diet to their needs and lifestyle.

CHAPTER 9

CONCLUSIONS AND PROPOSALS FOR

FURTHER WORK

9.1 Medication Monitors in Compliance Research

Medication monitors are a great advance in the measurement of compliance in that they allow the complete pattern of medication taking to be studied. Previous methods have only allowed an overall check at a given point in time. From the data available for medication monitors the total number of doses taken, the number of days when the doses were taken in accordance with the prescribed daily frequency and the length of intervals between doses can be assessed. The device used here was found to be robust and reliable with a failure rate of only 2.4%. It fulfilled the criteria of being unobtrusive in that most patients accepted it without suspicion.

The main disadvantage of medication monitors is that they do not guarantee that the medication is being taken. It would seem unlikely however, that where there was a regular pattern of openings that this would fail to correspond to ingestion. In the diabetes study where patients were aware of monitoring, we found that all serum samples analyzed contained the drug, Chapter 8 section 8.3.4.2. This would therefore seem to be equally true in the oncology studies where patients were unaware of monitoring, chapters 5-7.

9.2 Definitions of Compliance and the Assessment of Compliance Data

Definitions of compliance vary and compliance data have been analyzed in many different ways. Much of the published compliance research has consisted of descriptive alarms and the simplistic dichotomy of compliant and non-compliant (Dirks & Kinsman 1982, Rudd & Marshall 1987). An example of this is seen in a recent paper on compliance in non-insulin dependent diabetics with glibenclamide (Babiker et al 1991). Compliance was measured by pill-count in 18 patients on three

occasions over 6 weeks. The authors found that only 50% of patients achieved compliance of 95-105% and interpreted this as a "considerable degree of non-compliance". Overall however, 15 (83%) of patients were compliant between 90-110% with the remaining 3 patients being 60%, 114% and 125% compliant. There is no evidence that compliance with oral hypo-glycaemic agents needs to be within the stringent limits of 95-105% leading to the conclusion stated.

Three measures of compliance have been developed from the monitor data to represent the total amount of medication taken over the monitoring period (Overall compliance), the daily discrepancy in monitor openings with respect to the prescribed number (Daily Irregularity Index) and the regularity of the hourly intervals between doses (Hourly Irregularity Index). The hourly irregularity index was devised to represent the consistency of the patients own hourly pattern of dosing and not to relate this to any supposed ideal pattern. The distribution of the length of intervals for all patients was analyzed to give some idea of the actual length of dosage intervals used.

No data were found for the medications used in the oncology or diabetes patients to give a level of compliance below which patients would be failing to gain the full benefit of the treatment. For this reason the compliance data were reported as they stood without setting an arbitrary level below which patients were classified as non-compliant.

It is interesting that in two previous studies using electronic monitors to assess compliance in situations where the clinical outcome was readily measurable the authors concluded, in both cases, that the empirically fixed dose was too high and that fewer doses could have been prescribed (Cheung et al 1988a, Kruse et al 1990b).

9.3 Ethical Considerations of Compliance Research

To estimate how people take their tablets in as unbiased a way as possible would require that the patient is unaware of the monitoring procedure. Indeed, in patients aware of monitoring in the lymphoma group the compliance was different to those who were unaware, see chapter 5 section 5.3.1. Moreover, there are clearly situations when it would be of value if the clinician knew that the failure of therapy was not due to non-compliance by the patient. In the diabetes study, the general practitioners considered, that the investigation should not be conducted without the full knowledge of the patients. Their concerns were that such a procedure would be an unacceptable infringement of the patients' privacy and could potentially undermine the future patient-doctor relationship.

In compliance studies utilizing medication monitors, the problem of informed consent has been treated in different ways. Some researchers have told the patients about the device (Cramer et al 1989, Rudd et al 1990). Other researchers have invented a reason for the device that was unrelated to the study. Kass et al (1986a) told the patients that the medication was a free sample and if they returned the eye drop bottle the drug company would replace it. Cheung et al (1988a & 1988b) asked the patients to evaluate the suitability of the pill box for use by the elderly and disabled. In two other studies patients were not told the nature of the recording device until the data collection was complete. Informed consent was subsequently obtained before the records were printed (Norell et al 1980b, Kruse et al 1990a).

The World Medical Association has set out in the Declaration of Helsinki recommendations as a guide in clinical research. This states that if at all possible, the doctor should obtain the patient's freely given consent after the patient has been given

a full explanation. There are two separate aspects of this requirement. The first is what constitutes valid consent and the other deals with what constitutes a full explanation. Some have argued that monitoring compliance without any intervention is not clinical research since the patients treatment is not being altered in any way so that the Declaration of Helsinki does not apply. However others feel that monitoring compliance without full informed consent is in fact a form of covert research the ethics of which has recently been debated in the Pharmaceutical Journal (Dingwall et al 1992). It has been suggested by some researchers that it is acceptable not to tell patients the full truth at the outset of the study but that informed consent must be obtained before using the data (Kruse et al 1990a). This however adds its own problems in that it raises the question: is the compliance of the patients who ask you to erase the data from the monitor different to that of those who consent to its use?

In the oncology studies which were carried out without the knowledge of the patient, patients were not told anything about the monitor that was not true. The aspect of the study that was emphasised was the monitoring of the side-effects. In the early study in lymphoma patients when patients asked additional questions about the monitor its recording nature was revealed. This occurred in 4 patients, none of whom subsequently refused to participate in the study, and their data were treated separately. In the two further oncology studies, when patients asked additional questions about the monitor, verbal consent was obtained to explain the study more fully after they had participated and no patients objected to this. Patients who did not ask any further questions about the monitor were not told at any stage of the study. An additional measure to protect the patients privacy was that the doctors of patients in the study were not told the data from individual patients in their care but were informed of the

data from the study population as a whole.

9.4 Overall Conclusions and Proposals for Future Work.

A summary of the compliance data is shown in table 9.1. The mean overall compliance in each of the studies was greater than 90% and indicates that medication compliance may not be a problem for oncology patients and non-insulin dependent diabetics. This further suggests that if the therapeutic outcome was not as expected that factors other than medication compliance would have to be considered.

The lymphoma group who were aware of monitoring had the best values for all the compliance measures considered together. Aware of being monitored and on a single daily dose, the diabetes group had the lowest hourly irregularity index and the highest number of days with the prescribed number of openings. In the "unaware" lymphoma patient group with their far more complex dosing regimens, there was a decrease in overall compliance as the prescribed daily frequency increased. This finding, in conjunction with that reported by Cramer et al (1989) and Jacobs et al (1988) that compliance with four times daily regimens was lower again than three times daily regimens, indicated that compliance in the ovarian cancer group might be lower than the other groups. However, the ovarian cancer group had compliance data equivalent to a twice daily regimen, see table 9.1.

In the oncology groups the effect on the three compliance measures of the eight diary card scores was measured. In the lymphoma group a relationship was found between increase in nausea score and prescribed daily frequency and decrease in compliance. No correlation was evident between the measures of compliance and years since diagnosis, drug type or number of courses of treatment measured.

Prescribed Daily Frequency	Once Daily		Twice Daily		Three Times Daily	Four Times Daily	Once, Twice & Three Times Daily
Patient Group	Diabetes 13 patients 44 courses (aware)	Lymphoma 16 patients 41 courses	Lymphoma 11 patients 16 courses	SCLC 10 patients 21 courses	Lymphoma 5 patients 10 courses	Ovarian Cancer 6 patients 13 courses	Lymphoma 4 patients 13 courses (aware)
Main drugs monitored	Glibenclamide	Chlorambucil Prednisolone	Prednisolone	Etoposide	Prednisolone Procarbazine	Altretamine	Chlorambucil Prednisolone Procarbazine
Overall Compliance (%)	95.5 (12.0)	111.5 (27.5)	96.4 (8.9)	94.7 (6.7)	90.9 (6.5)	95.5 (7.5)	101.7 (5.7)
Daily Irregularity Index	0.07 (0.13)	0.20 (0.21)	0.11 (0.09)	0.22 (0.11)	0.16 (0.09)	0.11 (0.05)	0.08 (0.03)
Hourly Irregularity Index	0.22 (0.16)	0.35 (0.22)	0.31 (0.18)	0.31 (0.14)	0.45 (0.11)	0.24 (0.09)	0.30 (0.12)
Percentage of days with the prescribed daily frequency	93.1	86.2	80.7	62.9	55.0	67.0	84.1

Table 9.1 Summary of compliance data for the different groups studied.

In the SCLC group there was a small decrease in hourly irregularity associated with increase in nausea score and decrease in overall compliance with decrease in the activity of the patient. No association was found between months since diagnosis or course number and measures of compliance. Although the variations in compliance with these variables were statistically significant, they are likely to have little clinical impact given the overall high adherence to the dosage regimens.

The high levels of compliance in these studies are, however, in conflict with a number of published studies. This may in part be explained by differences in methodology, definitions of compliance and disease state. Despite the unpleasant side-effects of these medications patients perceptions of cancer are such that they have been found willing to opt for very demanding therapies with very low chance of benefit and this applied equally to those patients questioned before and after therapy (Slevin et al 1990). This can be explained in terms of the Health Belief Model where the perceived severity and vulnerability to the condition would be high and the potential treatment benefit would outweigh the barriers.

In the diabetes study there was no decrease in the compliance measures over the three month period of monitoring and compliance was also unrelated to the measures of diabetes control. It is of interest that compliance as measured by the medication monitor did not correlate with the physicians' assessment of their patients' tablet-taking habits. In this sample of patients it seems clear that they are aware of their vulnerability to further serious sequelae and also believe that they are in a position to exert a degree of personal control over the progress of their disease.

To date, little published data exists which relate to the compliance of oncology or diabetic patients with oral therapy. Further work should be undertaken

to confirm these encouraging results in larger patient samples. Using the new electronic monitor developed by the Aprex Corporation[1] should permit larger multicentre studies to be carried out. Compliance researchers need to move away from categorising persons as compliant or non-compliant and the link between the level of compliance required to achieve the desired therapeutic outcome needs to be addressed. Finally methods of analyzing the data from electronic medication monitors require further discussion and standardisation since this would allow easier comparison between studies.

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[1] *APREX Corporation, Fremont, CA 94539, USA*

APPENDICES

APPENDIX 1

PATIENT INFORMATION SHEET, ONCOLOGY STUDIES

PATIENT INFORMATION SHEET

Thankyou for participating in this study. We want to see how you are getting on with your treatment and what side reactions, if any, you experience. Your capsules will be given to you in light proof containers from the clinic.

Please note:

1. The containers have been specially made for the study and are therefore expensive, so please remember to return them next time you attend the clinic so they can be reissued.

2. The containers have not got child-resistant caps, so please make sure they are kept out of reach of children and remember to keep the cap on.

3. Please keep the capsules in the special container (i.e. do not transfer them to any other container or purse).

4. On the accompanying diary card we would like you to record the way you have felt each day and any side reactions you have experienced. Please make every effort to fill it in, then bring it to the clinic next time you attend.

APPENDIX 2
SHEET FOR PHYSICIANS' ASSESSMENT OF COMPLIANCE
DIABETES STUDY

DIABETES STUDY

Dear

As you will be aware   has taken part in the
diabetes study to assess their compliance with the oral hypoglycaemic agent
glibenclamide. For the purpose of this study I would like you to rate how well you
estimate this person adheres to their tablet regimen.

Do they take their tablets :

Almost all the time

Three-quarters of the time

Half of the time

Quarter of the time

Practically never

Please circle one response and feel free to make any additional comments.
Please leave the completed sheet with the receptionist for me to collect.

Many thanks for your help.

APPENDIX 3
LETTER ACCOMPANYING QUESTIONNAIRES
DIABETES STUDY

Dear

You have been given a number of questionnaires to complete at home. These are to help me in my evaluation of the treatment of tablet treated diabetes. The questions cover how satisfied you are with your treatment, benefits and barriers you see to your treatment and your general wellbeing. Please answer all the questions and be as honest as possible. Your doctor will not see your answers to the questions.

When you have completed all the questionnaires please return them to me at the Surgery in the stamped addressed envelope provided.

Thankyou for your help in my study.

HEALTH BELIEFS ABOUT TABLET-TREATED DIABETES

Scales developed specifically for non-insulin dependent
patients treated with oral hypoglycaemic agents.

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*NB Researchers who wish to use these scales should contact
the authors for possible up-to-date revisions before
analysing their data.*

February 1989

EXPERIENCE OF TREATMENT BENEFITS AND BARRIERS

In this section would you please circle one of the numbers on each of the scales to indicate how strongly you agree or disagree with each of the following statements.

On these scales 0 would indicate that you strongly disagree
1 = moderately disagree
2 = mildly disagree
3 = neither agree nor disagree
4 = mildly agree
5 = moderately agree
6 = strongly agree

		strongly disagree						strongly agree
1.	By careful planning of diet and exercise, I can control my diabetes at least as well as most other people with diabetes	0	1	2	3	4	5	6
2.	Sticking to my diet makes eating out difficult	0	1	2	3	4	5	6
3.	High blood sugars can be prevented if I plan ahead	0	1	2	3	4	5	6
4.	It is just not possible to control my diabetes properly and live in a way that is acceptable to me	0	1	2	3	4	5	6
5.	Sticking to my diet causes inconvenience to other people	0	1	2	3	4	5	6
6.	Controlling my diabetes well interferes with my social life	0	1	2	3	4	5	6
7.	Good control of my diabetes reduces the possibility of developing complications	0	1	2	3	4	5	6
8.	It is important to take all my tablets at the times recommended by the doctor if I am to achieve good control of my diabetes	0	1	2	3	4	5	6
9.	The diet I am supposed to follow is rather dull and uninteresting	0	1	2	3	4	5	6
10.	I find that keeping to a diet is helpful in controlling my diabetes	0	1	2	3	4	5	6

PLEASE MAKE SURE THAT YOU HAVE CONSIDERED EACH OF THE 10 STATEMENTS AND HAVE CIRCLED A NUMBER ON EACH OF THE SCALES.

BELIEFS ABOUT SEVERITY

In this section would you please circle a number on each of the scales to indicate how serious you think the following problems would be if you were to develop them.

On these scales   0   would indicate that the problem is not serious at all
                  1   =   not serious enough to be worrying
                  2   =   moderately serious
                  3   =   very serious
                  4   =   extremely serious

If you are unable to rate the seriousness of a problem because you are not sure what the problem is, please tick the box on the right-hand side.

		not serious at all				extremely serious	not sure what the problem is
1.	High blood pressure	0	1	2	3	4	☐
2.	Stomach ulcer	0	1	2	3	4	☐
3.	Blindness	0	1	2	3	4	☐
4.	Ear infection	0	1	2	3	4	☐
5.	Kidney disease	0	1	2	3	4	☐
6.	Aching legs	0	1	2	3	4	☐
7.	Leukaemia (cancer of the blood)	0	1	2	3	4	☐
8.	Gum disease	0	1	2	3	4	☐
9.	Bronchitis	0	1	2	3	4	☐
10.	Deafness (complete loss of hearing)	0	1	2	3	4	☐
11.	Numbness in the feet	0	1	2	3	4	☐
12.	Heart disease	0	1	2	3	4	☐
13.	Asthma	0	1	2	3	4	☐
14.	Failing eyesight	0	1	2	3	4	☐
15.	Loss of hearing (partly deaf)	0	1	2	3	4	☐
16.	Gangrene	0	1	2	3	4	☐
17.	Your diabetes now	0	1	2	3	4	☐
18.	Your diabetes in 10 years time	0	1	2	3	4	☐

PLEASE MAKE SURE THAT YOU HAVE CIRCLED ONE NUMBER ON EACH OF THE 18 SCALES.

BELIEFS ABOUT VULNERABILITY

In this section we are asking you to make two ratings for each of the problems listed.

FIRST: Consider an **average person** with your kind of diabetes who is
- your age
- your sex
- follows the same kind of treatment as yourself
- has average control over his or her diabetes

and indicate how likely you feel it is that this person will develop the following problems.

SECOND: Indicate how likely you feel it is that **you** will develop the following problems.

On these scales 0   would indicate that you feel that the development of the problem is very unlikely
1 = quite unlikely
2 = neither likely nor unlikely
3 = quite likely
4 = very likely

If you already have or think you may have any of these problems, please tick the box on the right-hand side.

	very unlikely				very likely	I already have this problem

1. High blood pressure

Average person with your kind of diabetes	0	1	2	3	4	
Yourself	0	1	2	3	4	☐

2. Stomach ulcer

Average person with your kind of diabetes	0	1	2	3	4	
Yourself	0	1	2	3	4	☐

3. Blindness

Average person with your kind of diabetes	0	1	2	3	4	
Yourself	0	1	2	3	4	☐

4. Ear infection

Average person with your kind of diabetes	0	1	2	3	4	
Yourself	0	1	2	3	4	☐

	very unlikely				very likely	I already have this problem
5. Kidney disease						
Average person with your kind of diabetes	0	1	2	3	4	
Yourself	0	1	2	3	4	☐
6. Aching legs						
Average person with your kind of diabetes	0	1	2	3	4	
Yourself	0	1	2	3	4	☐
7. Leukaemia **(cancer of blood)**						
Average person with your kind of diabetes	0	1	2	3	4	
Yourself	0	1	2	3	4	☐
8. Gum disease						
Average person with your kind of diabetes	0	1	2	3	4	
Yourself	0	1	2	3	4	☐
9. Bronchitis						
Average person with your kind of diabetes	0	1	2	3	4	
Yourself	0	1	2	3	4	☐
10. Deafness **(complete loss of hearing)**						
Average person with your kind of diabetes	0	1	2	3	4	
Yourself	0	1	2	3	4	☐
11. Numbness in the feet						
Average person with your kind of diabetes	0	1	2	3	4	
Yourself	0	1	2	3	4	☐

	very unlikely				very likely	I already have this problem

12. Heart disease

Average person with your kind of diabetes	0	1	2	3	4	
Yourself	0	1	2	3	4	☐

13. Asthma

Average person with your kind of diabetes	0	1	2	3	4	
Yourself	0	1	2	3	4	☐

14. Failing eyesight

Average person with your kind of diabetes	0	1	2	3	4	
Yourself	0	1	2	3	4	☐

**15. Loss of hearing
(partly deaf)**

Average person with your kind of diabetes	0	1	2	3	4	
Yourself	0	1	2	3	4	☐

16. Gangrene

Average person with your kind of diabetes	0	1	2	3	4	
Yourself	0	1	2	3	4	☐

17. Complications arising from diabetes

Average person with your kind of diabetes	0	1	2	3	4	
Yourself	0	1	2	3	4	☐

PLEASE MAKE SURE THAT YOU HAVE CIRCLED A NUMBER ON EACH OF THE SCALES.

APPENDIX 5
WELLBEING AND TREATMENT SATISFACTION
QUESTIONNAIRE

WELLBEING AND TREATMENT SATISFACTION

Scales developed specifically for non-insulin dependent patients
treated with oral hypoglycaemic agents

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NB   *Researchers who wish to use these scales should
        contact the authors for possible up-to-date revisions
        before analysing their data*

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WELL BEING QUESTIONNAIRE

Please circle a number on each of the following scales to indicate how often you feel each phrase has applied to you in the past few weeks:

		all the time			not at all
1.	I feel that I am useful and needed	3	2	1	0
2.	I have crying spells or feel like it	3	2	1	0
3.	I find I can think quite clearly	3	2	1	0
4.	My life is pretty full	3	2	1	0
5.	I feel downhearted and blue	3	2	1 .	0
6.	I enjoy the things I do	3	2	1	0
7.	I feel nervous and anxious	3	2	1	0
8.	I feel afraid for no reason at all	3	2	1	0
9.	I get upset easily or feel panicky	3	2	1	0
10.	I feel like I'm falling apart and going to pieces	3	2	1	0·
11.	I feel calm and can sit still easily	3	2	1	0
12.	I fall asleep easily and get a good night's rest	3	2	1	0
13.	I have been happy, satisfied, or pleased with my personal life	3	2	1	0
14.	I have felt well adjusted to my life situation	3	2	1	0
15.	I have lived the kind of life I wanted to	3	2	1	0
16.	I have felt eager to tackle my daily tasks or make new decisions	3	2	1	0
17.	I have felt I could easily handle or cope with any serious problem or major change in my life	3	2	1	0
18.	My daily life has been full of things that were interesting to me	3	2	1	0

PLEASE MAKE SURE THAT YOU HAVE CONSIDERED EACH OF THE 18 STATEMENTS
AND HAVE CIRCLED A NUMBER ON EACH OF THE 18 SCALES.

SATISFACTION WITH TREATMENT

The following questions are concerned with the form of treatment you are using now and your experience over the past few weeks. Please answer each question by circling a number on each of the scales.

How satisfied are you with your current treatment?

very satisfied 6   5   4   3   2   1   0   very dissatisfied

How well controlled do you feel your diabetes has been recently?

very well   6   5   4   3   2   1   0   very poorly
controlled   controlled

How often have you felt that your blood sugars have been unacceptably high recently?

most of the time 6   5   4   3   2   1   0   none of the time

How often have you felt that your blood sugars have been unacceptably low recently?

most of the time 6   5   4   3   2   1   0   none of the time

How convenient have you been finding your treatment to be recently?

very convenient 6   5   4   3   2   1   0   very inconvenient

How flexible have you been finding your treatment to be recently?

very flexible   6   5   4   3   2   1   0   very inflexible

How satisfied are you with your understanding of your diabetes?

very satisfied   6   5   4   3   2   1   0   very dissatisfied

How satisfied would you be to continue with your present form of treatment?

very satisfied   6   5   4   3   2   1   0   very dissatisfied

PLEASE MAKE SURE THAT YOU HAVE CIRCLED ONE NUMBER ON EACH OF THE SCALES.

APPENDIX 6
PERCEIVED CONTROL QUESTIONNAIRE

PERCEIVED CONTROL OF TABLET TREATED DIABETES

Scales developed specifically for non-insulin dependent
patients treated with oral hypoglycaemic agents

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*NB   Researchers who wish to use these scales should contact the authors
for possible up-to-date revisions before analysing their data*

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INSTRUCTIONS FOR COMPLETION OF SCALES

PERCEIVED CONTROL OF TABLET TREATED DIABETES

The following questions are about the causes of situations which you may have experienced recently.

While events may have many causes, we want you to pick only one (the major cause) of the situation as you see it.

Please write this cause in the space provided after each event.

Next, we want you to answer some questions about the cause by circling the most appropriate number of a sliding scale from 0 to 6.

Imagine that you have recently become unacceptably overweight.

Write down, in the space below, the single most likely cause of becoming overweight.

_____

_____

Now rate this cause on the following scales:

1.   To what extent was the cause due to something about you?

Totally due to me   6   5   4   3   2   1   0   Not at all due to me

2.   To what extent was the cause due to the treatment recommended by your doctor?

Totally due   6   5   4   3   2   1   0   Not at all due
to treatment   to treatment
recommended   recommended

3.   To what extent was the cause something to do with other people or circumstances?

Totally due   6   5   4   3   2   1   0   Not at all due
to other people   to other people
or circumstances   or circumstances

4.   To what extent was the cause due to chance?

Totally due   6   5   4   3   2   1   0   Not at all due
to chance   to chance

5.   To what extent was the cause controllable by you?

Totally   6   5   4   3   2   1   0   Totally
controllable by me   uncontrollable by me

6.   To what extent was the cause controllable by your doctor?

Totally   6   5   4   3   2   1   0   Totally
controllable   uncontrollable
by my doctor   by my doctor

7.   To what extent do you think you could have foreseen the cause of becoming overweight?

Totally   6   5   4   3   2   1   0   Totally
foreseeable   unforeseeable
by me   by me

1

Imagine that for several days you have found high levels of sugar when you tested your urine.

Write down the single most likely cause of the high sugar levels in the space below.

_____

_____

Now rate this cause on the following scales:

1.   To what extent was the cause due to something about you?

Totally due to me   6   5   4   3   2   1   0   Not at all due to me

2.   To what extent was the cause due to the treatment recommended by your doctor?

Totally due
to treatment   6   5   4   3   2   1   0   Not at all due
recommended   to treatment
recommended

3.   To what extent was the cause something to do with other people or circumstances?

Totally due
to other people   6   5   4   3   2   1   0   Not at all due
or circumstances   to other people
or circumstances

4.   To what extent was the cause due to chance?

Totally due
to chance   6   5   4   3   2   1   0   Not at all due
to chance

5.   To what extent was the cause controllable by you?

Totally
controllable by me   6   5   4   3   2   1   0   Totally
uncontrollable by me

6.   To what extent was the cause controllable by your doctor?

Totally
controllable   6   5   4   3   2   1   0   Totally
by my doctor   uncontrollable
by my doctor

7.   To what extent do you think you could have foreseen the cause of the high sugar levels?

Totally
foreseeable   6   5   4   3   2   1   0   Totally
by me   unforeseeable
by me

2

Imagine that you have been able to keep your weight at an acceptable level for a period of several weeks and you have felt fit and well.

Write down, in the space below, the single most likely cause of this period of good weight control and sense of general well-being.

_____

_____

Now rate this cause on the following scales:

1. To what extent was the cause due to something about you?

Totally due to me   6   5   4   3   2   1   0   Not at all due to me

2. To what extent was the cause due to the treatment recommended by your doctor?

Totally due   6   5   4   3   2   1   0   Not at all due
to treatment   to treatment
recommended   recommended

3. To what extent was the cause something to do with other people or circumstances?

Totally due   6   5   4   3   2   1   0   Not at all due
to other people   to other people
or circumstances   or circumstances

4. To what extent was the cause due to chance?

Totally due   6   5   4   3   2   1   0   Not at all due
to chance   to chance

5. To what extent was the cause controllable by you?

Totally   6   5   4   3   2   1   0   Totally
controllable by me   uncontrollable by me

6. To what extent was the cause controllable by your doctor?

Totally   6   5   4   3   2   1   0   Totally
controllable   uncontrollable
by my doctor   by my doctor

7. To what extent do you think you could have foreseen the cause of the period of good weight control?

Totally   6   5   4   3   2   1   0   Totally
foreseeable   unforeseeable
by me   by me

Imagine that you have successfully avoided the complications of diabetes such as problems with your feet.

Write down, in the space below, the single most likely cause of the successful avoidance of diabetic complications such as problems with your feet.

_____

_____

Now rate this cause on the following scales:

1.   To what extent was the cause due to something about you?

Totally due to me   6   5   4   3   2   1   0   Not at all due to me

2.   To what extent was the cause due to the treatment recommended by your doctor?

Totally due   6   5   4   3   2   1   0   Not at all due
to treatment   to treatment
recommended   recommended

3.   To what extent was the cause something to do with other people or circumstances?

Totally due   6   5   4   3   2   1   0   Not at all due
to other people   to other people
or circumstances   or circumstances

4.   To what extent was the cause due to chance?

Totally due   6   5   4   3   2   1   0   Not at all due
to chance   to chance

5.   To what extent was the cause controllable by you?

Totally   6   5   4   3   2   1   0   Totally
controllable by me   uncontrollable by me

6.   To what extent was the cause controllable by your doctor?

Totally   6   5   4   3   2   1   0   Totally
controllable   uncontrollable
by my doctor   by my doctor

7.   To what extent do you think you could have foreseen the cause of successfully avoiding complications?

Totally   6   5   4   3   2   1   0   Totally
foreseeable   unforeseeable
by me   by me

4

Imagine that you have reduced your weight to a satisfactory level after a period when you gained too much weight.

Write down the single most likely cause of this weight reduction in the space below.

_____

_____

Now rate this cause on the following scales:

1.   To what extent was the cause due to something about you?

Totally due to me   6   5   4   3   2   1   0   Not at all due to me

2.   To what extent was the cause due to the treatment recommended by your doctor?

Totally due   6   5   4   3   2   1   0   Not at all due
to treatment   to treatment
recommended   recommended

3.   To what extent was the cause something to do with other people or circumstances?

Totally due   6   5   4   3   2   1   0   Not at all due
to other people   to other people
or circumstances   or circumstances

4.   To what extent was the cause due to chance?

Totally due   6   5   4   3   2   1   0   Not at all due
to chance   to chance

5.   To what extent was the cause controllable by you?

Totally   6   5   4   3   2   1   0   Totally
controllable by me   uncontrollable by me

6.   To what extent was the cause controllable by your doctor?

Totally   6   5   4   3   2   1   0   Totally
controllable   uncontrollable
by my doctor   by my doctor

7.   To what extent do you think you could have foreseen the cause of the weight reduction?

Totally   6   5   4   3   2   1   0   Totally
foreseeable   unforeseeable
by me   by me

APPENDIX 7
PATIENT CONSENT FORM
DIABETES STUDY

PATIENT VOLUNTEER'S CONSENT FORM

Consultant...... Dr P Julian ...... Investigator. Ms R Lee ....

Purpose of the study and brief description of procedure to be carried out

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You will be aware that diabetics take their tablets at different times of the day. We are interested in seeing whether this makes any difference to the control of your diabetes. If you agree to take part in the study, you will be given your tablets in a special container which will record the time a tablet is removed. The pot has been specially made for this study and is thus expensive, so please return it so it can be reissued each time you visit the surgery. Please only take tablets from this container and do not transfer them to anything else.

This container has not got a child-resistant cap, so remember to keep it well out of reach of children and keep the cap screwed on. We would like you to carry on taking your tablets as normal and to return every three weeks over a period of three months for a further supply of tablets and to have a blood sample taken. Each time you return to surgery you will be asked to give about two teaspoonsful of blood. In the course of the study you will also be asked some questions about diabetes and the drugs you are taking.

This study has been explained to me and I understand:

(a)   What the study involves
(b)   That refusal to participate will not affect my treatment in any way
(c)   That I may withdraw at any time

I therefore agree to take part in this study

Signature of Patient............................ Date..................

I HAVE BEEN PRESENT WHILE THE PROCEDURE HAS BEEN EXPLAINED TO THE PATIENT
AND I HAVE WITNESSED HIS/HER CONSENT TO TAKE PART

Signature of Witness............................ Date..................
(The Witness should be a person not connected with the study)

Full name and address of patient: ....
                                    ....
                                    ....
                                    ....

APPENDIX 8
PATIENT INFORMATION SHEET, DIABETES STUDY

Patient Information Sheet

Thankyou for participating in this study. Different people take their tablets at different times of the day. We are interested in seeing whether this makes any difference to the control of your diabetes.

Your glibenclamide tablets will be given to you in a special tablet pot from the surgery. This pot records the time of day the tablets are taken.

Please note:

1. For the study you will be asked to come to the surgery every 3 weeks over a period of 12 weeks. Each time you come you will be given a further supply of glibenclamide tablets and a blood sample will be taken. You do not need to fast the morning you are coming to the surgery and can take your tablets as normal.

2. The tablet pot has been specially made for this study and is therefore expensive, so please remember to return it every three weeks wheen you come to the surgery so that it can be re-issued.

3. The tablet pot has not got a child-resistant cap so please make sure it is kept out of the reach of children and remember to keep the cap on.

4. Please keep on taking your glibenclamide tablets as normal. Only take them from the special tablet pot and do not transfer them from this to any other container or purse.

5. At the end of the study you will be asked to fill in some questionnaires about your diabetes and treatment.

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