

UNIVERSITY OF SOUTHAMPTON

THE CLINICAL EFFECTS OF ACUPUNCTURE: METHODS OF EVALUATION

VOLUME II

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CHAPTER 11  
ACUPUNCTURE AND SMOKING

Introduction

This study was carried out as part of a prolonged fourth year medical student project at the University of Southampton. For the purposes of this thesis, we shall call this Study D. The author was aided in this investigation by Ms J. Gillams who was actively involved in the design of the project, the collation and collection of results, establishing and actually running the research clinics. A review of the literature concerning acupuncture and smoking cessation has already been presented (vide supra).

Smoking is a common addiction; 20 million people in the UK smoke (Russell 1979). Recent surveys show that the percentage of smokers in the population is decreasing; in 1972 52% of males and 41% of females smoked compared with 45% and 37% respectively in 1978 (British Medical Journal, 1981). About 18% of the male population and 12.5% of the female population in the UK are ex-smokers (Eiser 1978). Over the last 10 years these figures have changed further and there are now probably 15-20% less smokers in the United Kingdom than when this study was carried out in the early part of 1982. Most of the medical risks associated with smoking are reversible. On smoking cessation the risks drop dramatically in the first year and begin to compare with the general population after 10-15 years (Doll and Hill, 1964). The need for constructive anti-smoking measures is therefore obvious.

The major anti-smoking method available in the late 70s and early 80s were:

1. Aversive conditioning.

2. Drug therapy.
3. Hypnosis.
4. Behaviour modifications.
5. Education and group support activities.
6. Acupuncture.

This trial concerned itself with the two latter methods, that is acupuncture and education and group therapy.

At the time this study was conceived the anti-smoking literature was vast. Unfortunately, the majority of trials were descriptive and uncontrolled. The general impression gained from these studies and certainly supported by Ter Reit's meta-analysis into the effects of acupuncture on addiction (Ter Reit et al, 1990) suggests that most anti-smoking therapies have limited effectiveness. The majority of therapies appear to be effective at inducing smoking cessation during and immediately after treatment but the relapse rates are usually high. It has been suggested that if all those beginning treatment are adequately followed up, there are seldom more than 13% of the initial entrants who are abstinent at 3-6 months. It appears that less than one third of those who are abstinent immediately after therapy manage to maintain themselves as non-smokers 6 months later (Elliott and Douglas, 1978). Success rates are often interpreted from the overall reduction in the mean number of cigarettes smoked (Bernstein 1969; McFall and Hammen, 1971; Hunt and Matarazzo, 1973; Hunt and Belpalec, 1974; Bernstein and MacAlister, 1976; Lichtenstein and Danaher, 1976). Virtually any treatment is capable of reducing smoking levels by 30-40% of the pre-treatment mean, but it usually returns to about 75% of baseline level within 3 months.

Aversive therapy aims to associate smoking with repulsion. A commonly used

technique is to force the patient to smoke many cigarettes very rapidly at pre-defined times. Early studies quote high success rates (Leventhal and Cleary, 1980). However, on closer inspection, many of these studies on aversive therapy did not include those who failed to complete the treatment, and other authorities suggest a reduction of approximately 20% at 6 months (Lando 1955; Sutherland et al, 1975; Lando 1976).

The drug therapy employed usually involves a substitution of nicotine by nicotine chewing gum. This has recently received great publicity. However, Hunt noted in 1974 that prolonged success rates using nicotine chewing gum were unlikely to be greater than 8% or 9% (Hunt and Bospalec, 1974). Recent literature would tend to support these figures (Jarvis et al, 1982).

Education and group support has also had many enthusiasts, some of whom have reported 80% abstinence after 1 year's treatment. However, Hunt and Matarazzo (1973) suggested that where follow-up includes those who failed to complete the course of treatment, a one-year abstinence rate of between 14% and 17% represents a more likely outcome.

Hypnosis involves a one to one confrontation using deep relaxation and auto-suggestion. Details of the technique vary and again some of the results reported would appear to be quite outstanding. Miller (1975) reports success rates of 70% at 1 year. However, in general, results vary from 15% to 90% abstinence after 1 year's treatment. Perry (1979) found that aversion therapy on its own resulted in a success rate of 24% total abstinence at 6 months, hypnosis on its own 8% total abstinence at 6 months and both treatments combined resulted in 25% total abstinence at 6 months.

Schwartz (1979) reviewed the results of 67 smoking trials between 1969 and

1977. His monograph suggested that 40% of the studies claimed 35% abstinence, 20% claimed between 22% and 35% abstinence and 40% claimed below 22% abstinence. However, his critique of the literature in the late 70s was damning. Most trials did not describe their subjects or their method of entering and selecting the patients for the study. For instance, age and sex are important and Chen (1979) found that women were more difficult to cure than men. His work also showed that the younger age group who had been smoking for a shorter length of time appeared to be more responsive to treatment. Very few of the studies reported whether treatment was provided free or at a charge. Attanasio (1982) suggests that a payment for therapy is a powerful motivational factor and may have a significant influence on outcome.

The treatments provided in the studies reviewed by Schwartz were also confusing. In some studies the methodology was not clearly described. Sometimes just one treatment was given, and occasionally it appears that treatment was continued until the patient either dropped out from the study or ceased to smoke. The results of many of the smoking cessation studies were presented in a confusing manner. Some studies included those who dropped out as failures while others did not. In general, follow-up was poor and few studies followed up all their patients for 6 months. End points were also poorly defined; in some studies both smoking cessation and smoking reduction at the end of treatment were viewed as successful outcome while others used complete cessation to define the success or failure of treatment.

Ter Reit et al (1990) produced a generally negative review of the effect of acupuncture on smoking cessation. However, this must be seen against a background of the limited success of almost all treatments in promoting

smoking withdrawal. Perhaps it is relevant to ask whether it is worthwhile treating patients at all? Schwartz (1979) suggests quite clearly that some intervention is important. The current strength of the anti-smoking lobby and the clear indication that smoking is detrimental to health, in itself represents a powerful tool educating the public to perceive smoking as a damaging and undesirable habit. Even with such information very few addicts would give up smoking. It is therefore reasonable to argue that it is worthwhile treating this problem, but it is also reasonable to conclude that there is no ideal treatment. Furthermore, the treatments available all have limited success rates.

#### How does acupuncture work?

The detailed review of the physiological mechanisms of acupuncture (vide supra) makes it quite clear that acupuncture is mediated through the endogenous opioid system. Some researchers have suggested that when electro-acupuncture is used to aid withdrawal from hard drug addiction, there was a concomitant reduction in the addict's smoking habit (Omura 1975; Shakur and Smith, 1979). Although the relationship between the natural opioid system and smoking is unclear, it seems possible that the withdrawal symptoms experienced by smokers may at least in part be endorphin mediated. Consequently, a treatment that promotes the production and excretion of both endorphins and enkephalins should in theory have a clear clinical effect in aiding smoking withdrawal by artificially increasing the body's endogenous opiates. The link between smoking addiction and natural opiates is far from proven, however it represents an attractive hypothesis which certainly seems to fit the clinical observations of many acupuncturists. Patients receiving low frequency electro-acupuncture for smoking cessation will often become very

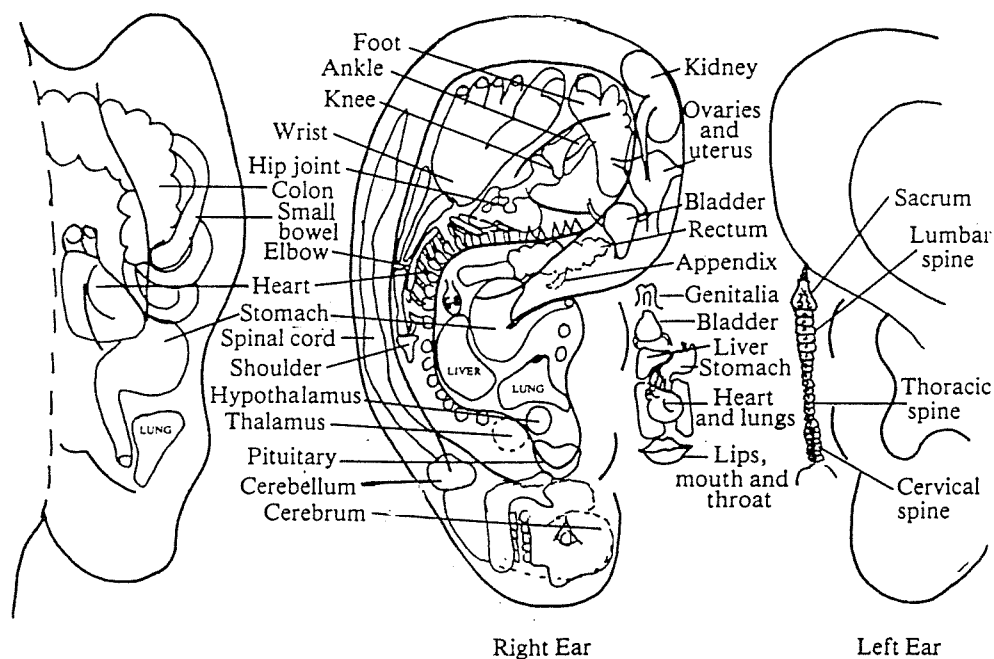
relaxed and frequently fall asleep. A similar effect is noted in those who receive electro-acupuncture for heroin addiction. Heroin addicts are known to have low CSF endorphin and serum enkephalin levels and it can be shown quite clearly that as electro-acupuncture artificially raises the levels of these natural opiates in the body, it also controls the symptoms of drug withdrawal (Sjolund et al, 1977; Rees 1981). It is therefore possible that a similarly mediated and opiate related addiction/withdrawal mechanism may be occurring in some smokers.

#### Methods of acupuncture treatment

Smoking withdrawal with acupuncture is a relatively recent development, it began to appear in the literature concerning acupuncture and smoking cessation about 30 years ago. The technique involved has nothing to do with traditional Chinese medicine. It involves inserting an acupuncture needle into the lung point on the ear (Fig. 11.1).

Figure 11.1

#### The somatotopic mapping of the ear



Nogier was the first to develop ear acupuncture and define the ear map (Nogier 1972). The somatotopic mapping of the ear was examined in a carefully controlled double blind study by Oleson et al (1980). Oleson et al used two standard methods for examining the ear, both examination methods had been defined previously by Nogier. The first is to gently probe the ear with a spring-loaded probe. A point that is said to be "diseased" will become substantially more tender than the surrounding ear tissue. The acupuncturist usually has a good general knowledge of the "ear map", and will therefore probe gently but firmly with the blunt spring-loaded probe over the area that is likely to be tender. The point that requires treatment is the most tender point and this is usually only a millimetre or so in diameter. The ear tender points also correlate very closely with decreased skin resistance.

The localised decrease in electrical resistance can be easily measured with an acupuncture point detector. This involves asking the patient to hold an electrode connected to a small resistance meter. It is usual for the resistance meter to emit an audio signal in order to reflect the skin resistance, and for the skin resistance to be measured with a blunt spring-loaded probe. If the blunt spring-loaded probe is passed over the diseased ear point, then a rapid decrease in electrical resistance will be noted (with an audio signal, this usually represents a marked increased in noise). Oleson et al (1980) used these two observations in order to redefine the ear map in their controlled trial of orthopaedic patients. These two approaches also represent the standard method of examining the ear in order to define the tender point for treatment.

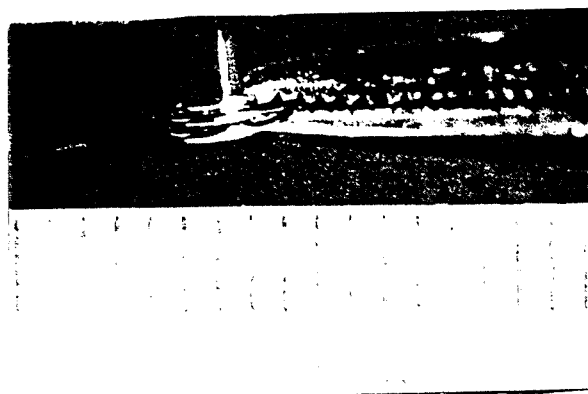
All smokers have abnormal lung ear acupuncture points. Consequently, the standard method of promoting smoking cessation has been to needle the lung



ear point and use a low frequency electrical stimulation (electro-acupuncture below 10 Hz) or to place a small semi-permanent needle into the ear. Semi-permanent needles look like tiny drawing pins and these can be placed into the lung ear point and covered over with a small plaster.

Figure 11.2

The type of stud used for ear acupuncture



A number of other acupuncture techniques have been used in order to promote smoking withdrawal. In some studies body acupuncture was used designed to promote sedation while in others, alternative ear points were suggested. However, it is quite clear from the available literature reviewed by Ter Reit et al (1990) that in the vast majority of studies the lung ear point was used as the mainstay of treatment. The use of semi-permanent needles in the lung ear point was also the commonest method of treatment.

#### Hypothesis

In this study, acupuncture was compared with group therapy as a method of smoking withdrawal. Group therapy was chosen as the comparative "conventional treatment" as the local Southampton Smoking Act for Health Group (SAHG) had already established an active programme of group therapy in order to aid smoking withdrawal. Those running the group therapy sessions claimed that 70% of their smokers had ceased smoking completely as

a result of specific group therapy techniques. The literature available on smoking cessation suggests that these psychological techniques are as good as any of the other available approaches for smoking addiction. As researchers we therefore had access to an active smoking programme and it was also fairly simple to learn and execute this particular technique within our own research clinics. This study therefore tested two hypotheses:

1. Acupuncture is more effective than group therapy in producing smoking cessation.
2. Acupuncture in the commonly used "lung point" is more effective than acupuncture in an inappropriate point on the ear, in producing smoking cessation.

## METHOD

Schwartz (1969) reviewed and evaluated many methods of smoking withdrawal. He suggested some general guidelines for the research which were followed in this particular study.

1. The inclusion of adequate control groups.
2. The necessity to follow up at least 95% of the patients entered into the study.
3. The importance of following patients up for at least 6 months after the completion of treatment in order to evaluate long-term outcome.
4. The inclusion of basic information on all subjects starting treatment. This information should include age, sex, the length of time each patient has been smoking and the number of cigarettes smoked by each patient entering the study.

The study model required was substantially different from that already discussed in the evaluation of painful conditions. Smoking cessation study can be constructed to have very clear end points; those entering the study have either ceased smoking during or after treatment, or they continue to smoke during or after treatment. While there is some debate about the best method for smoking withdrawal, it is uniformly accepted among acupuncturists that treating an active or diseased lung point on the ear is the most common approach used to manage this condition. Furthermore, the studies published on acupuncture and smoking cessation suggest quite clearly that if treatment has failed to work after 3 or 4 treatment sessions, it is unlikely to do so.

## Ethical approval and informed consent

Ethical approval for this study was obtained from the local ethics committee at Southampton General Hospital. As with the previous studies

on pain, patients were not told that an ineffective form of acupuncture was to be used to aid smoking cessation. The consent form stated clearly that:

"I understand I am taking part in a research project to assess the effect of group therapy or acupuncture as a treatment for smoking cessation. The study methods have been explained to me to my satisfaction. I realise that these treatments may not be effective, and I am prepared to accept a very small risk of ear infection if I receive acupuncture. I agree to be available throughout the 4 weeks of the trial in order to attend clinics and at 3 and 6 months after the trial for the purposes of follow-up. I accept that I am under no obligation to continue with treatment if I choose not to."

The only known adverse reaction to leaving a small semi-permanent needle in the ear for a week at a time is a small risk of ear infection. Although all those entering the trial had this risk explained to them, during the trial no patient suffered a localised ear infection at any time. Patient hand-outs were provided (Appendix 11.1 and 11.2).

#### Randomisation

The study group was randomised in the same manner as that described previously for the three studies involving painful conditions. Randomisation was dictated by a random computer programme, and the treatment defined by this programme was recorded on a sealed card and placed into an envelope. The investigator opened the envelope at the time of randomisation and then allocated the patients to their appropriate treatment group. This study involved three treatment groups:

- A. Patients who received acupuncture in the lung point.
- B. Patients receiving acupuncture in a sham point.

### C. Patients receiving group therapy.

It was intended that a comparison between groups A and B would test the second hypothesis and a comparison between groups A and C would test the first. It was intended that approximately 30 patients would be entered into each treatment group and all patients entered would be followed-up at 3 and 6 months.

Randomisation was stratified by sex so that the male/female ratio of the groups was evenly balanced.

### Referrals

Sixty-one patients were referred from Health Centres in Southampton. The trial was advertised in waiting rooms and explanatory leaflets were available in the surgery. Smokers were asked to inform their GP if they would like to join the trial, and in addition GPs at these Centres were told about the trial and asked to refer appropriate smokers.

Nineteen patients were self-referred, having heard about the trial from friends or relatives. Due to the staggered nature of treatments 8 of these self referrals joined the trial after a friend had received treatment.

Referrals were screened to exclude pregnant women; those on steroids or immuno-suppressives and those suffering from a chronic debilitating disease.

Patients were entered into the study if they smoked more than 50 cigarettes per week, they had smoked 5 years or more and they were over the age of 16.

### Introductory meeting

The referrals made appointments to attend an introductory meeting in groups of 15-20. At this meeting they were randomly allocated to group A, B or C. Males and females were randomised separately.

The smokers were then given an 'educational package' in the form of verbally presented information and a booklet - 'The Smokers' Guide to Non-Smoking'. This is produced by the Health Educational Council and represents standard information literature used in many anti-smoking treatments in the UK. A table of nicotine and tar contents was also provided.

A discussion about reasons for giving up smoking followed and the smokers were encouraged to analyse their reasons for smoking and question every cigarette they then smoked.

It was stressed that nothing could stop a smoker smoking unless he wanted to give up, but that the two forms of treatment, group therapy and acupuncture, could help.

A £5 deposit was collected from each subject. This was returned at the last attendance for treatment, regardless of smoking habits. A study by Paxton (1981) concluded that deposits which were only returned if the subject was abstinent affected initial success rates (though long term success rates were not affected).

#### Treatment

Treatment consisted of four once-weekly sessions. The number of acupuncture sessions as reported in the literature ranges from 1 - about 8. SASH suggested about 5 sessions for group therapy.

## Acupuncture

### Point-selection for ear acupuncture

The left ear was used initially in most subjects. Bilateral stimulation can be used, but it seems from the published studies that unilateral treatment is as effective as bilateral treatment in smoking withdrawal. As there is a minimal risk of local infection or tenderness at the needling site, it is a reasonable safety precaution to use only one ear and change to the other if any adverse reactions occur.

### Detection: Group A

As mentioned earlier, the lung point in smokers is tender and shows increased electrical conductivity. Other points near the lung point do not share these characteristics, unless underlying disease is present.

The lung point was found using the NOMA Super 4 electro-acupuncture stimulator. This machine is useful in auricular diagnosis as it is sensitive enough to detect the electrical properties of 'active' ear points. In all subjects the point was successfully found.

The relevant part of the NOMA consists of a wheatstone bridge and two leads. One lead is attached to a metal rod which the subject holds in his hand, and the other lead is connected to a spring loaded probe. The machine is switched on and the probe used to 'search' for the lung point on the ear. The circuit is designed so that an increase in current produces a high pitched noise, hence this is emitted when the probe is over an 'active' acupuncture point.

This method was used successfully to find the lung point in all of group A.

### Precautions

The ear was cleaned before point selection as sweat and grease increase conductivity. Conductivity of the circuit can also be increased by local

pressure on the skin: the spring loaded probe cushions any accidental pressure applied by the operator so that errors are not made.

#### Detection: Group B

The acupuncture point for group B was also chosen with the NOMA Super 4. However, in these subjects a site with no change of electrical resistance was found and pressure deliberately applied to produce the high pitched noise.

Subjects in both groups were told that emission of this noise indicated their active anti-smoking point had been found.

The probe was used to mark the selected point in both groups. A small stud was inserted and a drop of Fucidin Gel applied to minimise the chances of infection. A small square of Johnsons non-allergic waterproof adhesive tape was put over the stud to keep it in place. Subjects were told to stimulate the point by massaging the pin between their finger and thumb when they felt the desire to smoke.

The stud was removed at the following treatment session and the procedure outlined above repeated.

Each treatment lasted from five to ten minutes.

#### Group Therapy

The group met four times once a week for an hour. The aim of the sessions was to cover certain topics and to discuss the progress of each group member.

The plan for the four sessions was as follows:

- 1st To discuss and analyse why each member smoked, and to plan the following week.
- 2nd To discuss the previous week, each member to describe successful anti-smoking advice and the pitfalls he encountered.



- 3rd As for the second session, and also the benefits of stopping smoking.
- 4th To discuss the previous weeks and plan for maintaining withdrawal without group support.

#### Collection of Data

Data were collected by questionnaire (see Appendix 11.3 and 11.4). Baseline data were collected at the introductory meeting, this established smoking history and other facts which were thought to affect the outcome such as the number of years the patient had been smoking, how many cigarettes they smoked per week, whether they smoked low, middle or high tar cigarettes, whether they smoked a pipe and cigars as well as cigarettes and if so, how much tobacco this involved. Questions were also included about whether they shared accommodation with a person who smoked and whether they had had previous anti-smoking treatment. The follow-up questionnaires were filled in at the end of treatment, at 3 months after the completion of treatment and finally at 6 months after the completion of treatment. These questionnaires asked for information about what type and how many cigarettes had been smoked during the last week. It also ascertained information about whether the participants were smoking pipes and/or cigars. Data were collected at 3 and 6 months by the use of postal questionnaires with a stamped addressed envelope for reply (Appendix 11.5 and 11.6). Those who did not reply were then contacted either by phone or via a domiciliary visit.

#### Assessment of results

The questionnaires were completed by the subjects themselves. The baseline smoking habit was taken from the initial assessment form and the number of cigarettes smoked per week used as the basis upon which subsequent success was measured. The end point was total abstinence,

reduction in the amount smoked was not considered to be representing success.

Those who withdrew were asked to provide an explanation and to continue to fill in the questionnaire.

#### Data analysis

The end point was total abstinence. The number of individuals claiming total abstinence was then expressed as a percentage of the total number entered into the group. The results obtained immediately after treatment and at 3 and 6 months were then entered into the University's mainframe computer. At the design stage, a simple statistical analysis involving a  $\chi^2$  test was all that was intended. This simple test of statistical significance was to be executed at the 3 main assessments (at the end of treatment, 3 months and 6 months). The study was designed to show a 35% treatment difference with 80% power between groups A and C and A and B.

## RESULTS

### 1. Study Groups

Eighty-one subjects entered the trial. Sixty-one were referred from 4 Health Centres in Southampton and 20 were self-referred, having heard about the trial from friends or relatives.

These subjects were randomised into groups A, B and C. See Table 11.1.

Information about the patient's age, the number of years they had smoked and the number of cigarettes smoked per week was collected for each participant. The ranges and means for each group (males and females) are given in Table 11.2. There appeared to be no major differences between the three groups based on these entry criteria.

Eight subjects rolled their own cigarettes, 3 males in group A, 5 males in group B and 1 male in group C. 1 gram of tobacco was taken to represent 1 cigarette. One female smoked 100 cigars a week and was randomly allocated to group A. Those who only smoked a pipe were excluded. One patient in group A was a pipe smoker, who also smoked 10 cigarettes a day. He gave up his cigarettes but was still smoking his pipe at 6 months and was therefore considered to be a failure because he had not ceased smoking.

A number of other factors which might have some influence on outcome were also assessed. These included a history of previous anti-smoking treatment, cohabiting with someone who smoked more than 5 cigarettes a day, a history of knowing somebody who had stopped smoking with acupuncture and whether any of the individuals entered had a particular preference for the treatment they might receive (group therapy, hypnosis or acupuncture). Seven subjects had previously attempted to give up smoking, 4 using group therapy and 3 hypnosis. All these individuals were entered into our study and only 1 was abstinent at 6 months. The remaining 74 subjects had not

had previous anti-smoking treatment and 11 of these were abstinent at 6 months. The numbers are small, but the proportions of success and failure in each group is much the same. Therefore a history of previous anti-smoking treatment does not seem to have biased the results in any major way.

Thirty-seven of those entered into our study lived with a smoker and 5 were abstinent at the end of 6 months. Forty-four did not live with a smoker and 7 were abstinent at the end of 6 months. Again, numbers are small, but in the context of this study cohabiting with a smoker did not appear to affect outcome (Table 11.3). Twenty-four of the patients entered knew somebody who had successfully ceased smoking with the aid of acupuncture, 5 of these twenty-four were abstinent at 6 months. Of the 57 patients who were entered but did not know someone who had stopped smoking with acupuncture, only 7 were abstinent at 6 months (Table 11.4). Those who knew somebody who had given up smoking with acupuncture were allocated fairly evenly between each of the 3 groups, although all 5 who successfully ceased at the end of the study were in either group A or B. It is therefore possible (although not in any way statistically significant) that knowing somebody who had previously given up smoking with acupuncture, might increase the chance of success.

Acupuncture was the first choice of anti-smoking treatment in 90% of those entered into the study. Six per cent placed hypnosis first and 4% group therapy. This suggests that acupuncture is a highly acceptable form of therapy and at least in part may explain the very high drop-out rate in group C.

### Withdrawals

Table 11.5 shows the number of smokers in each group who did not attend the full course of treatment.

Six withdrew in groups A and B, 4 for domestic problems and 2 because they were admitted to hospital for an unrelated reason. In group C, 19 withdrew, 15 because they lacked interest in group therapy, 1 because they could not attend due to domestic problems and the remaining 3 for other unspecified reasons. The non-attenders in group C were all smoking at 6 months follow-up. The results in group C are therefore expressed as 2 groups, C and C1. C represents the success rate of the whole group including non-attenders. C1 represents the success rate of those attended at all sessions.

### The results of treatment

The end point for defining successful treatment was total abstinence from smoking. Smoking reduction was not considered as it has been shown that this is an inaccurate representation of the outcome as, unless abstinent a smoker who has reduced his smoking is likely to revert to earlier levels (Gilbey and Neumann, 1977). Results are expressed as percentages of all subjects allocated to groups immediately, 3 months and 6 months after treatment. Table 11.6 shows these results.

### Significance of the results

The results demonstrate the clear pattern shown in most studies designed to evaluate treatments for smoking cessation. Immediately after treatment, between one third and one quarter of the patients entered had ceased to smoke. However, this tailed off dramatically and at 6 months only a relatively small percentage of those entered had managed to remain abstinent.

There was no significant difference between group A (real acupuncture) and group B (sham acupuncture) at any stage in the study. There was no significant difference between groups A and C (group therapy) at any stage in the study. Therefore, the null hypothesis was valid in both instances. It would appear that acupuncture and group therapy are equally good (or bad) methods of smoking cessation. Furthermore, it would seem that the site of needle insertion, claimed by most acupuncturists to be of central importance, would appear, according to this study, to be largely irrelevant.

**TABLES FOR CHAPTER 11**

Table 11.1

The number of males and females randomly allocated to groups

Group	Males	Females	Total
A	13	15	28
B	11	16	27
C	11	15	26



**Table 11.2** Table comparing males and females in groups for age, no. of years smoking, and no. of cigarettes smoked per week.

Group	A			B			C		
	Male	Female	Total	Male	Female	Total	Male	Female	Total
Sex									
AGE	13	15	28	11	16	27	11	15	26
range =	21-50	19-62	19-62	25-59	27-61	25-61	28-67	26-65	26-67
mean =	36	36	36	38	39	38.5	42.5	40.5	41
No. of cigarettes per week									
n =	13	15	28	11	16	27	11	15	26
range =	50-350	70-280	50-350	50-280	120-280	50-280	100-315	80-320	80-320
mean =	176	172	174	137	179	162	172	155	162
No. of years smoking									
n =	13	15	28	11	16	27	11	15	26
range =	8-38	5-34	5-38	15-43	10-47	10-47	14-49	10-40	10-49
mean =	20	19	23	22	22	23.5	23.5	22	23

Table 11.3    **Those entering the study who lived with a smoker**

Live with smoker	Do not live with a smoker	n = 81
5	7	Abstinent at 6 months
32	37	Smoking at 6 months

Table 11.4    **Those entering the study who knew somebody who had given up smoking with acupuncture**

Knew someone	Did not know someone	n = 81
5	7	Abstinent at 6 months
19	50	Smoking at 6 months

**Table 11.5**      **No of patients withdrawing from the study by group**

Group	Male	Female	n	%
A (n = 28)	2	1	3	11
B (n = 27)	0	3	3	11
C (n = 26)	7	12	19	73

**Table 11.6**

Overall results at 0 (immediately post treatment), 3 and 6 months post-treatment.

Percentage of each group abstinent				
	A	B	C	C1
n = 100%	100% (28)	100% (27)	100% (26)	100% (7)
0 months	32% ( 9)	30% ( 8)	23% ( 6)	57% (4)
3 months	18% ( 5)	30% ( 8)	11% ( 3)	43% (3)
6 months	18% ( 5)	14.5% (4)	11% ( 3)	43% (3)

## DISCUSSION

### Study model

Smoking cessation with acupuncture is a relatively modern form of treatment. The treatment protocols accepted and effected by most acupuncturists are simple and therefore it is an easy treatment to investigate. Furthermore, the end points are clear and objective, not muddled and subjective as in the treatment of painful conditions. Therefore the study model is clear and concise. As the assumption among acupuncturists is that the use of the lung point represents a point specific effect it is therefore reasonable to suggest that this assumption should be tested. The results clearly indicate, when comparing groups A and B, that acupuncture is not a point specific effect. It may well be as Le Bars and others have suggested (*vide supra*) that the non specific effects of needle puncture may activate the natural opiate system and therefore mediated the physiological effects of smoking withdrawal in a non point specific manner.

The previous studies that have analysed auricular acupuncture in controlled situations suggest abstinence rates of between 5 and 25% at between 3 and 6 months after the cessation of treatment. Our study falls into this general range and therefore further validates the use of auricular acupuncture as a mechanism for smoking withdrawal. A 6 month abstinence rate of 18% complies very much with our expected result and is probably an accurate representation of the success of auricular acupuncture.

If we accept Ter Reit et al's (1990) rather depressing view of the effect of acupuncture on smoking withdrawal, it would be reasonable to suggest that it is not worthwhile providing any treatment. The success of this study is far greater than within the general population who find they can

"just give up smoking" on their own and without any help. Acupuncture is certainly a popular treatment, and for the vast majority of those entering the study it was their first choice of anti-smoking treatment. It could therefore be argued that the very act of giving patients treatment may allow them to focus on their addiction and take time to try and resolve the complex psychological, social and physiological aspects of nicotine addiction. It could even be argued that if educating the general public is the best way to stop them smoking, then perhaps the best way to educate smokers is to offer them acupuncture and then educate them while they receive treatment!

Acupuncture certainly was able to attract patients who wished to give up smoking, and could certainly produce results comparable with other anti smoking treatments at the end of 6 months. As we have clearly shown, the acupuncture was not point specific, but this does not necessarily mean that there was no physiological effect from random auricular needling.

A further question that needs asking is can one ever get a real control group when attempting smoking cessation treatments? Almost everyone in the United Kingdom is aware that smoking is bad for you. Consequently, the educational message about smoking is there for all to see. It is therefore difficult to know how you would construct a true placebo group if, as has been suggested, random needling is likely to be as physiologically effective as needling the correct point.

It is very simple to construct adequately controlled pharmacological studies using either nicotine gum or nicotine patches. It is therefore possible to tease out the difference between the effects of drug treatment from the general effects of treating a smoker who may wish to cease. However, with acupuncture it may be impossible to do this in the context of

a real versus sham acupuncture model. This is largely because the effects of using sham acupuncture in the treatment of addiction may be exactly equivalent to that of using real acupuncture; both may stimulate endorphins, thereby mediating the withdrawal process, although this hypothesis has yet to be properly validated.

It would be possible to use an acupuncture versus mock TNS model as one might assume that mock TNS was only eliciting a placebo response rather than a true physiological or pharmacological effect. The null hypothesis we aimed to test within this study was that there was no difference between real and sham acupuncture, and the results suggest that our null hypothesis is correct. Therefore, we can either conclude that acupuncture is having a purely placebo effect or that there is the same real physiological effect occurring in both groups A and B.

The available evidence suggests that acupuncture may be having as good an effect as any other method for promoting smoking withdrawal; perhaps all methods of smoking withdrawal are purely based on a placebo effect? It is important for us to understand the mechanism of acupuncture in smoking withdrawal and indeed in all addictions more completely. These investigations must centre around a better understanding of the endorphin and enkephalin mechanisms involved in the addiction process and also in the whole placebo response. Further studies might look at the use of real acupuncture compared with non-physiologically active placebos such as mock TNS.

Acupuncture was compared with group therapy because this was a convenient, accessible and successful treatment. It was available within Southampton and it was easy to learn the group therapy techniques suggested by SASH. The withdrawal rates from group C at first gave great cause for concern, as



it seemed this would invalidate the whole study. However, when those running the SASH group therapy sessions were questioned more closely, it became apparent that their drop-out rates were similar. Yet again it seems that their high success rate (initially claimed to be 70% of those entering) was a substantial misrepresentation. Many individuals wishing to give up smoking contacted SASH, and came for an initial group therapy session. However, approximately 60% of those coming for the initial group therapy session failed to go through the whole course of treatment. The results claimed by SASH (70% cessation at the end of treatment) compare very closely with our group C1. Here we noted approximately 60% cessation at the end of treatment with 43% cessation at 6 months. An excellent result and one which mirrors the experience of SASH very closely. Therefore, while the level of withdrawal was at first quite alarming, it became rapidly apparent that this was a well recognised problem for those running group therapy sessions. It was pleasing to know that we appeared to be managing the group therapy sessions correctly and were, as a result, able to obtain largely equivalent results to those using group therapy as their main form of treatment.

Smoking withdrawal is a complex process. Firstly, the smoker must want to stop. Though this is a personal decision, the environment, education and availability of anti-smoking therapies are all factors which might influence the outcome of this decision.

Our society is becoming increasingly anti-smoking. Non-smoking signs and health campaign posters are a common sight, the social status once associated with smoking has almost been reversed and the price of tobacco is increasing dramatically. It is well known and widely accepted that smoking is unhealthy. Even so, many people smoke in face of the facts.

For those who want to stop but cannot manage to do so alone, a specific anti-smoking treatment may help them at least for a while. Such a therapy should approach the problem from several angles, these should include education, practical advice, support, and a "treatment". Acupuncture, as this trial shows, is a highly acceptable method with good compliance and is also associated with clear enthusiasm among those entered for treatment. Patients who have relapsed since the completion of treatment have requested a further course of acupuncture. In addition, acupuncture is cheap, simple to administer, and has no side effects.

Many of the other methods of smoking withdrawal require a specialist such as a psychologist or hypnotist, whereas simple acupuncture can quickly be learnt and practiced by a GP or Practice Nurse.

Acupuncture for smoking cessation is usually offered to the general public on a private basis. Much of the high success rate claimed by complementary practitioners may be due to the selection of highly motivated smokers who, if they are willing to part with their money, will possibly find it easier to part with their habit! The results of this trial do not dispute the claim that acupuncture can aid smoking cessation, but it does question some of the more extravagant claims for the success of acupuncture when it is provided free to the general public, on a controlled basis as an alternative method for smoking withdrawal.

In summary, auricular acupuncture compares adequately with other methods in light of available data. It is not a 'cure' for smoking, but it could be a useful and important therapy in combating smoking.

**APPENDICES TO CHAPTER 11**

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## Appendix 11.1

There are lots of people who want to give up smoking, but it isn't easy. Lots of different methods have been used to help people stop, two of these are Group therapy and Acupuncture treatment.

Both of these treatments have been successful, and we want to find out just how successful.

We want to help you stop smoking.

There is very little commitment involved in joining this research project,

- five attendances at Aldermoor Health Centre,
- a few forms to fill in.

If you have been smoking fifteen or more cigarettes a day for at least five years - and you want to stop, and you are willing to join this research project, please read on .....

## Appendix 11.2

### WHAT THE TRIAL INVOLVES

The trial will take place at Aldermoor Health Centre. There will be an introductory meeting at the centre, when the details of the methods will be explained.

From your point of view you will be asked to attend the centre one evening a week for four weeks; during October/November/December 1981, at times that are convenient to you.

At these times you will either join a therapy group or receive a short acupuncture treatment - you will find out which at the introductory meeting.

The Acupuncture treatment will involve the stimulation of a certain "point" on the ear. This may help you to stop smoking. A tiny metal stud will be pressed into the skin at this point and secured with tape.

The Special therapy group involves group meetings and discussions one evening in the week.

### WHAT TO DO

Firstly tell your Doctor that you want to join the trial. Then contact the Aldermoor Health Centre and make an appointment to attend the following introductory meeting on:

FRIDAY 20th November 6 - 7 p.m.

The receptionist can be contacted at:

Southampton 783111 extension 40

Treatments will start on Monday November 23rd for those allotted to Group Therapy, and on other weekdays 6-8 pm for those receiving Acupuncture Therapy, (Nov. 24th - Dec. 17th).

The treatments are free, though we do ask for a £5 deposit.

Thank you for your interest, we look forward to seeing you, at the meeting.

**Appendix 11.3**

Anti Smoking trial. Oct/Nov/Dec 1981 : Aldermoor

**Questionnaire A**

To be completed by each participant before treatment starts and returned to Judy Gillams, Aldermoor Health Centre, Aldermoor.

Please leave boxes blank.

1 

P	M	8	1	0	2	A	L	D
---	---	---	---	---	---	---	---	---

Name: \_\_\_\_\_

Address: \_\_\_\_\_

Tel no: \_\_\_\_\_

Date of birth: \_\_\_\_\_

Sex: \_\_\_\_\_

(male = 1; female = 2)

10 

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16 

--	--

The following questions concern your trial card.

Trial number \_\_\_\_\_

Random no. \_\_\_\_\_

Treatment group: A/B/C (Please circle correct letter)

(A = 1, B = 2, C = 3)

18 

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24 

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26 

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29 

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Please answer the following questions.

1) At what age did you start smoking? \_\_\_\_\_

(no. of years of smoking)

2) How many cigarettes did you smoke last week?

(If for some reason this number is very different from the amount you usually smoke in one week, please state your "usual" amount. \_\_\_\_\_)

3) What brand, or brands of cigarettes do you smoke?

\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

(Low tar = 1, Low/M = 2, M = 3, High = 4)

31 

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33 

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36 

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#### Appendix 11.4

Questionnaire A : continued

38 

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Trial number \_\_\_\_\_

47 

--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--

- 4) If you also smoke a pipe .....  
How much do you smoke in one week?

55 

--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--

\_\_\_\_\_

(25 grammes is about one ounce, please give your answer in grammes).

- 5) If you also smoke cigars ...  
What sort of cigars do you smoke? \_\_\_\_\_  
How many cigars do you smoke in one week? \_\_\_\_\_

58 

--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--

- 6) Do you smoke  
a high tar cigarette \_\_\_\_\_  
a middle tar cigarette \_\_\_\_\_  
a middle/low tar cigarette \_\_\_\_\_  
a low tar cigarette \_\_\_\_\_  
don't know? \_\_\_\_\_

61 

--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--

(1 = ✓, 2 = X or don't know)

- 7) Do you share accommodation with a person who smokes more than 5 cigarettes a day?

63 

--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--

\_\_\_\_\_

(Yes = 1, No = 2)

- 8) Have you attended a clinic for anti smoking treatment before?

65 

--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--

Yes/No

(Yes = 1, No = 2)

If so..... What method of treatment was used?

\_\_\_\_\_

## Appendix 11.5

Anti Smoking trial. Oct/Nov/Dec 1981 Aldermoor

### Smoking Questionnaire

To be completed and handed in at each attendance for treatment, and at follow up. If found, please return to Judy Gillams, Aldermoor Health Centre, Aldermoor.

Please leave boxes blank.

1 P M 8 1 0 2 A L D

Name: \_\_\_\_\_

Address: \_\_\_\_\_  
\_\_\_\_\_

Trial number: \_\_\_\_\_

10   
16

This is the 1st/2nd/3rd/4th time that you have attended for treatment.

OR This is 3 month follow up \_\_\_\_\_

6 month follow up \_\_\_\_\_

(please indicate as necessary)

(1st = 1, 2nd = 2, 3rd = 3, 4th = 4

3 month = 5, 6 month = 6)

18 ☐

Please answer the following questions.....

1) How many cigarettes did you smoke yesterday? \_\_\_\_\_

20

2) How many cigarettes have you smoked in the last week? \_\_\_\_\_

22

3) Have you switched to a different brand of cigarettes? \_\_\_\_\_  
Yes/No

(Yes = 1, No = 2)

If so, which one(s) \_\_\_\_\_  
\_\_\_\_\_

25 ☐

(0 = no change in tar; 1 = change in tar)

(Low = 1, Low/M = 2, M = 3, High = 4)

27 ☐

If you also smoke a pipe ....

How much did you smoke last week? \_\_\_\_\_

(25 grammes is about one ounce, please give your answer in grammes).

(0 = no change, 1 = down, 2 = up)

29 ☐

If you also smoke cigars .....

How many cigars did you smoke last week? \_\_\_\_\_

(0 = no change, 1 = down, 2 = up)

34 ☐

36

39 ☐



**Appendix 11.6**

ANTI-SMOKING TRIAL.

ALDERMOOR

SMOKING QUESTIONNAIRE 2:

NAME: \_\_\_\_\_

RANDOM NUMBER: \_\_\_\_\_

DATE: \_\_\_\_\_

Please answer the following questions:

How did you find out about this trial?

Do you think that acupuncture will help you to give up smoking? YES/NO

Do you know of anyone who has been helped to stop smoking with acupuncture treatment?

There are three different anti-smoking treatments listed below, please put this in your order of preference. (1st, 2nd, 3rd)

Group therapy \_\_\_\_\_

Acupuncture \_\_\_\_\_

Hypnosis \_\_\_\_\_

In your own words, what do you expect your smoking habit will be like during treatment with acupuncture, after treatment with acupuncture, and in six months time after acupuncture?

**RAW DATA RELEVANT TO CHAPTER 11**

# **RAW DATA ON SMOKING STUDY**

No.	Sex	Treatment	Age	Age Began Smoking	Years Smoked	AT ENTRY No. of cigarettes last week	Usual number	Tar - High, Medium or Low	Pipe Cigar	Live With Smoker	Previous Treatment Y/N	End of Treatment	NUMBER SMOKED 3 mth follow up	6 mth follow up	Change or Comment
1	M	B	35	14	21	150	280	L	-	N	N	0	0	0	
2	F	C	45	18	27	160	160	H	-	Y	N	150	150	180	
3	F	C	47	17	30	100	100	L	-	Y	N	0	0	0	
4	F	A	34	16	18	210	210	M	-	Y	N	120	210	220	
5	M	B	21	13	8	160	160	L	-	N	N	45	120	350	
6	M	C	43	18	25	315	315	M	-	Y	N	250	235	-	
7	F	A	36	16	20	150	150	H	-	N	Y	0	0	0	
8	M	B	31	7	24	150	150	H	-	Y	N	30	250	-	
9	M	C	39	14	25	100	100	M	-	Y	N	80	70	90	
10	F	B	33	19	14	150	150	M	-	N	N	110	150	150	
11	F	C	36	16	20	80	80	L	-	Y	N	80	70	70	
12	M	C	35	32	3	150	150	M	-	Y	N	100	150	150	
13	F	B	28	18	10	280	280	M	-	Y	Y	220	230	220	
14	F	B	41	27	14	180	180	M	-	Y	N	50	140	-	
15	F	A	18	13	5	200	200	M	-	Y	N	40	-	-	
16	F	B	29	18	11	200	200	M	-	N	N	150	-	-	
17	F	C	31	17	14	140	140	M	-	Y	N	100	100	120	
18	F	A	31	16	15	280	280	H	-	N	N	140	160	210	
19	M	C	36	16	20	140	140	H	-	N	Y	250	-	-	
20	M	A	40	15	25	60	60	L	-	N	Y	0	0	0	
21	M	C	43	18	25	170	170	M	-	N	N	0	0	0	
22	M	A	41	20	21	210	210	M	-	N	Y	0	0	0	

No.	Sex	Treatment	Age	Age Began Smoking	Years Smoked	AT ENTRY		Tar - High, Medium or Low	Pipe Cigar	Live with Smoker	Previous Treatment Y/N	NUMBER SMOKED/WEEK			Change or Comment
						No. of cigarettes last week	Usual number					End of Treatment	3 mth follow up	6 mth follow up	
23	M	A	50	14	36	200	200	H	-	N	N	0	0	0	
24	M	B	38	15	23	105	105	L	-	Y	N	0	0	0	
25	F	A	26	16	10	70	70	M	-	N	N	0	0	0	
26	M	A	52	14	38	210	210	M	-	N	N	100	100	100	
27	F	C	65	20	45	140	140	H	-	Y	N	60	70	100	
28	M	C	44	14	30	250	250	M	-	Y	N	20	350	-	
29	F	B	32	17	15	130	130	H	-	N	N	0	0	0	
30	F	C	49	15	34	140	140	H	-	N	N	150	120	120	
31	F	B	61	13	48	210	210	M	-	N	N	0	0	200	
32	M	A	44	13	31	175	175	H	-	N	N	70	150	-	
33	M	C	28	14	14	140	140	M	-	Y	N	30	140	-	
34	F	C	26	12	14	105	105	L	-	Y	N	25	90	80	
35	F	B	39	14	25	160	160	M	-	N	N	160	120	100	
36	M	C	39	15	24	175	175	M	-	N	N	175	200	180	
37	M	C	33	13	20	140	140	M	-	Y	N	0	35	70	
38	F	B	40	14	26	150	150	M	-	Y	N	140	140	150	
39	M	B	42	27	15	250	250	H	-	N	N	4	140	-	
40	F	A	38	12	26	200	200	M	-	Y	N	40	50	130	
41	F	A	26	12	14	200	200	M	-	N	N	0	0	120	
42	M	A	36	15	21	100	100	M	-	Y	N	50	110	80	
43	F	A	33	17	16	140	140	L	-	Y	N	70	100	150	
44	M	C	49	21	28	140	140	M	-	N	N	0	-	-	
45	F	A	36	16	20	140	140	M	-	N	N	10	120	140	
46	F	C	53	33	20	100	100	L	-	Y	N	100	-	-	
47	F	C	43	17	26	250	250	M	-	Y	N	200	200	20	
48	M	A	28	15	13	200	200	H	-	Y	N	0	0	0	

No.	Sex	Treatment	Age	Age Began Smoking	Years Smoked	AT ENTRY		Tar - High Medium or Low	Pipe Cigar	Live With Smoker	Previous Treatment Y/N	NUMBER SMOKED/WEEK			Change or Comment
						No. of cigarettes last week	Usual number					End of Treatment	3 mth follow up	6 mth follow up	
49	F	A	57	20	37	100	100	M	-	Y	N	0	70	100	
50	F	A	36	15	21	280	280	M	-	Y	N	200	150	200	
51	F	C	55	19	36	15	80	L	-	N	N	30	100	100	
52	F	C	32	14	18	320	320	M	-	N	N	140	-	-	
53	F	B	42	15	27	200	200	M	-	Y	N	100	200	200	
54	M	B	28	12	16	150	150	H	-	N	N	0	0	0	
55	F	B	54	16	38	120	120	L	-	N	N	30	50	95	
56	F	A	48	14	34	130	130	L	-	Y	N	90	120	120	
57	F	A	42	14	28	-	-	H	100	N	N	90	100	100	
58	M	C	67	18	49	150	150	M	-	Y	N	20	35	-	
59	M	A	46	16	30	220	220	H	-	N	N	7	90	100	
60	M	B	36	11	25	100	100	H	-	N	N	0	0	70	
61	M	B	31	20	11	-	-	H	50	N	N	4	70	20	
62	F	B	52	11	41	140	140	M	-	Y	N	10	100	120	
63	F	B	32	17	15	260	260	M	-	Y	N	28	105	120	
64	M	A	24	14	10	200	200	H	-	Y	Y	80	120	200	
65	F	A	22	14	8	210	210	H	-	Y	N	140	175	200	
66	F	A	30	15	15	160	160	M	-	N	N	80	50	-	
67	M	B	59	16	43	70	70	M	-	N	N	0	20	-	Changed to pipe but still smoking
68	F	B	44	18	26	240	240	M	-	N	N	15	200	200	
69	F	C	29	16	13	180	180	M	-	N	N	160	180	200	
70	M	B	41	14	27	160	160	M	-	N	N	150	150	150	

No.	Sex	Treatment	Age	Age Began Smoking	Years Smoked	No. of cigarettes last week	AT ENTRY Usual number	Tar - High Medium or Low	Pipe Cigar	Live with Smoker	Previous Treatment Y/N	NUMBER SMOKED/WEEK End of Treatment	3 mth follow up	6 mth follow up	Change or Comment
71	F	C	25	16	9	140	140	M	-	Y	N	70	30	80	
72	M	A	31	15	16	280	280	M	-	N	N	0	100	150	
73	M	B	27	15	12	140	140	M	-	N	N	40	100	120	
74	F	C	54	14	40	280	280	M	-	N	N	280	260	280	
75	F	A	64	26	38	140	140	L	-	N	N	0	70	70	
76	M	A	43	15	28	350	350	M	-	Y	N	350	300	280	
77	M	A	44	18	26	60	80	M	-	Y	Y	0	0	0	
78	M	B	38	12	26	70	70	M	-	N	N	70	70	70	
79	F	C	34	13	21	120	120	M	-	N	N	0	60	80	
80	M	B	36	14	22	140	140	M	-	Y	N	0	0	0	
81	F	B	31	17	14	140	140	M	-	N	N	0	0	20	

## CHAPTER 12

### ACUPRESSURE FOR NAUSEA

#### Introduction

This chapter describes two studies in which acupressure has been used to treat nausea. In both studies, acupressure has been used at pericardium 6 (P6), a point frequently described as particularly useful in the management of both nausea and vomiting caused by a whole variety of different pathologies (Lewith and Lewith, 1979; An Outline of Chinese Acupuncture, 1975). Both studies were carried out by Fourth Year Medical Students and involved the use of Sea-Bands. These are small elasticated bracelets with plastic buttons inserted into them. These plastic buttons are placed over P6 and massaged in order to provide acupressure (see Figure 12.1).

The first study conducted under my supervision by Heather Price was in the field of medical oncology. Sea-Bands were evaluated on a single-blind cross-over basis in order to assess their ability in alleviating both nausea and vomiting in patients receiving chemotherapy. For the purposes of further discussion, this will be termed 'Study E'. This study was carried out within the Department of Medical Oncology at the University of Southampton with the cooperation of Dr. Chris Williams, Senior Lecturer in that department.

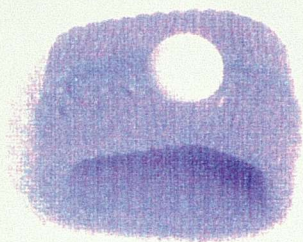
The second study looked at early morning sickness (EMS). The primary researcher here was Jane Bayreuther, a Fourth Year Medical Student. This study was of a double-blind cross-over nature and was carried out in a number of Southampton general practices. For the purposes of future discussion, this study will be termed 'Study F'.

The general case for the use of P6 acupuncture and acupressure as an anti-emetic has already been discussed, however it is important to place these concepts in context when considering chemotherapy induced nausea and EMS. Pericardium 6 or P6 is located 2 cun (Chinese inches) above the medial wrist crease between the radius and the ulna (Anon, 1975) (see Figure 12.1). It is the sixth point on the pericardium channel and is represented bilaterally.

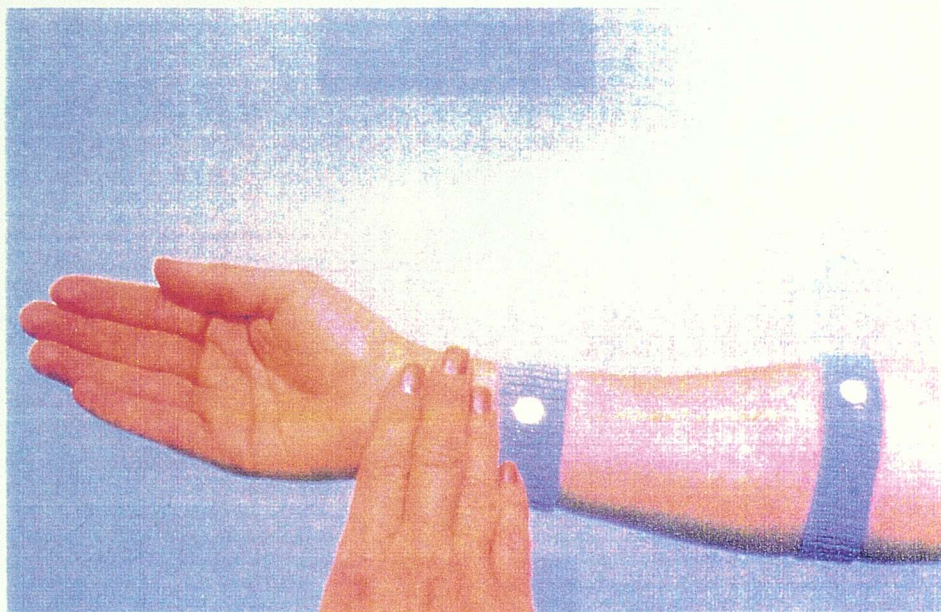


Figure 12.1

SEA-BANDS.



A SEA-BAND.



DEMONSTRATION OF THE P6 AND PLACEBO POSITION. USED IN  
THE TREATMENT OF E.M.S.

### CHEMOTHERAPEUTICALLY INDUCED NAUSEA

Nausea and vomiting are very common in cancer chemotherapy. Bonadonna and Valagussa have described it as being a potentially "fatal toxicity" in patients who stop treatment because of the side effects yet whose disease is highly responsive to chemotherapy (Bonadonna and Valagussa, 1981). Anti-emetic therapy is often ineffective when intensive chemotherapy is used. Until about 10 years ago very little research had been published which looked seriously at the nausea and vomiting following chemotherapy. However, over the last 10 years this situation has changed.

The frequency and severity of nausea and vomiting following chemotherapy has increased with the introduction of combination chemotherapy as there is often an additive effect. Furthermore, the use of drugs with high emetogenic potential such as cisplatin, has increased the incidence of chemotherapeutically induced nausea and vomiting. Many tumours sensitive to chemotherapy have steep dose-response curves, and so often need large doses of drugs. This in turn can produce toxic levels, which can lead to dose reductions, delayed treatment, or refusal of either potentially curative therapy or useful palliative treatment (Laszlo 1983).

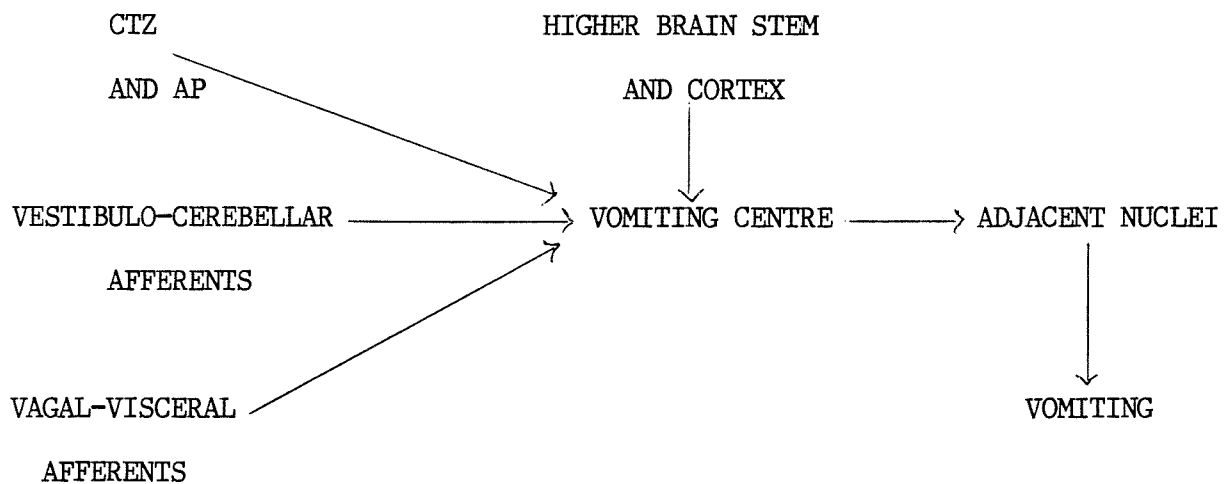
In 1988, when this research protocol was designed, the exact mechanism of chemotherapeutically induced nausea was poorly understood (Edwards, 1988). Vomiting occurs as the result of various coordinated activities in the medulla oblongata and the vomiting centre. The dorsolateral region of the reticular formation is the final common pathway. There are at least four different inputs:-

- (a) vestibulo-cerebellar afferent fibres
- (b) vagal-visceral afferent fibres

- (c) higher brain stem and cortex (psychogenic)
- (d) chemotactic trigger zone (CTZ) beneath the area postrema (AP) in the floor of the fourth ventricle.

Recent work carried out by Leslie and Reynolds (1992), based largely on animal experimentation in ferrets, identifies 5HT<sub>3</sub> receptors in the brain stem, at the terminus of the gastric vagal afferent fibres. Lower levels of 5HT<sub>3</sub> receptors are also found in the area postrema and the dorsal motor nucleus of the vagus. Antagonists acting at the 5HT receptors such as ondansetron are powerful anti-emetics (Leslie et al, 1990)

The main inputs are summarized below:-



These different components to the emetic pathway involve several neurotransmitters and so the most efficient anti-emetic regime might block different inputs into the pathway, rather than providing a universal anti-emetic by stopping the general expression of vomiting. Although recent research would suggest that blocking 5HT receptors is likely to have the greatest anti-emetic effect (Leslie and Reynolds, 1993). There is a delay between the emetic stimulus and response, which varies with the different

chemotherapy agents since they act in different ways. For example, it is thought that 5-fluorouracil stimulates the CTZ directly, whereas cis-platin probably acts via peripheral mechanisms.

The psychogenic factors involved in stimulating the cerebral cortex are manifested as anticipatory nausea and vomiting (ANV). The more severe the post-treatment nausea and vomiting, the more likely a patient is to develop ANV during subsequent treatment cycles. Several studies show that ANV develops with a gradual onset after several months of treatment, becoming more severe over time (Nerse et al, 1980; Morrow et al, 1982). Vomiting should therefore be prevented whenever possible to reduce the risk of ANV with future courses of chemotherapy. Precipitating factors include the odour or thought of the clinic, or taste-smell aversions to the drugs. The ANV often continues when patients return to the clinic for routine follow-up, which may not involve chemotherapy.

Post-treatment emesis generally begins within the first few hours after chemotherapy, peaking at around 4-10 hours and subsiding by 12-24 hours. However, emesis with cyclophosphamide often begins 12 or more hours after administration and cisplatin may cause vomiting for up to 7 days. Tolerance to chemotherapy develops with some prolonged continuous infusions (e.g. 5 days), but there is loss of tolerance between courses so there is a repeated pattern of nausea and vomiting at the start of each course.

There are therefore various emetic syndromes to be recognised in patients receiving chemotherapy, which need to be distinguished for good management:-

- (a) acute chemotherapy-induced emesis
- (b) anticipatory emesis
- (c) persistent or delayed emesis

(d) emesis not related to the chemotherapy received.

#### Pharmacological anti-emetics

Different chemotherapy agents and the combinations they are used in have varying emetogenic potential, and there are several anti-emetics which are used to reduce this with varying degrees of success. It is apparent from pharmacological studies that "no universal treatment has yet been found ..... many drugs are partially ineffective" (Dalzell, Bartlett & Lilleyman, 1986). The most commonly used anti-emetics work on the principle of antagonising specific receptors such as dopamine, 5HT histamine or acetylcholine. Some newer drugs have been introduced, used either as single agents or in combination regimens, and they are thought to work through other mechanisms. For example, cannabinoids may act on opioid receptors and inhibit the Vomiting Centre (VC), or they may stimulate the  $\mu$  receptors in the medullary reticular formation leading to enkephalin release (Edwards 1988).

Anti-emetic drug combinations are being used increasingly and by using more than one anti-emetic agent, it is hoped to reduce the total input of stimuli to the vomiting centre, which is the final common pathway in the initiation of the vomiting process. It should be possible also to attack several of the inputs to the vomiting centre. However, side effects occur with the use of most types of anti-emetics including drowsiness, depression and extrapyramidal effects. These effects are amplified with drug combinations. Also, some drugs, such as metoclopramide, have a short duration of action, and need to be given as a continuous infusion to provide effective antiemesis (Assaf, Dundee & Samuel, 1974). A recent study showed that the administration of domperidone and dexamethasone to patients 24 hours in advance of their receiving cancer chemotherapy is of

greater benefit than starting these drugs at the time of treatment (Williams et al, 1988).

The following anti-emetics were used in the chemotherapy department at the Royal South Hants Hospital (RSH) in 1988, during this study. They were used in various combinations, since the emetic potential of the chemotherapy influences the choice of the anti-emetic regimen:-

- metoclopramide
- domperidone
- lorazepam
- corticosteroids

#### Metoclopramide

This is similar to the phenothiazine group. It acts centrally by blocking the CTZ dopamine receptors. It is thought also to act peripherally as a "cholinergic stimulant" on gut motility and so is particularly useful in emesis associated with gastroduodenal, hepatic and biliary disease. A high dose is needed for the prevention of the nausea and vomiting associated with cytotoxic drug therapy. Its side effects are extrapyramidal, causing acute dystonic reactions particularly in children and young adults. Gralla et al found it to be most effective when given intravenously and in high doses, rather than when given orally in lower doses (Gralla, Itri & Pisko, 1981).

#### Domperidone

This acts at the CTZ, and is a "peripheral" dopamine receptor blocker. It does not cross the blood brain barrier, and so has a lower incidence of CNS side effects than metoclopramide. It is used more for the relief rather than prevention of nausea and vomiting associated with cytotoxic chemotherapy. Swann et al found it to be more active than metoclopramide



in controlling nausea and vomiting from chemotherapy (Swann et al, 1979).

#### Lorazepam

This is a short acting benzodiazepine, which when given in sufficient doses induces drowsiness or sleep (Maher 1981). It is usually used only for severe emesis on the day of treatment and can be combined with either of the above two drugs. Lorazepam seems to control some symptoms that have previously been refractory to standard anti-emetics, however poor recall of emesis (anterograde amnesia) may contribute to its therapeutic effect. The main side effect is dependence, and there may also be withdrawal problems.

#### Corticosteroids

Corticosteroids, such as dexamethasone, are sometimes used in severe emesis in combination with the above drugs. Their exact mechanism of action is unknown. Uncontrolled trials have shown control of vomiting in between 50% and 60% of patients.

#### Behavioural techniques

There are several behavioural techniques used to control nausea and vomiting and they seem to be successful for patients with an open minded approach. However they are time consuming both for the patient and the therapist (Warren 1988). Distraction and guided self imagery use techniques where the person blocks the negatively conditioned stimuli from the cerebral cortex and the body then responds physiologically to the pleasant image in the patient's thoughts. Other techniques include progressive muscle relaxation, slow stroke back massage, systemic desensitisation (particularly for ANV), and hypnosis (this is only to be used if the patient has positive beliefs and expectations in it).

#### Acupressure at P6 with the Sea-Band

The Sea-Band is an elasticated stretch bracelet, with a button, which when

worn correctly exerts pressure on Neiguan, an acupuncture point (also known as P6), without causing adverse effects on the circulation. Acupuncture points run along 14 different channels of the body, and Neiguan is situated on the pericardium channel. The Neiguan point is two cun (Chinese inches) from the ventral wrist crease, between the tendons of palmaris longus and flexor carpi radialis. A cun is equivalent to the distance between the creases of the proximal and distal interphalangeal joints of the flexed index finger. Two cun is approximately the width of three fingers (index, middle and ring), and this is used to find neiguan from the uppermost wrist crease. All measurements are made using the patient's own fingers.

The manufacturers of the Sea-Band (Sea-Band U.K. Ltd.) claim that it alleviates nausea through the technique of acupressure. Acupressure makes use of the system of acupuncture, by stimulating the same points with deep massage rather than needling. The Sea-Band can be used before and after the onset of nausea, and should be worn on both wrists continuously for maximum effect. Previous descriptive observation suggests it takes from two to five minutes to become effective and offers continual protection while worn (Sea-Band). Acupressure is not known to have any side effects. This, together with the recent publicity given to Sea-Bands for the prevention of sea-sickness makes them generally quite acceptable to patients.

The sickness associated with cancer chemotherapy was surveyed initially by Dundee (1988). In an unselected group of 71 consecutive patients, 76% complained of distressing emetic symptoms following their cancer chemotherapy, and of these 96% complained of further distressing sickness after subsequent chemotherapy. This compares with a more recent survey



involving 204 patients receiving chemotherapy (Dundee, Yang & Ghaly, 1990). Some degree of sickness was reported in 77% of the subjects and in 60% the sickness was severe and prolonged. In a study with 105 patients, who were sick following a previous course of cancer chemotherapy, P6 electroacupuncture was combined with the subsequent treatment. 67% had no sickness over a period of 8 hours, 29% had some alleviation of sickness and 4% had a poor response (Dundee 1988).

Two studies have been carried out evaluating the use of electroacupuncture at P6 in chemotherapy associated nausea and vomiting (Dundee et al, 1987a; Dundee et al, 1987b). In both studies all patients had suffered severe sickness on a previous occasion. The control in one study was a sham point near the right elbow (Dundee et al, 1987a), the other used P6 with no current (Dundee et al, 1987b). Both results showed there were significantly less chemotherapeutically induced nausea when electroacupuncture at P6 was used rather than a sham point. In both instances the sham acupuncture groups noted only a 30% response to sham acupuncture and real treatment a 60-65% response. Both studies conclude by saying that P6 acupuncture is time-consuming and invasive, and the anti-emetic effect of acupuncture is limited to 8 hours. It was suggested therefore that self-administered acupressure could be used instead.

A small trial has been published looking at the use of acupressure (Sea-Bands in chemotherapeutically induced nausea and vomiting (Stannard 1989). The result supported their use in chemotherapy, but the size of the trial (18 patients during 3 months) does not allow us to draw statistically valid conclusions. Each patient wore the bands in some courses but not in others. The outcome for the 2 groups was then compared. A record of progress was kept by both the patient and staff involving subjective

measures and there was also a diary for recording objective measures such as frequency of vomiting and the amount of drugs given. The results demonstrated that nausea was reduced, but rarely abolished. Vomiting was reduced by 75% in some patients. Anti-emetics were usually still needed, but in reduced amounts and could be taken orally. Some people tolerated oral fluids and less depression was reported.

While we understand a substantial amount about the mechanism of acupuncture in the relief of chronic pain, its mechanism in the relief of nausea and vomiting is unclear. It is possible that acupuncture and acupressure may be operated through an endorphin-mediated mechanism in order to trigger this effect. Equally, it may be that subtle changes in the neurotransmitters and/or the autonomic nervous system produced by acupuncture may be having a central effect on the vomiting centre. In spite of the fact that the mechanism remains unclear we know acupuncture and acupressure to be safe in this context. No adverse reactions have been reported. It therefore seems perfectly reasonable to investigate this therapeutic effect in a more careful and controlled manner.

The aim of this study was to assess by means of a single blind cross-over model, if acupressure by the Sea-Band on P6 point (real acupressure) versus acupressure on a non-active ankle point (sham acupressure) reduces nausea and vomiting in patients receiving cancer chemotherapy at the RSH.

### EARLY MORNING SICKNESS

Early morning sickness (EMS) affects at least 75% of pregnant women. Typically it occurs six weeks after the first missed period and continues for six to twelve weeks (Handbook of Obstetrics & Gynaecology, 1971; Williams Obstetrics, 17th Ed). Symptoms may be very mild causing little or no disruption to the woman's life or they may lead to hyperemesis gravidarum which requires immediate hospitalisation and intravenous feeding (Midwinter 1971; Maternity Care, 1977; Jarnfelt-Samsioe et al, 1983; Alley 1984; Vellacot et al, 1988).

There are many pathological causes of vomiting in pregnancy which include: pre-eclampsia, hydatidiform mole and hydramnios. In spite of this there is often there is no obvious cause for EMS and despite extensive research, the precise aetiology of EMS is still poorly understood. It is however accepted that vomiting is more common in first and twin pregnancies. Possible physiological causes include: metabolic and hormonal changes, especially an increased level of human chorionic gonadotrophin (Dilorio, 1988) and gastrointestinal disorders such as gastro oesophageal reflux. Though the mean intragastric pressure is unaltered in pregnancy, the mean lower oesophageal pressure is said to be reduced (Bainbridge et al, 1984). Vomiting is believed to occur more frequently in the morning due to alterations in the carbohydrate metabolism, especially poor glycogen storage (Bourne 1972).

Psychological causes of EMS have also been suggested. There is an increased risk of experiencing both nausea and vomiting, rather than just nausea, and for the symptoms to continue into the third trimester of pregnancy, in unplanned and unwanted pregnancies and in women who had an

unhappy relationship with their own mother (Fitzgerald 1984). EMS is also said to be increased in tense women (Masson, Anthony & Chau, 1985; Samsioe et al, 1986; Jarnfelt-Samsioe 1987). An American study reported a decreased risk of nausea and vomiting in caucasian professionals who enjoyed alcohol prior to conception (Weigel & Weigel, 1988) and in women over thirty five who had experienced infertility for at least two years prior to conception.

A variety of remedies have been sought; the preferred therapies are avoiding fatty foods, while consuming frequent, small quantities of carbohydrates (Hyde 1989). Others include hibernotherapy, ginger, intravenous honey and infusion of the father's testosterone! There are no randomised controlled studies to support the value of these approaches.

#### Drugs in Pregnancy

In the past numerous antiemetics have been used in the treatment of EMS. All drugs are known to have side-effects but initially effects on an unborn fetus were not considered (Hays 1983; McCredie et al, 1984; Elbourne 1985). Drugs were not tested on pregnant women. Even now that we are aware of the possible teratogenic effects of drugs, specific effects are often difficult to prove (Leathem 1986). The congenital limb defects caused by Thalidomide in 1956 (Dilorio 1988) are well documented and have made women, doctors and the drug companies very wary of the use of any drugs in early pregnancy. Therefore, drugs are not normally prescribed for EMS unless the sickness is such that the woman's daily life is severely disrupted. Phenobarbitone, hyoscine, pyridoxine, antihistamines, debendox and phenothiazines have been the drugs normally prescribed, when indicated. They were viewed as safe for many years, but as recently as the 1980's a query was raised over debendox. Some studies have suggested

that continued use of debendox may increase the risk of cleft palates and some limb malformations (Aselton et al, 1984) although recent evidence suggests that this may have been based on false data.

Pregnant women are unwilling to test drugs and so it now seems unlikely that the nausea and vomiting of early pregnancy will ever be fully treatable with conventional pharmacological agents.

The teratogenic effects are caused by drugs result from the drugs crossing from the mother's circulation into the baby's blood. This occurs more readily in early pregnancy when maternal blood nourishes the embryo through a lacunar network. It is only by the twelfth week of pregnancy that the separate fetal and maternal portions of the placenta are recognisable and act as a protective barrier against many substances, including drugs, crossing from the maternal to the fetal circulation. Trials have been carried out using women undergoing abortion to monitor the rate of transfer of drugs from the maternal to the fetal circulation. In the case of benzodiazepine derivatives this has been shown to be very rapid (Jorgensen et al, 1988).

It is not just antiemetic drugs which have been known to cause problems in pregnancy, even aspirin doubles the risk of truncus arteriosus deformities (Zierler & Rothman, 1985). A study of Finnish nurses revealed that occupational exposure to antineoplastic drugs during the first trimester of pregnancy is related to an increase in miscarriages (Selevan et al, 1985). Therefore, a side-effect free treatment such as acupuncture seems very attractive, particularly if it can be self-administered (acupressure) and is of proven effectiveness.

#### Acupuncture Trials

Acupuncture has been used by the Chinese for centuries as a cure for all

ailments (Dilorio 1988). As the Chinese have begun to use Western medical techniques, people in the West are beginning to realise the possible uses of acupuncture. Acupuncture is used for many complaints: smoking, obesity, insomnia, anaesthesia and enuresis (Richardson & Vincent, 1986; Fung, Chow & So, 1986; Jobst et al, 1986). Most controlled clinical trials have concentrated on the role of acupuncture in the treatment of pain, emesis and addiction.

There has been much debate about the best clinical trial methodology for evaluating acupuncture. In this study it was decided to utilise a sham versus real acupuncture model. The patients must believe that each treatment will be equally effective to prevent negative bias towards the placebo and positive bias towards the true treatment. Any treatment which a patient believes to be effective will have a greater therapeutic effect. Vincent has used a rating to ensure the credibility of placebos (Vincent 1990) and this study design allows for the evaluation of the credibility of sham acupressure.

Crossover trials are more desirable than parallel groups trials for treatments of pain and nausea as they are both subjective complaints with patients acting as their own controls (Vincent & Richardson, 1986). We chose to use a crossover model as the duration of action of acupressure is so short that there were likely to be very few carry-over effects between each arm of the study.

In China acupuncture has been used to treat morning sickness for thousands of years. As with most traditional Chinese medicine the precise treatment depends upon the individual problem. Morning sickness is divided into three broad categories: stomach deficiency, liver heat or stagnancy of phlegm. Numerous different points are used in each condition, though the

principal points are: P6 (Neiguan), Ren12 (Zhongwan), St36 (Zusanli) and Sp4 (Gongsun) (Outline of Chinese Acupuncture, 1975). Chinese research has suggested this treatment is effective, and this conclusion was supported by a report from Chagxin (Chagxin 1988). In a study of 39 pregnant women, Rongjun found acupuncture to be "effective" in 38 cases, there was no record of the duration of action, or how the effectiveness was measured. The acupuncture was administered twice daily for 30-40 minutes each time. There were no control groups, nor any measure of nausea levels in the untreated group (Rongjun 1987).

The Chinese used acupressure at P6. This was more convenient for people who wish to continue with their normal daily routine, rather than taking time away from home or work for twenty minutes' acupuncture. Acupressure relies on the same points as acupuncture, although it is less exact and possibly less effective, it maintains some therapeutic effect over a more prolonged period (Dundee & McMillan, 1991).

Recent studies of the efficacy of acupressure in the treatment of morning sickness have highlighted the need for further trials. A non placebo controlled cross-over trial (Hyde 1989) suggested favourable results: acupressure reduced the morning sickness in twelve out of sixteen women. The women received five days of acupressure at P6 and five days of no treatment in random order. The women chose how long they wore the acupressure bands during the five day period. Nausea levels were recorded using a five point Likert scale at the end of each five day period. Suggestions for further trials included involving greater numbers of patients and including women from varying socioeconomic settings. There was a drop-out rate of 27% in Hyde's study.

Dundee's parallel group study in 1989 again suggested this approach was

effective in controlling EMS. It involved three groups of women. There was a control group who received no acupuncture, a group receiving acupressure at P6 and a group having placebo acupressure near the elbow. Approximately 120 people were entered into each group but many dropped out of the study, 50% of the treatment and placebo groups and 30% of the control group failed to complete the protocol. Symptoms were recorded over four days. Nausea was reduced in both the acupuncture and placebo group when compared with the control group. True acupuncture showed a greater effect than the placebo acupuncture. However, the group receiving P6 acupuncture were all a week further in their pregnancy when their EMS may have been decreasing naturally (Dundee et al, 1988). The difference in drop-out rate between the treatment and control groups is an area of great concern.

The aim of this study was to conduct a randomised double blind controlled cross-over trial to see if acupressure at P6 is a better treatment for EMS than acupressure at a placebo position. It was also intended to assess the credibility of the placebo basing the method on the one used by Borkovec and Nau (1972).



## METHOD

### Introduction

The methodology of both these studies involved a cross-over model. Study E involved a cross-over at each cycle of chemotherapy, i.e. with a 3 or 4 week interval. The point was selected in random order, varying between a real (P6) and sham (ankle) point. The primary investigator was aware of which point was being used, but the patients were not aware as to which point was likely to be effective. This study was therefore a single blind cross-over one. The second study, F, involved both patient and investigator being blind as to the nature and order of treatment. Whereas in Study E the investigator instructed each patient on how to use the Sea-Band at each chemotherapy cycle, in Study F the investigator gave both real and sham acupressure instructions simultaneously. These instructions were supported by a clearly written hand-out (see Appendix 12.1 and 12.2) and therefore Study F could be considered to be a double-blind cross-over study.

### Ethical approval

As with the previous studies involving the use of acupuncture in painful conditions, patients were asked to consent to acupressure being used at one of two sites on the body. In Study E, real acupressure at P6 was compared with ankle acupressure, in Study F, real acupressure at P6 was compared with acupressure initially just above and subsequently just below the elbow. It was suggested to patients that neither of these positions may be effective, and that their approval to enter the study was based on that premise. In Study E it was made quite clear to the patients that drugs would be used to control their nausea and vomiting and one of the outcome variables used to assess the efficacy of acupressure would be the amount of

anti-emetic therapy required. Similarly, in Study F, patients were assured that both points might or might not prove to be effective, and that acupressure could not in any way be harmful to the progress of their pregnancy. Patients were told that they could withdraw from the study at any time and that the primary investigator would make herself available to answer any queries. Both studies received approval from the local ethics committee. The Appendix contains the relevant patient hand-outs and consent forms. (Appendix 12.3 and 12.4)

### Randomisation

In both studies randomisation involved the same procedure. A random computer programme generated by the Medical Statistics Department at Southampton General Hospital was used. In Study E the patients were stratified into 4 groups, the reasons for this will be explained in the detailed study method. Within these 4 groups randomisation was then based on treatment order: those receiving sham acupressure are denoted by ankle (A) and those receiving real acupressure are denoted by wrist (W). In Study F, the patients were randomised into 2 groups: group 1 was to receive acupressure at P6 first and then subsequently sham acupressure. Group 2 was to receive sham acupressure first and then subsequently real acupressure.

In Study E the treatment order was written on a small card and placed in sealed envelopes. After entry into the study, the sealed envelopes were opened and treatment began. In Study F instructions denoting the Sea-Band placement and "order of treatment" were given to the patients in sealed envelopes.

### Statistical analysis

After discussion with a biostatistician, an estimate of the number of

patients required for both studies was ascertained. In Study E, the statistician was Dr. Michael Campbell and in Study F the statistician was Dr. Ruth Pickering, both from the Department of Medical Statistics at the University of Southampton Medical School. In both studies it was decided to assume a treatment difference of 30% between real and placebo acupuncture. Consequently, in order to obtain statistical significance at the 0.05 level, with an 80% power, 53 pairs of results were required. In Study F, similar calculations were made and the study was designed so that 60 patients would enter and complete the study.

#### The cross-over model

Study E involved using acupuncture in 2 consecutive cycles of chemotherapy. Chemotherapeutically induced nausea is produced solely by the administration of cytotoxic agents. As the two cycles of chemotherapy would be at least 3 weeks apart, it was felt that there would be little chance of a carry-over effect between one treatment and another. The evidence available from previous studies on acupuncture suggests the duration of action of this particular technique is fairly short lived, at the most 24 hours. A three week gap between treatments was therefore felt to be a more than adequate "wash-out period". Using a cross-over model minimised inter-patient variation and allowed a more significant statistical result to be obtained while involving fewer patients in the study.

Study F involved the patients wearing the Sea-Bands at one position for 7 days, a 2-day wash-out period and then using the second treatment position for a further 7 days. Again on the basis of previously available information, it was felt that the 2-day wash-out period was more than adequate to allow for any carry-over effect between the first and second

treatment regimes. However, in this study, non parametric analysis was carried out on the final data in order to exclude the presence of any carry-over effect from the first to the second treatment period.

### CHEMOTHERAPEUTICALLY INDUCED NAUSEA: DETAILED METHODOLOGY

Patients were entered into this study from the Department of Oncology at the Royal South Hants Hospital. All patients entered received standard pharmacological anti-emetics as required throughout the study. These were usually a combination of domperidone, metoclopramide, lorazepam and steroids, and they were all available in their standard dose.

When randomising the chemotherapy patients to treatment groups, two stratification variables had to be taken into consideration. The first of these was whether or not the patient has had previous chemotherapy, in order to allow for anticipatory nausea and vomiting (ANV). The second variable was the potential emetic intensity of the chemotherapy agents used. Below is a list of the common drugs used, and they have been categorised as having a high incidence of emesis (Dundee et al, 1986) or a low incidence of emesis (Dundee et al, 1988).

#### Emesis incidence of chemotherapy agents used

(Gralla et al, 1984)

Cisplatin	1
Dacarbazine	1
Carmustine	1
Lomustine	1
Doxorubicin (adriamycin)	1
Cyclophosphamide	2
Procarbazine	2
Mitomycin	2
Cytarabine	2
Etoposide	2
Methotrexate	2
5-Fluorouracil	2
Vinblastine	2
Bleomycin	2
Chlorambucil	2

1 = high incidence emesis

2 = low incidence emesis

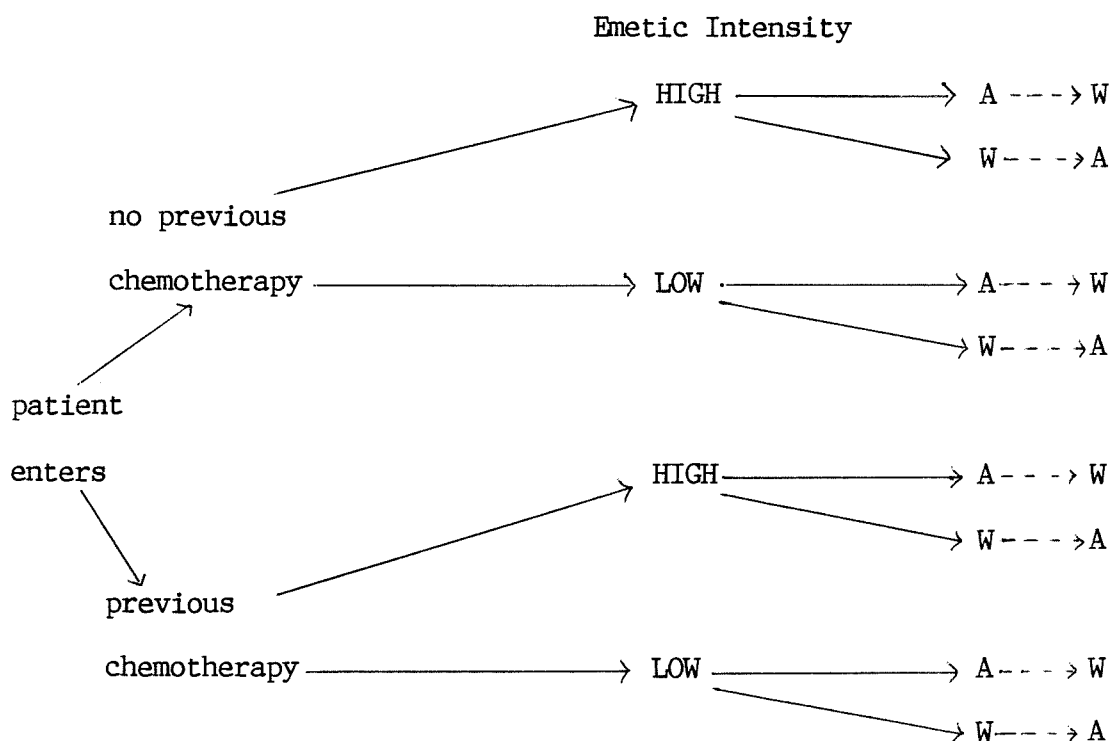
Since chemotherapy agents are often used in combination, there were

mixtures of drugs with differing levels of emesis incidence. For the purpose of this study, combinations containing both high and low incidence emetic agents were placed in the high emesis incidence group. When there were treatment regimens with two different combinations alternating, the same combination was used for each arm of the study, so that the potential emetic intensity of chemotherapy was identical each time.

The randomisation scheme is summarized in Figure 12.1.

**Figure 12.2**

**Randomisation procedure**



**Exclusion criteria**

Patients eligible to enter the study were those receiving cytotoxic chemotherapy at the RSH Hospital.

There were some exclusions:-

- known intracranial metastases
- bowel obstruction
- metabolic problems
- simultaneous radiotherapy

Some physical factors excluded participation in this group:-

- lymphoedema of arms in patients with breast cancer
- ankle swelling associated with cardiovascular problems
- leg ulcers associated with varicose veins

The nature of the study was explained to eligible subjects verbally, and those willing to participate were given information sheets and asked to sign the consent form (Appendix 12.3). Only after the consent form had been signed did the investigator look up the randomisation scheme to see which order this particular patient was going to receive the wrist and ankle acupressure.

At this stage the patient's G.P. was contacted by letter (Appendix 12.5) explaining that his/her patient was involved in this study. Any consultants involved in caring for this patient were also contacted.

#### Administration of treatment

Once the patient had been accepted into this study and the order of the treatments confirmed, the patient was given a pair of Sea-Bands to wear continuously either on both wrists or both ankles for 7 days. Some patients found a normal sized Sea-Band too tight at the ankle, so the company Sea-Bank U.K. made some larger bands. The correct positioning of the bands was shown to the patients, and the need to wear both bands continuously was emphasised.

The Sea-Bands were put on just prior to the start of the administration of

the chemotherapy course. The patient was asked to apply additional pressure for approximately one minute to the ankle or wrist points once every hour he/she was awake during the first 24 hours, and subsequently whenever he/she felt sick during the next 6 days. In order to encourage patient compliance and the recording of symptoms on the diary card the investigator telephoned some patients at home if it was felt necessary. In the next chemotherapy course the patient wore the bands at the other site, applying pressure as before at the new pressure point.

When P6 was being used for patients having an IV infusion, the nurses administering chemotherapy were asked to position the IV needle above this area, preferably in the ante-cubital fossa. If this was not possible and it had to be placed in the back of the hand, the Sea-Band on that side could not be worn until immediately after chemotherapy administration. However it was still possible for the patient to press the P6 point himself.

#### Outcome measures

All patients were given a diary card on which to record their symptoms of sickness, nausea, mood, anxiety and overall condition at the end of each day for the 7 days of wearing the bands. These diary cards had been previously validated and used in a number of studies to assess the well-being of patients during chemotherapy (Williams et al, 1988) (Appendix 12.6). They were asked to bring their card at the next visit and were given another card to fill in for wearing the band at the other site. After wearing the bands at both points they were asked to fill in a short questionnaire comparing the two points (Appendix 12.7). They returned this and the second diary card either by post, or at their next appointment.



These diary cards along with the extent of anti-emetic therapy required were then used to evaluate treatment differences between the 2 groups.

### EARLY MORNING SICKNESS: DETAILED METHODOLOGY

Having obtained approval from the Ethics Committee, 12 G.Ps were contacted by post to see how many practices would be willing to help in the recruitment of patients. Large general practices were selected with the advice of doctors at Aldermoor Health Centre. Practices from most areas of Southampton were approached to try and attract women from all social groups. Midwives and doctors at the Princess Anne Hospital were also approached but none felt they would be able to help, as they saw women after 18 weeks' gestation.

Five practices agreed to help. The number of women likely to present in the early stages within three months was discussed with the doctors. Seventy-five women were expected to present to their doctors during the study period. Allowing for 25% not to experience any nausea, for women outside the age limit and for those unwilling to participate in the study, sixty women were expected to participate. As time progressed and insufficient patients had been entered into the study, six more distant practices agreed to help.

#### Exclusion criteria

The age limits were set at 18-35 to exclude young mothers who may have been unreliable and unwilling to make their pregnancy well known, and older women who are more likely to experience complications of pregnancy.

The women were to be in the first 16 weeks of pregnancy and experiencing EMS. EMS most commonly occurs in the first 18 weeks of pregnancy, recruiting women up to the 16th week of pregnancy allowed for the two week treatment period.

#### Treatment

The women were to wear the Sea-Bands either at P6, or a placebo position,

continuously for 7 days and then to have 2 days' wash-out before commencing the second treatment. A wash-out period of 2 days was considered adequate; acupressure must be administered continuously as it is believed that the effects only last a few hours. A placebo position above the elbow position was initially chosen, for its convenience and acceptability to young women in the early stages of pregnancy and its lack of any known therapeutic action. After the first few results it was realised that this position was too uncomfortable, as even the extra large bands were too small for many of the women and so a different placebo position, just below the elbow, was selected.

#### Recruitment of patients

G.Ps distributed introductory leaflets to eligible women (Appendix 12.8). The leaflet explained that there was a project in the use of Sea-Bands in the treatment of morning sickness. There was a detachable section at the end of the leaflet for women who were interested in the study to fill in their name, address and telephone number.

As the women returned these leaflets to the receptionists the names were collected and the women were contacted by telephone to arrange a convenient meeting time, usually at the woman's home, to explain the study in further detail.

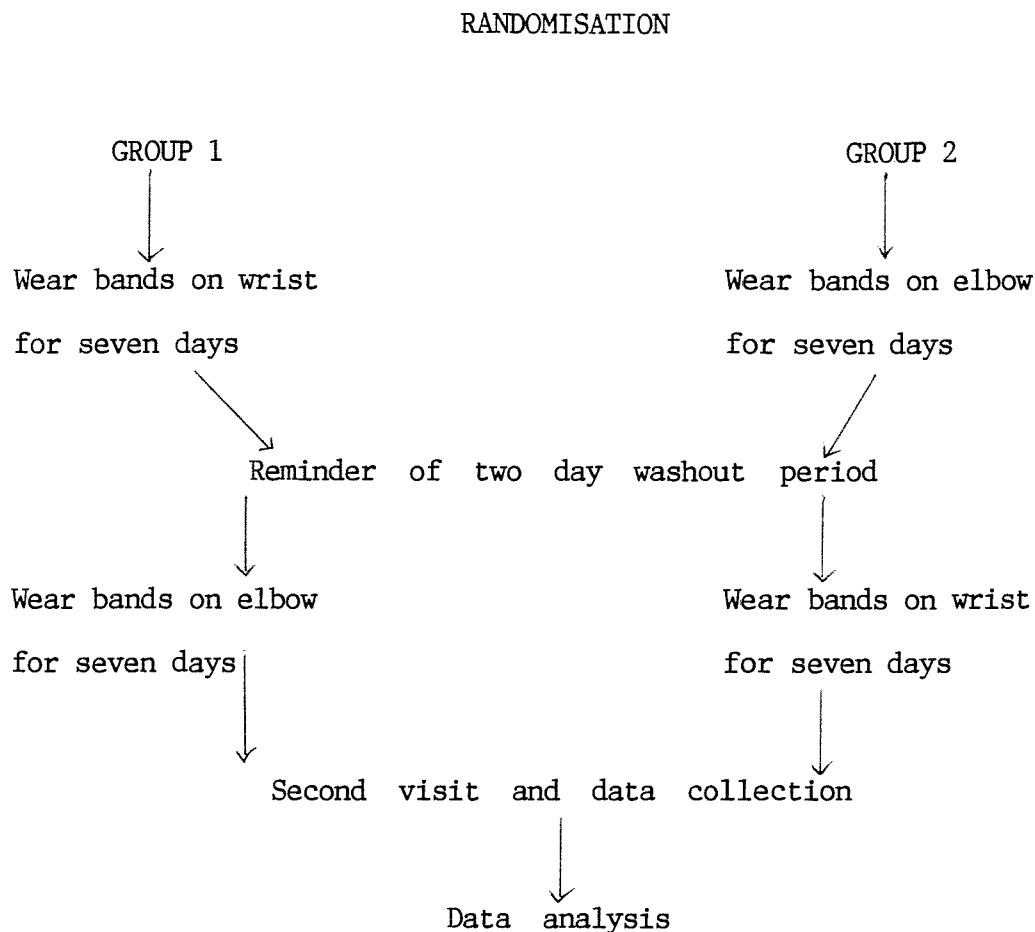
At this meeting the women were asked to sign a consent form (Appendix 12.4) before the questionnaire was administered, the women were asked questions regarding their age, marital status, parity, gestation and any previous knowledge of Sea-Bands and the interviewer then rated this on a scale of 1-3 (1 no previous knowledge, 2 heard of, 3 previously used or insight into mechanism of action) (Appendix 12.9).

The women were shown how to wear the Sea-Bands in both positions and

provided with the randomisation envelope which contained detailed written instructions. It was explained that the study was to see which was the more effective of two acupressure points in treating the nausea and vomiting of early pregnancy. The women were told that acupressure had previously been used with safety and success for this condition. The women were shown how to complete the visual analogue cards and the second questionnaire. They were given the opportunity to ask any questions and a telephone number in case they thought of any questions, or had any problems.

After seven days the women were sent a postcard or telephoned to remind them to stop wearing the Sea-Bands for two days and then to start wearing them in the second position. The Sea-Bands and completed forms were collected from the women at the end of the study. This provided a useful opportunity to check that the forms were completed correctly, and to discover any problems which the women may have had (see Figure 12.4).

**Figure 12.3** Treatment protocol



**Assessment of response**

The women were asked to complete daily visual analogue cards (Appendix 12.10) to assess their nausea. The lines were each of 10 cm and the value for each day was measured by a blinded assessor, to the nearest millimetre. They were also asked to state how many times they vomited each day. At the end of the trial they were asked to complete a second questionnaire (Appendix 12.11), in which they were asked whether they felt that the

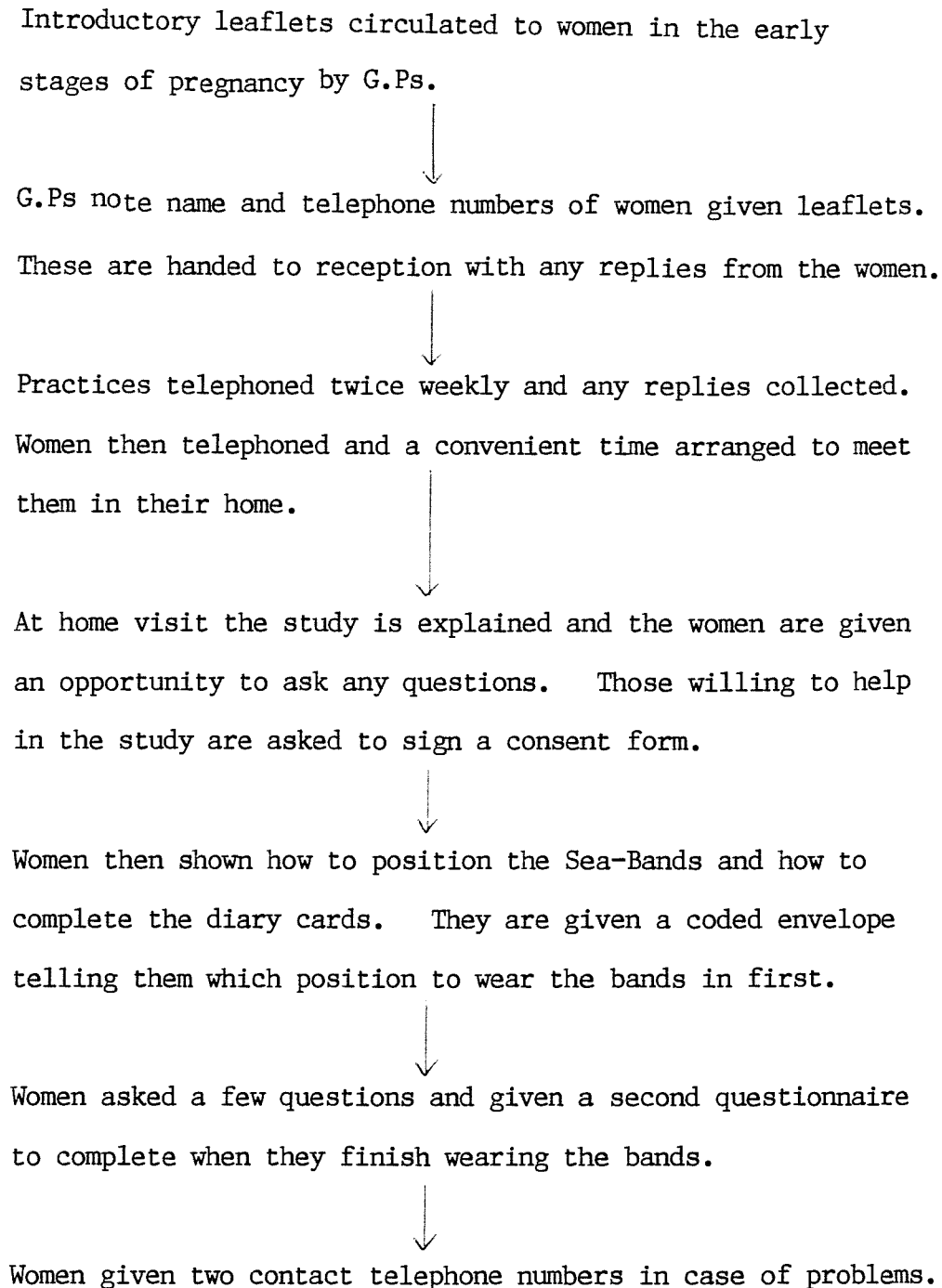
acupressure had improved their nausea at either position and which position they had found most beneficial.

#### Assessment of placebo credibility

At the beginning of the study the interviewer administered a questionnaire (Appendix 14.11) and asked the women how credible and how logical the women felt each acupressure position to be. At the end of the study the women were asked how confident they would be in recommending each position to a friend and how successful they felt each position would be in the treatment of other complaints.

These questions were based on previous studies (Borkovec & Nau, 1972; Vincent 1990), but had to be modified as the previous studies had not been cross-over trials and tended to involve people who had sought acupuncture treatment, rather than being asked to participate in an acupressure trial. People in the previous trials were more likely to have a greater insight into the uses of acupuncture and therefore be better informed for answering the questions.

**Figure 12.4 Summary of Method for EMS Study**



## RESULTS

The results obtained for studies E and F will be presented separately. Fundamentally, these two studies follow the same pattern; a cross-over study comparing real with sham acupressure as a treatment for nausea and vomiting. Both studies have relatively high drop-out rates and these will be discussed in relation to the patient demography. Both studies also involved a patient questionnaire and patient diary cards. The questionnaires in Study E were given to the patients after they had finished treatment in order to evaluate their response to treatment; a similar situation pertained in Study F. The major difference between the two studies is that Study F was an attempt at a double blind study and also involved a specific questionnaire to evaluate the credibility of placebo acupressure.

It could be argued that Study F was double blind in nature as neither the investigator nor the patient knew which acupressure point was likely to be effective. Furthermore, the order of treatment was unknown to the investigator. In this context, both the investigator and the patient were effectively "blind" to the exact nature of the treatment. However, it is possible that some of the patients may have known which acupressure point is normally used for nausea, and therefore some investigators would quite reasonably argue that it is incorrect to use the term "double blind" in this context. Furthermore, the investigator was aware of which treatment was likely to be effective and which likely to be ineffective, again in the context of a normal pharmacological study, the investigator would be unaware of the likely effect of a specific medication.

It is therefore quite reasonable to criticise the use of the term "double



blind" in this context, but after considerable thought it seems, with the above reservations, to best describe the study methodology used in the investigation of early morning sickness.

## ACUPRESSURE IN THE TREATMENT OF CHEMOTHERAPEUTICALLY INDUCED NAUSEA AND VOMITING: DETAILED RESULTS

### Patient demography and drop-out rates

Fifty three patients were admitted to the study, 38 (72%) of whom completed the study and provided results suitable for analysis. Fifteen patients (28%) withdrew at some point after entry and failed to produce a complete set of results for analysis. Table 12.1 provides information about those patients entered, the type of chemotherapy used and whether they had had previous chemotherapy, and also the order of acupressure treatments.

Table 12.2 provides information about the age, sex and primary diagnosis of all patients entered.

Table 12.3 shows the treatment status of the 38 patients completing the study. The groups are relatively comparable between those entering and completing the study. It is noticeable however that those in the high emetic group who had had previous chemotherapy appeared slightly less able to complete the required treatment protocol. In the majority of instances, this was because chemotherapy was discontinued during the study, as Table 12.4 demonstrates.

The other major reason for patients failing to complete the study was the fact that the bands were too tight, this was largely because of lymphoedema. The single largest group entering the study were those with breast cancer, and a number of these patients experienced lymphoedema and therefore found it impossible to wear the Sea-Bands.

### Patient Questionnaire

This questionnaire was completed at the end of the study (Appendix 12.7). Thirty-eight patients completed the study and the questionnaire and the results are shown in Table 12.5.

McNemar's test for paired alternatives was used to analyse questions 1,2 and 3, where only the united results contributed to this test statistic. A continuity correction was used to allow for the fact that a discrete distribution (the binomial) was being approximated by a continuous distribution (the normal). The statistical calculations are shown in Table 12.6.

These results show that there is a clear and significant difference in patient preference for active P6 acupressure over sham acupressure in the control of nausea and vomiting, and also to the question that relates to general well-being. Question 4 shows clearly that a number of patients were unable to wear the bands continuously. Again the main reason for this was that the bands were too tight and the patients who found them particularly uncomfortable dropped out rather than wearing them intermittently. Questions 5 and 6 in Table 12.5 give unequivocal results and show that the patients who were able to wear the bands had no problems keeping them in the correct position and applying pressure at the wrists. Question 7 suggests that pressure at the ankles was a little more difficult to apply regularly, but still possible for most patients. Two thirds of the patients were more than happy to use the Sea-Bands again to control nausea and vomiting.

The final two questions on the questionnaire attempted to elicit information about side effects: 17 patients had no side effects. Two noted that the ankle was sore while 5 suggested that they had some soreness over the wrist. A further 2 noted that the seams of the Sea-Band were digging in and found this a little uncomfortable and 6 again noted that the Sea-Bands were too tight (Table 12.7).

Those entering the study were given the freedom to make general comments

about how they felt and these varied substantially; comments ranged from "helpful and good" to "disappointing and no use at all". Two patients mentioned that they did not have much sickness from their chemotherapy and felt that the Sea-Bands would be of more use in other circumstances while another patient mentioned that her indigestion was considerably improved while she was wearing the Sea-Band. Two patients found pressing the ankles difficult, largely due to physical restrictions or because it made the nausea and vomiting worse and several patients felt that larger Sea-Bands would be more comfortable for them.

The patient questionnaires provided fairly unequivocal results; a significant number of patients preferred the wrist position and while the major criticism of the Sea-Bands was that they were too tight, the patients who completed the study were able to use the Sea-Bands competently and within the protocol requirements.

#### Individual diary cards

The diary cards were analysed in a variety of ways assessing the results for the overall group and also for comparison within the group. The control of the 5 variables recorded on the diary cards were analysed for days 1-5 combined to analyse the effect of P6 acupressure in a sham versus real position. Days 6 and 7 were not analysed as there were a large amount of missing data for these days. Analysis was completed for the overall group, the group receiving chemotherapy with a high emetogenic potential and the group receiving chemotherapy with low emetogenic potential. These results are presented in Table 12.8 and show that significant improvement was obtained in both the overall group and in the group receiving drugs with a high emetogenic potential for sickness, nausea, mood and overall condition. However, no significant results were

obtained in the group receiving drugs with low emetogenic effect. The results were calculated by combining the scores from days 1 to 5 for the whole group.

The diary card scores and the mean scores for sickness, nausea, mood anxiety and overall condition were calculated for each day when wearing the Sea-Band at wrist and ankle. This has been represented both graphically and in tabular form. Each symptom measured on the diary card has been presented separately, comparing the overall results for each day between those receiving wrist (real) acupressure with those receiving ankle (sham) acupressure. Table 12.9 and Graph 12.1 show the average sickness scores, Table 12.10 and Graph 12.2 show the average nausea results, Table 12.11 and Graph 12.3 show the results for mean mood score, Table 12.12 and Graph 12.4 show the mean anxiety results and finally Table 12.13 and Graph 12.5 show the mean overall condition results. Significance levels are clearly marked on each of these tables and graphs.

#### Comparison within the overall group

A parametric t-test was used to compare the means in the two samples for the following groups:

- high and low emetic intensity chemotherapy
- previous and first chemotherapy
- ankle then wrist treatment and wrist then ankle treatment

#### High and low emetic intensity chemotherapy

The differences in this group were very clear. It appeared that in almost all the variables measured the effect of wrist acupressure was significantly greater than that of ankle acupressure and these differences were far greater in the high emetic intensity group as compared to the low emetic intensity group.

On days 2,3 and 4 there was a significant difference in the control of sickness between the wrist and ankle for the high and low emetic intensity groups. The high group had better sickness control with the wrist treatment on these days than the low emetic intensity group (Table 12.14 ). When measuring nausea (Table 12.15), significant differences were noted on days 3 and 4 between the high and low emetic intensity groups.

There was little difference in the groups when comparing first and previous chemotherapy in relation to the control of sickness, nausea and overall condition. Therefore it appears that anticipatory nausea and vomiting was not a significant factor in the context of this study. The order of wrist and ankle treatments also made no difference when exposed to statistical tests (parametric t-test). The variables measured were actual sickness, nausea and overall condition, and there were no significant differences between the two groups when analysing this information.

Because of the relatively large differences between the high and low emetogenic group, those receiving chemotherapy which was likely to produce nausea and vomiting were analysed separately. The following results look at this particular group in more detail. Table 12.16 shows the highly significant effects between wrist and ankle acupressure in those receiving high emetogenic chemotherapy. These differences are demonstrated between days 2 and 5 inclusive. Those receiving low emetogenic chemotherapy had no significant differences between wrist and ankle treatment for sickness.

Table 12.17 shows the results pertaining to nausea in the high emetogenic group, again highly significant results were obtained on the third and fourth day. Those receiving low emetogenic chemotherapy showed no significant difference when analysed in this manner. Table 12.18 shows mood changes only in the high emetogenic group. The low emetogenic showed

no significant differences between wrist and ankle treatment but the high emetogenic group showed significant differences on days 2, 3 and 4. When measuring anxiety there was little difference between the two groups in those receiving either high or low emetogenic chemotherapy. There were no significant differences when these two groups were analysed separately and wrist and ankle results were compared within each group. The low emetogenic group had no significant differences between wrist and ankle treatment for overall condition but in the high group there was a significant difference as demonstrated by table 12.19 on days 2 and 3. These results suggest that the most significant difference between the two groups occur in those receiving high emetogenic chemotherapy. Here the results become far more significant than when the groups were combined. It is also interesting to note that in those receiving low emetogenic chemotherapy, little difference could be measured. Order of treatment and previous chemotherapy did not seem to have any significant effect on these results.

**Table 12.1 Patients entered in relation to stratification  
criterion**  
Chemotherapeutically Induced Nausea

High emetic intensity	31 (58%)
Low emetic intensity	22 (42%)
Previous chemotherapy	39 (74%)
First chemotherapy	14 (26%)
Ankle, then wrist	25 (47%)
Wrist, then ankle	28 (53%)



**Table 12.2    Sex, age and primary diagnosis of entered patients**  
Chemotherapeutically Induced Nausea

Male	14 ( 26%)
Female	39 ( 74%)
20-29 years	2 ( 4%)
30-39 years	8 (15%)
40-49 years	16 (30%)
50-59 years	11 (21%)
60-69 years	11 (21%)
70-79 years	5 ( 9%)
Breast ca.	23 (43%)
Lymphoma	8 (15%)
Ovarian ca.	7 (13%)
Lung ca.	5 ( 9%)
Cervical ca.	2 ( 4%)
Myeloma	2 ( 4%)
Teratoma	2 ( 4%)
Bladder ca.	1 ( 2%)
Seminoma	1 ( 2%)
Ewing's sarcoma	1 ( 2%)
Oesophageal ca.	1 ( 2%)

**Table 12.3**    **Patients completing study**  
Chemotherapeutically Induced Nausea

	Entered into study	Completed study
HP	20	13
HN	11	8
LP	19	15
LN	3	2
A then W	25	17
W then A	28	21

HP    =    High emetic intensity & previous chemotherapy

HN    =    High emetic intensity & new to chemotherapy

LP    =    Low emetic intensity & previous chemotherapy

LN    =    Low emetic intensity & new to chemotherapy

Order of treatment:    Ankle then wrist

Order of treatment:    Wrist then ankle

**Table 12.4**    **Reasons for withdrawal**  
Chemotherapeutically Induced Nausea

Chemotherapy discontinued	6 (40%)
Bands too tight (ankle or wrist)	5 (32%)
Swollen ankles	1 ( 7%)
Swollen hands	1 ( 7%)
Ankle band appearance	1 ( 7%)
Chemotherapy continued outside Southampton	1 ( 7%)

**Table 12.5**      **Questionnaire response - Chemotherapeutically Induced Nausea**

1.	Preference for better control of vomiting	ankle	6 (16%)
		wrist	20 (53%)
		no difference	11 (29%)
		missing data	1 ( 2%)
2.	Preference for better control of nausea	ankle	7 (19%)
		wrist	21 (55%)
		no difference	10 (26%)
3.	Preference for feeling generally better	ankle	7 (18%)
		wrist	21 (55%)
		no difference	9 (24%)
		missing data	1 ( 3%)
4.	Able to wear bands continuously	Yes	29 (76%)
		No	9 (24%)
5.	Able to keep bands in correct position	Yes	38(100%)
		No	0 ( 0%)
6.	Apply pressure at wrists	Yes	38(100%)
		No	0 ( 0%)
7.	Apply pressure at ankles	Yes	33 (87%)
		No	5 (13%)
8.	Use Sea-Bands again to control nausea and vomiting	Yes	25 (66%)
		No	13 (34%)

**Table 12.6** McNemar's test of patient questionnaire  
Questions 1, 2 and 3  
Chemotherapeutically Induced Nausea

Questions analysed	Chi-squared value	Significance level
1. Vomiting control	6.50	$p < 0.02 *$
2. Nausea control	6.04	$p < 0.02 *$
3. Feel generally better	6.04	$p < 0.02 *$

$p < 0.05 *$  (one star)

$p < 0.01 **$  (two stars)

$p < 0.001 ***$  (three stars)

**Table 12.7**    **Reported adverse reactions to Sea-Bands**  
Chemotherapeutically Induced Nausea

None	17 (45%)
Ankle point sore	2 ( 5%)
Wrist point sore	6 (16%)
Seams of Sea-Bands digging in	2 ( 5%)
Sea-Bands too tight (either site)	6 (16%)

**Table 12.8**    **Combined results for the overall group and those receiving high and low emetogenic medication**  
Chemotherapeutically Induced Nausea

Variable	Overall group		High group		Low group
	t-value	Sig. Level	t-value	Sig.Level	
Sickness	-3.49	p<0.01	-6.71	p<0.01 **	NS
Nausea	-3.79	p<0.01	-4.74	p<0.01 **	NS
Mood	-4.24	p<0.01	-4.95	p<0.01 **	NS
Anxiety	-1.86	NS	-2.05	NS	NS
Overall condition	-4.97	p<0.01	-3.33	p<0.05 *	NS

(NS = Not significant)

**Table 12.9**    **Mean sickness results for all groups receiving chemotherapy**  
Chemotherapeutically Induced Nausea

Day	Mean wrist score	Mean ankle score	t-value	Sig.level
1	3.11	3.05	0.21	NS
2	2.76	2.97	-1.12	NS
3	1.89	2.63	-2.64	p<0.05 *
4	1.58	2.08	-2.39	p<0.05 *
5	1.34	1.59	-1.78	NS
6	1.40	1.56	-0.81	NS

Key for sickness score:-

1. None
2. Poor appetite
3. Felt sick but wasn't
4. Sick once
5. Sick more than once



**Table 12.10**    **Mean nausea results for all groups receiving chemotherapy**  
Chemotherapeutically Induced Nausea

Day	Mean wrist score	Mean ankle score	t-value	Sig.level
1	2.67	3.08	-2.03	p<0.05 *
2	2.45	2.92	-1.86	NS
3	2.00	2.58	-3.16	p<0.05 *
4	1.82	2.05	-1.33	NS
5	1.58	1.65	-0.66	NS
6	1.49	1.86	-0.70	NS
7	1.32	1.76	-0.55	NS

Key for nausea score:-

1. None
2. Transient nausea, not requiring treatment
3. Transient nausea, requiring treatment
4. Continuous nausea, responding to treatment
5. Continuous nausea, unresponsive to treatment.

**Table 12.11**    **Mean mood results for all groups receiving chemotherapy**  
Chemotherapeutically Induced Nausea

Day	Mean wrist score	Mean ankle score	t-value	Sig.level
1	3.08	3.26	-1.96	NS
2	3.13	3.26	-1.04	NS
3	2.71	3.00	-2.44	p<0.05 *
4	2.55	2.82	-2.13	p<0.05 *
5	2.39	2.49	-0.94	NS
6	2.40	2.53	-0.94	NS
7	2.41	2.56	-1.00	NS

Key for mood score:-

1.    Very happy
2.    Happy
3.    Average
4.    Miserable
5.    Very miserable

**Table 12.12**    **Mean anxiety results for all groups receiving chemotherapy**  
Chemotherapeutically Induced Nausea

Day	Mean wrist score	Mean ankle score	t-value	Sig. level
1	2.84	3.03	-1.87	NS
2	2.84	2.97	-1.18	NS
3	2.54	2.34	0.72	NS
4	2.32	2.45	-1.64	NS
5	2.27	2.35	-1.53	NS
6	2.14	2.38	-2.33	p<0.05 *
7	2.28	2.32	-0.20	NS

Key for anxiety score:-

1. Very calm
2. Calm
3. Average
4. Anxious
5. Very anxious

**Table 12 .13      Mean Overall Condition for all groups receiving chemotherapy**  
Chemotherapeutically Induced Nausea

Day	Mean wrist score	Mean ankle score	t-value	Sig. level
1	2.81	3.25	-2.03	p<0.05 *
2	2.94	3.25	-1.10	NS
3	2.53	3.10	-2.24	p<0.05 *
4	2.48	2.79	-0.94	NS
5	2.46	2.74	-0.04	NS
6	2.43	2.71	-1.00	NS
7	2.42	2.68	-1.04	NS

**Table 12.14    Sickness comparing wrist and ankle in the high  
emetogenic group.**  
Chemotherapeutically Induced Nausea

Day	Differences wrist/ankle (mm)	t -value	Significance level
1	1.05	-0.97	NS
2	0.46	-0.43	NS
3	13.30	-4.69	p < 0.01 **
4	12.20	-3.88	p < 0.01 **
5	1.20	-1.58	NS
6	-2.50	0.09	NS
7	0.50	-0.22	NS

**Table 12.15**      **Mean nausea levels comparing high and low emetic intensity groups**  
Chemotherapeutically Induced Nausea

Day	Differences Wrist/ankle (mm)	t-value	Significance level
1	1.05	-0.97	NS
2	0.46	-0.43	NS
3	13.05	-4.69	p < 0.01 **
4	12.20	-3.88	p < 0.01 **
5	1.20	-1.58	NS
6	-2.50	0.09	NS
7	0.50	-0.22	NS

**Table 12.16      Nausea for high emetogenic group ; wrist & ankle difference**  
Chemotherapeutically Induced Nausea

Day	Differences wrist/ankle (mm)	t-value	Significance level
1	1.05	-1.44	NS
2	5.63	-2.77	p < 0.05 *
3	13.5	-4.79	p < 0.01 **
4	12.83	-4.30	p < 0.01 **
5	3.04	-2.42	p < 0.05 *
6	1.14	-1.56	NS
7	0.04	-0.20	NS

**Table 12.17**      **Nausea for high emetogenic group; wrist & ankle difference**  
Chemotherapeutically Induced Nausea

Day	Differences wrist/ankle (mm)	t-value	Significance level
1	1.23	-1.52	NS
2	1.07	-1.39	NS
3	6.3	-3.30	p < 0.01 **
4	6.9	-3.51	p < 0.01 **
5	3.8	-1.67	NS
6	0.52	-0.49	NS
7	-3.2	0.32	NS



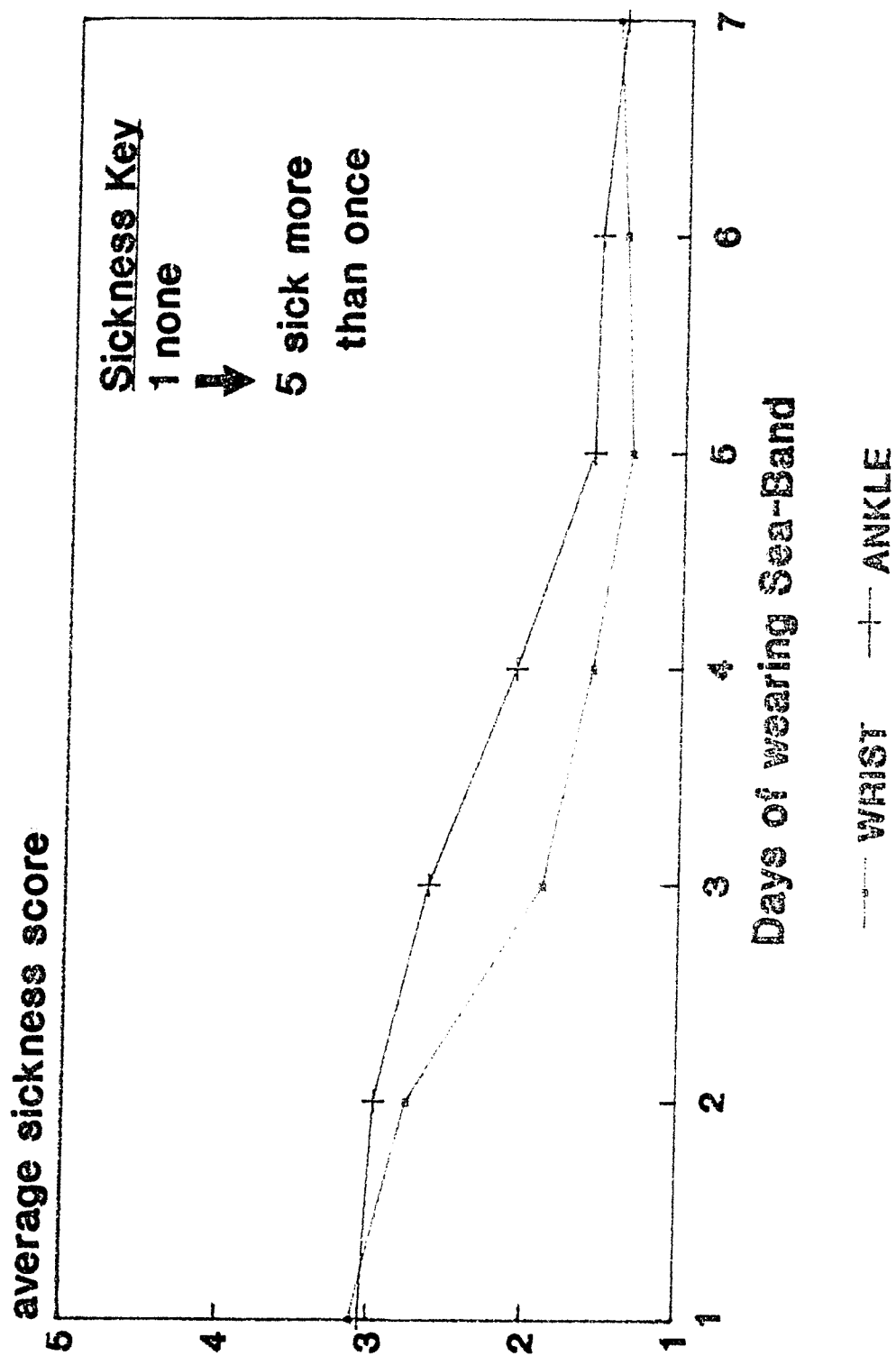
**Table 12.18**      **Mood for high emetogenic group; wrist & ankle differences**  
Chemotherapeutically Induced Nausea

Day	Differences wrist/ankle (mm)	t -value	Significance level
1	3.95	-1.79	NS
2	4.6	-2.61	p < 0.05 *
3	4.3	-2.26	p < 0.05 *
4	4.8	-2.63	p < 0.05 *
5	3.79	-1.67	NS
6	3.8	-1.68	NS
7	2.1	-0.82	NS

**Table 12.19 Overall condition for high emetogenic group; wrist & ankle differences - Chemotherapeutically Induced Nausea**

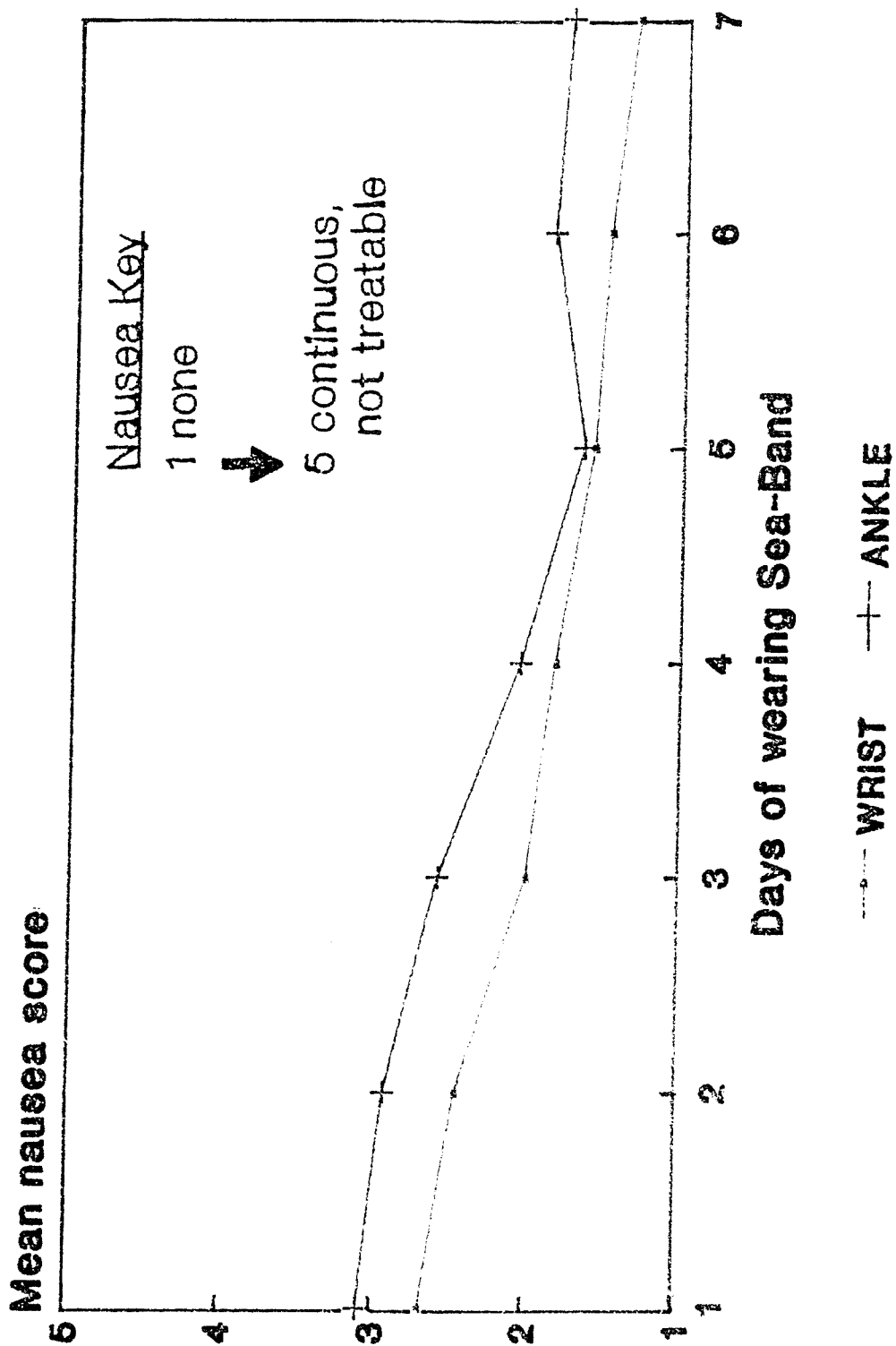
Day	Differences wrist/ankle (mm)	t -value	Significance level
1	3.8	-1.67	NS
2	6.05	-3.00	p < 0.01 **
3	7.1	-3.57	p < 0.01 **
4	3.7	-1.67	NS
5	2.6	-1.55	NS
6	3.8	-1.68	NS
7	2.2	-0.83	NS

Graph 12.1 - Average sickness: Wrist and Ankle  
Chemotherapeutically Induced Nausea



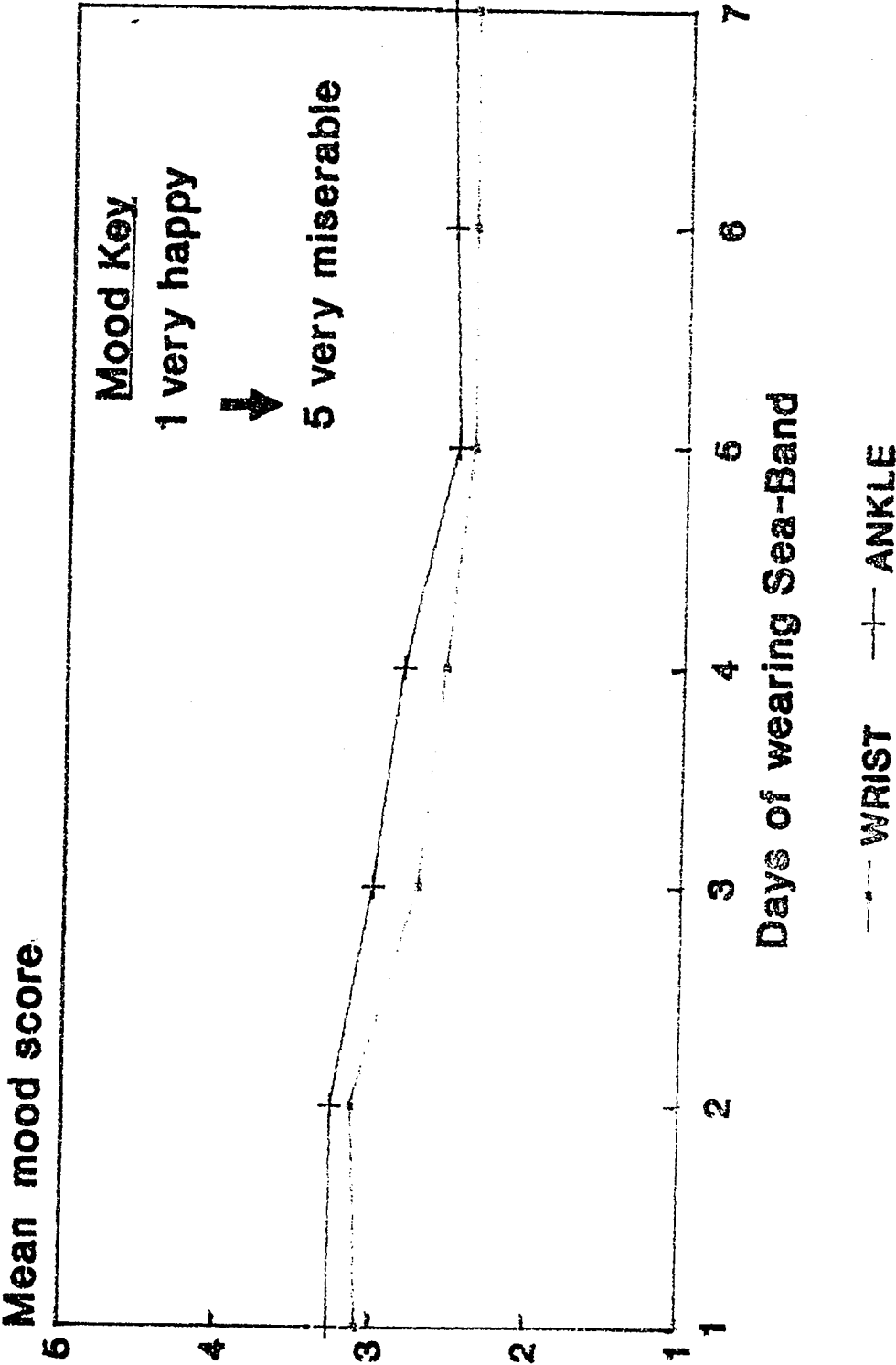
T-test: days 3 and 4 sig.  $p < 0.05^*$

Graph 12.2 - Average nausea: Wrist and Ankle  
Chemotherapeutically Induced Nausea



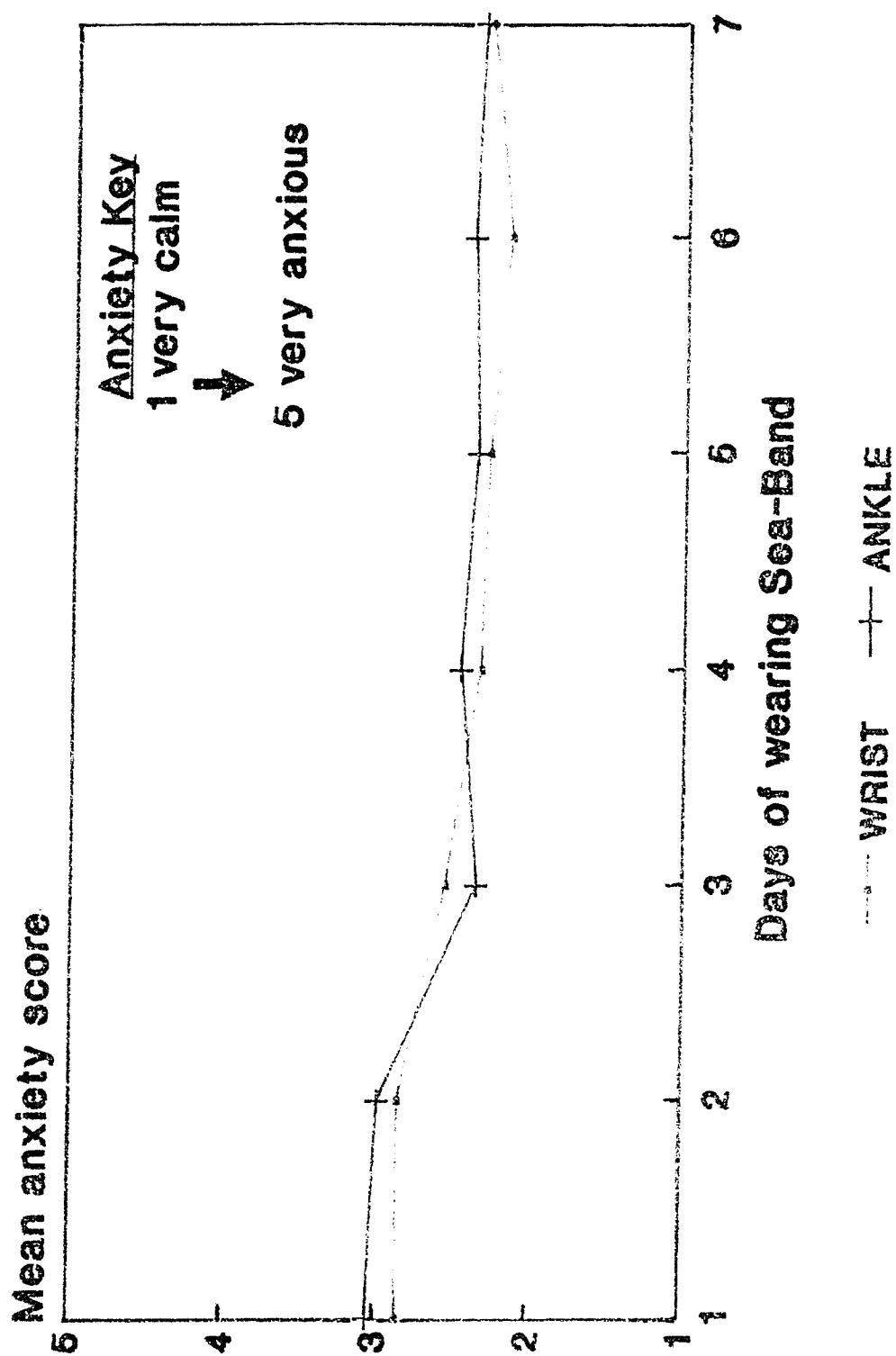
T-test: days 1 and 3 sig.  $p < 0.05^*$

Graph 12.3 - Average mood: Wrist and Ankle  
Chemotherapeutically Induced Nausea



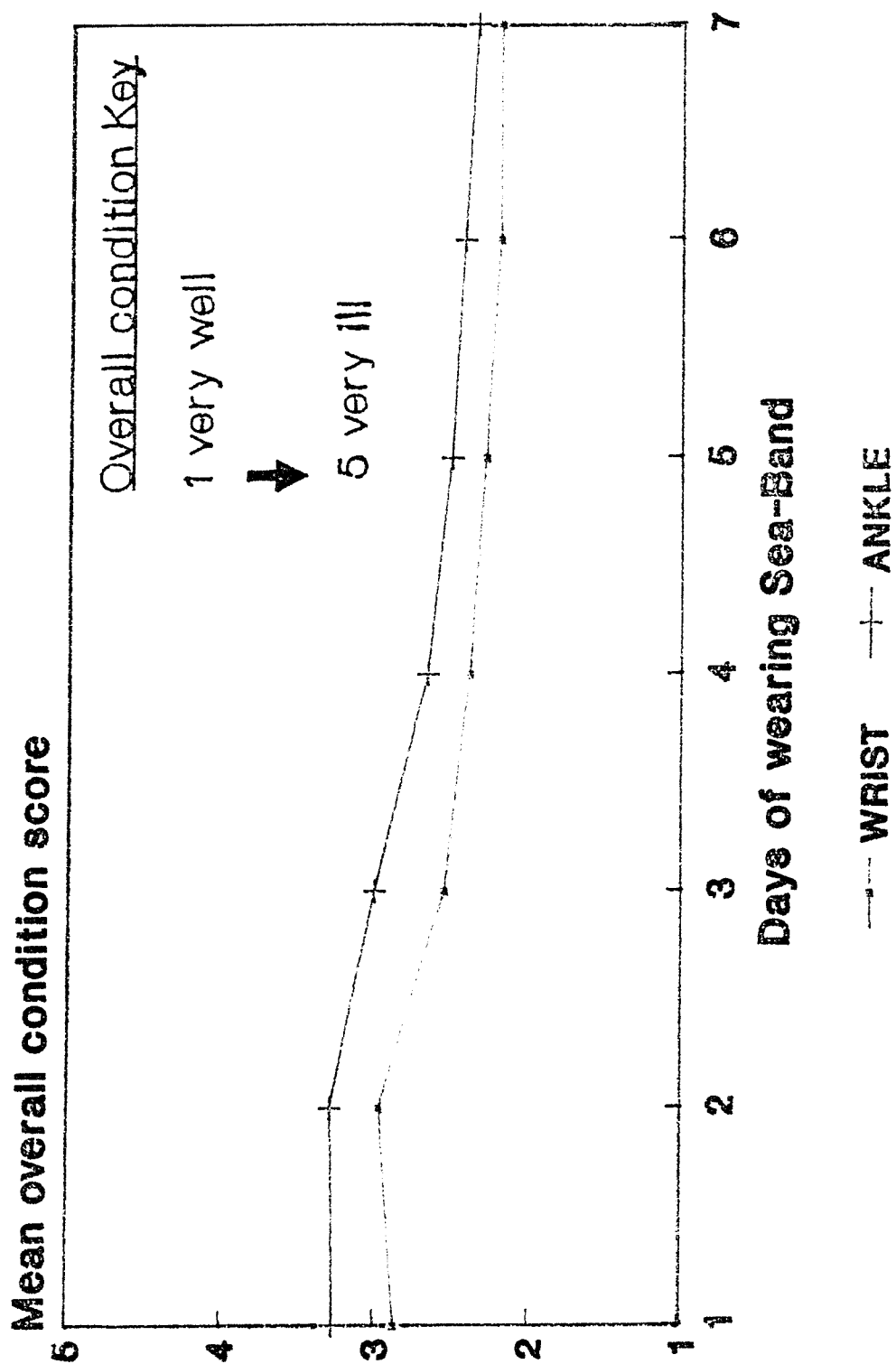
T-test: days 3 and 4 sig.  $p < 0.05^*$

Graph 12.4 - Average anxiety: Wrist and Ankle  
Chemotherapeutically Induced Nausea



T-test: day 6 sig.  $p < 0.05^*$

Graph 12.5 - Overall condition: Wrist and Ankle  
Chemotherapeutically Induced Nausea



T-test: days 1,2,3,4 sig.  $p < 0.05^*$

## ACUPRESSURE AND EARLY MORNING SICKNESS: DETAILED RESULTS

### Patient demography and drop-out rates

A total of 23 women entered the study. The main data analysis was for 15 women; 4 women from group 1 and 4 women from group 2 were excluded.

Two women had miscarriages. One had entered the study before experiencing any EMS, the other miscarried during the two day wash-out period, but it would have been insensitive to have insisted on collecting the forms from the first week. Neither of these two women expressed any concern that their miscarriage may have been related to the acupressure.

Four other women failed to complete or return their forms. None of these wore the Sea-Bands for more than a week. Two moved during the study period and one did not complete the forms and the fourth only gave a work address and was unobtainable.

Two of these four women said they had derived some benefit from the acupressure. However, one had stopped as the bands irritated a rash which was present before she began wearing the Sea-Band; the other said that her vomiting was reduced, but her nausea was unaffected and she preferred to vomit if she was feeling nauseous.

One woman was excluded for being a protocol violator at 36 weeks' gestation. The data for this woman are quoted in brackets. The final woman was excluded as she completed only one day of the visual analogue cards. She said that the acupressure had not been of benefit. The data from this woman's second questionnaire are still quoted.

Nineteen of the 23 women were married and 4 were single. All of the women who completed the study were married. The parity of both groups is shown in Table 12.20. Previous knowledge of acupuncture is shown in Table 12.21 and previous use of acupuncture in Table 12.22. The gestational age and



age distribution of the two groups is shown in graphs 12.6 and 12.7.

The two groups had a similar age distribution. The distribution of marital status was identical both for those entering and completing the study. Other factors showed some differences; women in group 1 were one and a half weeks further on in their gestation and this may have meant that they were experiencing less nausea. However, this group also contained a greater percentage of primigravids who would be expected to experience more nausea.

Previous knowledge and experience of acupuncture differed between the two groups. Seven of the 8 women for whom data had not been analysed having no prior knowledge of acupuncture, the other being one of the two who miscarried. Only 2 women had previously tried acupressure. The women with a slightly greater insight into and knowledge of the treatment all completed the study. Slight variations between the two groups were certainly acceptable as the study was of a cross-over design, but by and large the two groups represented a homogeneous and comparable population.

#### Analysis of patient preference questionnaires

Where two sets of results are quoted, the main results are based on 15 women and the results in brackets are based on 17 women. The extra 2 include the woman at 36 weeks' gestation and the other woman who completed the initial and final questionnaire but only 1 day of the daily diary cards.

Of the 15 women, 10 (66%) felt their nausea was reduced by acupressure at P6, whereas only 5 (33%) felt their nausea was reduced by acupressure at the placebo or sham point. The number of women in each group is shown in Table 12.23. Of the 13 women who expressed a preference, 9 (69%) found P6 more beneficial and 4 (31%) found the placebo more beneficial. The

remaining women had not found acupressure to be beneficial ( $\chi^2 = 5.30$ ,  $p = 0.074$ ).

Women preferred acupressure at P6 to the sham acupressure point. As the data were normally distributed, the results of non-parametric tests therefore show no carry-over effects between the two arms of the study. Parametric and non-parametric analysis demonstrated almost identical results. The questions asking women directly whether they had derived benefit from acupressure also supported these conclusions although the results were not statistically significant. There is no evidence of any group or treatment carry-over effect.

#### Did acupressure at P6 reduce nausea?

##### Analysis of the visual analogue diary cards

Of the 15 women only 11 vomited, 5 of these vomited an average of at least once a day. This symptom was not significantly affected by the use of acupressure at P6.

Nausea levels were averaged for each of the women and the mean levels of nausea for each group were calculated for both weeks, as were the mean levels of nausea with the bands worn at each position. Where two sets of results are quoted, the first results are based on 15 women and the results in brackets are based on 16 women including the woman at 36 weeks' gestation.

Analysis of nausea from the visual analogue scale (VAS) of 0-10 at each position found the mean level of nausea to be significantly lower at P6 (3.23 points on the VAS) compared with the placebo (4.92 points on the VAS), indicating nausea levels to be 1.69 points lower on the VAS with acupressure at P6 compared with acupressure at the elbow (see Table 12.24). Taking into account the order in which the treatments were received, there

was still a significant decrease in nausea at P6. New mean nausea levels were estimated to be 0.25 (0.36) points on the VAS higher in the first week compared with the second. This was not significant,  $p = 0.71$  (0.57). Results of analysis of these data are shown in tables 12.24 and 12.25.

Graph 12.8 shows the distribution of the average nausea levels for each woman for both positions. The nausea experienced by women wearing the placebo bands in the first position chosen are shown by the elbow 2 marks; those wearing the bands in the preferred second position are shown by the elbow 1 marks. It can be seen that nausea levels were similar for both placebos. Results were similar in both groups with the women having a varied experience and perception of EMS.

#### Was the placebo credible?

The results in this section are presented similarly to those of previous sections. The results in brackets include all women who completed the relevant questionnaire but may not have completed all the data required for the study.

The credibility of the placebo position was assessed by asking the women two questions relating to both P6 and the placebo; questions 9 and 10 in the initial questionnaire (Appendix 12.9). These questions were:

- How confident are you that acupressure at the wrist/elbow will improve your nausea?
- How logical does this treatment seem?

The table 12.26 shows the results in relation to confidence and logic of treatment at the beginning of the study. This demonstrates that the women were equally confident that acupressure would work at both positions and felt that the elbow was only a slightly less logical position to wear the Sea-Bands than the wrist. At each level the actual results for wrist and

elbow were almost identical and no significant difference emerged in the initial questionnaire.

At the end of the study the women were asked two further questions to see if their opinions of treatment had changed; questions 4 and 5. These questions were:

- How confident would you be in recommending acupressure at the wrist/elbow to your friends?
- How successful do you feel acupressure at the wrist/elbow would be in the treatment of other complaints?

Answers were rated on a scale of 0-6 and the results are shown in table 12.27. The women were significantly more confident in recommending acupressure at P6 compared with acupressure at the sham or placebo point. They also felt that P6 acupressure would be significantly better in the treatment of other complaints; the results are shown in table 12.28.

Using dot plots the data was not found to be skewed. Non parametric tests were carried out and they were also significant: the results are shown in table 12.29.

At the beginning of the study the women could not distinguish between true and placebo treatments. By the end of the study, as would be expected from the results obtained, they had far greater faith in the more successful real acupressure position (P6) than in the sham acupressure position either above or below the elbow.

**Table 12.20 Parity of the Groups entering the study**  
Early Morning Sickness

Parity	Group 1	Group 2	Overall Percent
1	5 (9)	1	40% (44%)
2	2	4	40% (26%)
3	0	3 (6)	20% (26%)
4	0	0 (1)	0% (4%)

Main results include 15 women, results in brackets include all women.

**Table 12.21**    **Previous knowledge of acupressure among  
the groups - Early Morning Sickness**

Knowledge of Acupressure	Group 1	Group 2	Overall percent
None	4 (8)	2 (5)	40% (57%)
Minimal	2	4 (5)	40% (30%)
Detailed	1	2	20% (13%)

Main results include 15 women, results in brackets include all women.

**Table 12.22** Previous use of acupressure in both groups  
Early Morning Sickness

Previously used Sea- Bands	Group 1	Group 2
Yes	2	0
No	5 (9)	8 (12)

Main results include 15 women, results in brackets include all 23 women.

**Table 12.23**    **Improvement in nausea at each of the positions**  
**Early Morning Sickness**

	Wrist Yes	Wrist No
Elbow Yes	4	1
Elbow No	6 (7)	4 (5)

P = 0.125 (0.070)

Main results include 15 women, results in brackets include 17 women.



**Table 12.24 Parametric analysis of mean levels of nausea**  
Early Morning Sickness

Test	Mean (W - E)	Confidence Interval	P - Value
Paired t-Test of treatment at each position	1.69 (1.57)	0.32, 3.06 (2.87, 0.27)	0.019* (0.021)
Two sample t- Test of group difference for each week	1.67 (1.56)	0.24, 3.10 (0.23, 2.91)	0.025* (0.025)

Main results include 15 women, results in brackets include 16 women.

Mean w-e indicates the treatment difference.

**Table 12.25**    **Non-parametric analysis of mean nausea levels**  
Early Morning Sickness

Test	Mean (W - E)	Confidence Interval	P - Value
Wilcoxon Test of treatment at each position	1.65 (1.96)	0.14, 3.16 (0.032, 3.42)	0.037* (0.022)
Mann Whitney test of group difference for each week	1.61 (1.55)	-0.01, 3.17 (-0.04, 3.11)	0.049* (0.059)

Main results include 15 women, results in brackets include 16 women.

Mean w-e indicates the treatment difference.

**Table 12.26**      **Confidence ratings in relation to the two treatments**  
**before the study**  
Early Morning Sickness

Scale	Confidence in Wrist	Confidence in Elbow	Logic of Wrist	Logic of Elbow
0 None	0 (1)	0 (0)	0 (0)	0 (0)
1	1 (1)	1 (1)	0 (0)	0 (0)
2	1 (2)	1 (4)	1 (1)	1 (1)
3	7 (10)	7 (10)	3 (7)	5 (10)
4	3 (6)	3 (4)	3 (5)	3 (4)
5	3 (3)	3 (3)	5 (7)	3 (5)
6 Great	0 (0)	0 (0)	3 (3)	3 (3)

Main results include 15 women, results in brackets include all 23 women.

**Table 12.27**      **Confidence in the two treatments at the end of the study**  
Early Morning Sickness

Scale	Recommend Wrist	Recommend Elbow	Success of Wrist	Success of Elbow
0	1	6	1 (2)	5 (6)
1	0	0 (1)	0	0 (1)
2	1 (2)	1 (2)	3	3
3	4	1	3	5
4	1 (2)	3	4 (5)	1
5	1	2	1	0
6	7	2	3	1

Main results include 15 women, results in brackets include 17 women.

0 = not recommended or successful  
6 = recommended and successful.

**Table 12.28**

**Confidence in each treatment at the end of the study  
as assessed by recommending acupressure for this or  
other conditions**

Early Morning Sickness

	Difference (W-E)	Confidence Interval	P-Value
Confidence in recommending acupressure	1.67 (1.69)	0.11, 3.23 (0.26, 3.03)	0.038 * (0.023)
Success of acupressure in the treatment of other complaints	1.53 (1.53)	0.18, 2.89 (0.32, 2.74)	0.029 * (0.016)

Main results include 15 women, results in brackets include 17 women.

Difference W-E is the mean difference in confidence between the 2  
treatments.

**Table 12.29**    **Non parametric results of analysis of difference in confidence**  
Early Morning Sickness

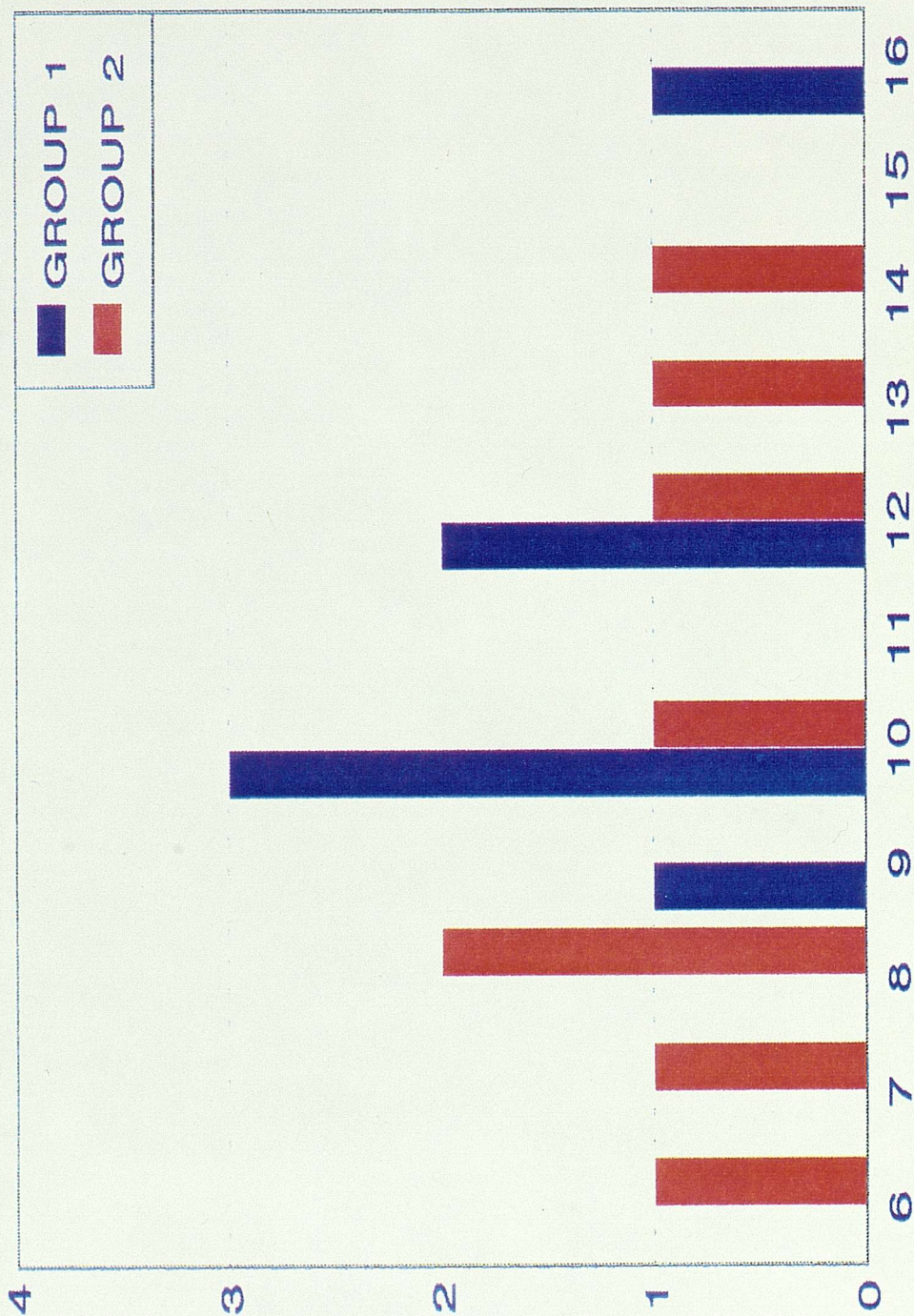
	Difference (W-E)	Confidence Interval	P-Value
Confidence in recommending acupressure	1.50 (1.65)	0.00, 3.5 (0.00, 3.00)	0.065 (0.039)
Success of acupressure in the treatment of other complaints	1 (1.0)	0.00, 3.00 (0.00, 3.00)	0.035* (0.021)

Main results include 15 women, results in brackets include 17 women.

Difference W-E is the mean difference in confidence between the two treatments.



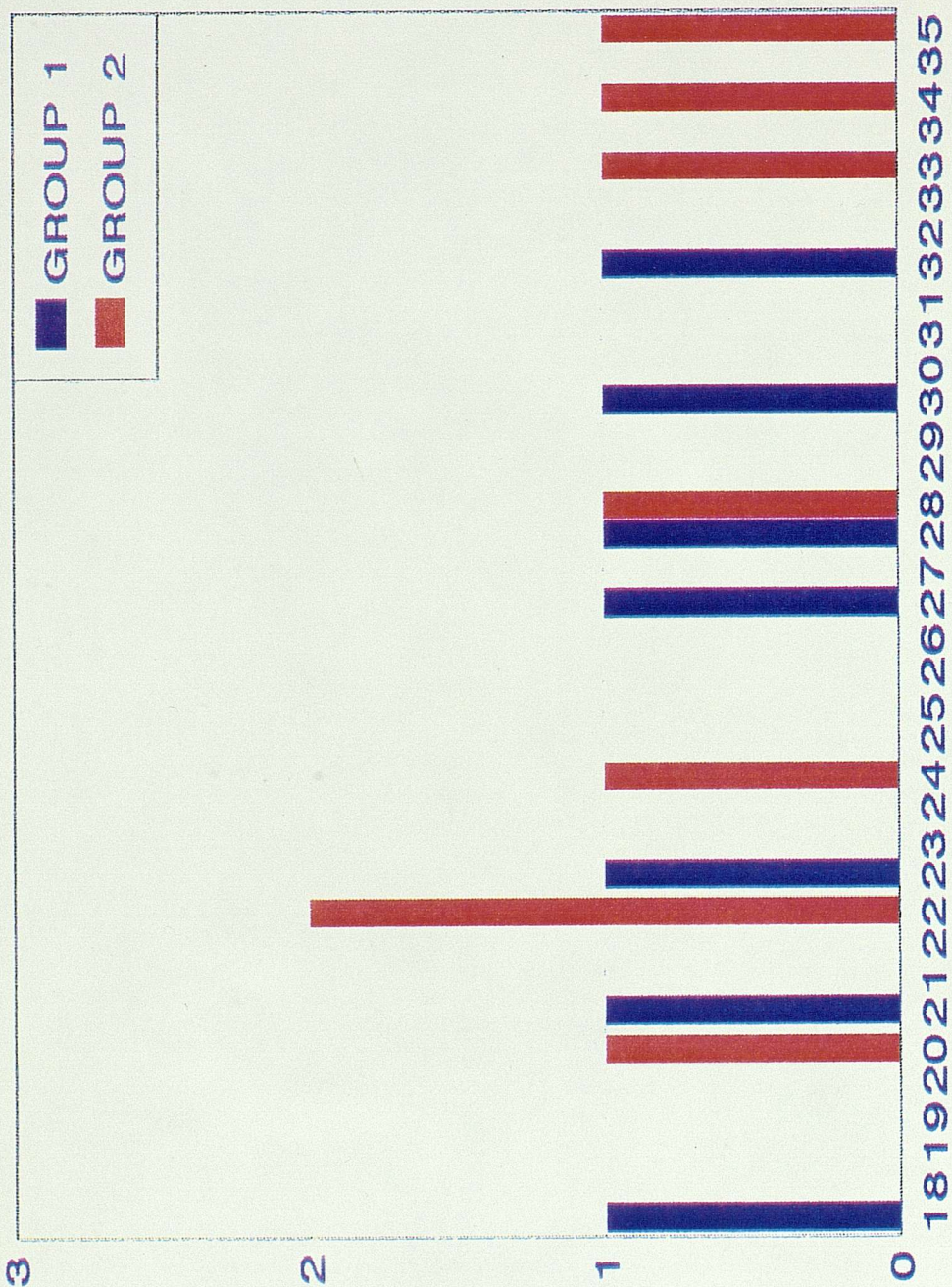
**Graph 12.6 - Gestation Status of Women in Groups 1 and 2**  
Early Morning Sickness Study



**DATA FOR 15 WOMEN**  
**MEAN FOR GROUP 1 = 11.3** (Wrist then Elbow)  
**MEAN FOR GROUP 2 = 9.8** (Elbow then Wrist)



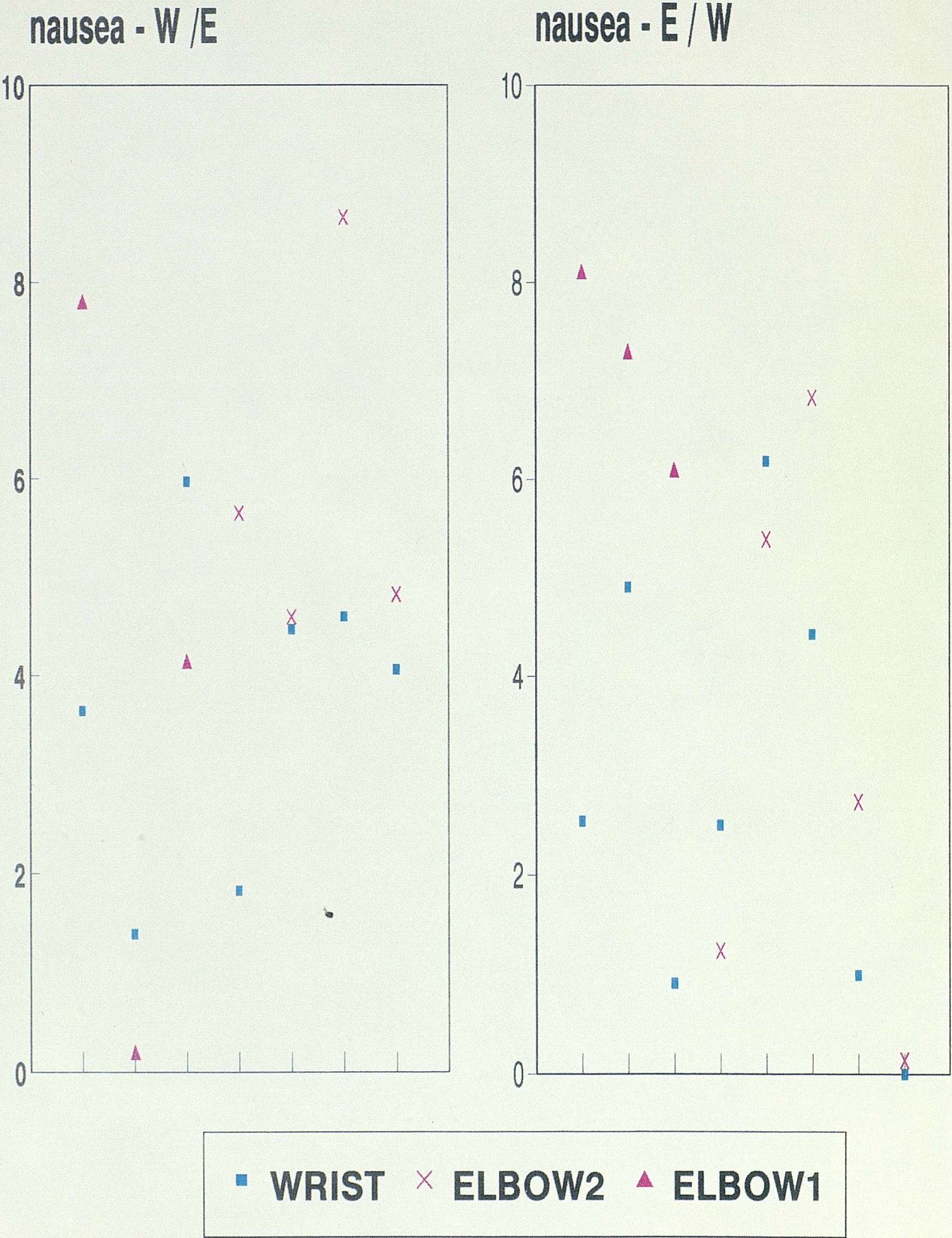
Graph 12.7 - Age of Women in Groups 1 and 2  
Early Morning Sickness Study



DATA FOR 15 WOMEN  
MEAN FOR GROUP 1 = 25.6  
MEAN FOR GROUP 2 = 27.3



**Graph 12.8 - Averaged Nausea Levels in Group 1 (Wrist then Elbow) and Group 2 (Elbow then Wrist)**  
Early Morning Sickness Study



## DISCUSSION

### Methodology

Both the acupressure studies involved a cross-over technique. In Study E this was fairly straightforward as different positions could be used for each chemotherapy cycle. As chemotherapeutically induced nausea is such an instant and self-limiting symptom, there was very little danger that there would be any carry-over between treatments given three weeks apart. Furthermore, all the empirical and clinical trial information that we have suggests that acupressure in this situation has a fairly short-term effect. The non-parametric analyses carried out in Study E further support the suggestion that a cross-over model here was valid and an adequate wash-out period included.

Study F also used a cross-over technique but here the wash-out period only involved two days. Again the non-parametric analysis carried out during this period supports the suggestion that there was little or no treatment effect carried over between the two arms of the study. In spite of the fact that EMS is a self-limiting condition, it seems quite clear from the available data that the women were suffering from EMS throughout the study period and that order of treatment appeared to have little effect on outcome. Again it is therefore reasonable to conclude that a two-day wash-out period was adequate and the main requirements for a cross-over study were fulfilled in both Study E and Study F.

Study E involved a single blind methodology as the researcher was aware of whether the patients were receiving real or sham acupressure. In the context of treatments given every 3 or 4 weeks, such as chemotherapy, it was not at the outset deemed particularly practical to give adequate instructions to cover both treatment cycles at entry into the study.

Patients were not aware as to whether they were receiving real or sham treatment, and (as has been outlined in the method section) consent was sought on that basis. As with all the previous studies discussed in this thesis, assessment was blind to outcome as it involved a patient self-assessment. Consequently, it is reasonable to suppose, as has been done previously, that patients were unaware as to whether they were receiving a real or sham treatment. The results describing the outcome of Study E would certainly support this hypothesis. However, in Study F a number of these assumptions were questioned.

The first change in Study F as compared to all the other studies discussed in this thesis is an attempt to make the study "double-blind". While this study could not perhaps be considered double-blind in the same way as a study on a pharmacological preparation, it is probably the closest that one can come to a double-blind study in the context of acupuncture. The patients were unaware as to which point was likely to be effective, and the investigator was unaware of which point was being used at any time during the study. However, as opposed to a conventional double-blind study, the investigator was aware of which point was likely to be effective, and the patients entering might have known which acupressure point would be used normally to alleviate nausea in this context. The whole study was explained clearly to the patients prior to entry into the study. The primary investigator was unaware of the order of treatment and consequently completely blind to whether a real or sham treatment was being used in any particular instance. This is particularly relevant when considering some of the previous studies involving acupuncture and acupressure as treatments for nausea. For instance, the majority of Dundee's studies were "open" studies and therefore subject to criticism on



that basis alone. Both the patients and investigators in many of Dundee's studies were aware whether they were receiving real or sham treatment, or indeed in some instances, no acupressure at all. Both studies E and F overcome this problem, but Study F takes the process one step further by attempting to construct a "double-blind" methodology. Again the primary mechanism for evaluating outcome in Study F was the use of patient questionnaires, and these were certainly completed independently in relation to treatment efficacy. The instructions given in Study F created no confusion among the patients, they were clearly understood and as far as we can gather in the context of this study, followed accurately.

Fundamental methodology involved in analysing the effects of P6 on nausea has therefore progressed with time. The initial studies by Dundee were descriptive and open, this was then followed by some comparative studies and finally the development of single blind studies. Study F is the first attempt at a double-blind study to evaluate the effects of P6 in nausea. The double-blind cross-over model appears to have proved an effective investigative tool as a basis for investigating the effects of acupressure on EMS.

#### The validity of the placebo

In the previous studies it has been assumed that the placebo treatment provided a true placebo response. As has been discussed previously (vide supra) there have been attempts at validating both minimal acupuncture and mock TNS as placebos. These investigations have not been attempted within the studies on pain (A,B & C) or the study on smoking (D). However, in Study F an attempt has been made to evaluate the patients' attitudes towards sham acupressure.

Sham acupressure is not without its own complications and problems. Five

patients in Study E were unable to continue with the study as they found the Sea-Bands too difficult to wear on the ankle. This may have been due partially to dependent oedema created either by the cancer, or by the chemotherapy, or by other associated problems such as heart failure. However, it is quite clear that 5 of the patients entered into Study E were unable to complete protocol treatment because they could not tolerate the bands on their ankles (sham acupressure). In Study F the first attempt at sham acupressure was to use the Sea-Bands above the elbow. Again this was unacceptable on comfort grounds to a number of patients. Therefore the sham acupressure position was changed so that the band was placed just below the elbow. In Study F it was decided not to use the ankle position, as it was felt that young women would be less prepared to wear the bands around the ankle for cosmetic reasons. Using a point on the arm was thought to be preferable and a point above the elbow was suggested initially as this was distant from P6. As it turned out, the initial suggestion was not practical and so the Sea-Bands were moved to just below the elbow. This was found to be acceptable to all patients in Study F and the sham point appeared to be far enough away from P6 to provide true sham acupressure. Therefore, when using acupressure, it is important to establish an acceptable and comfortable position while at the same time making sure that the sham acupressure point is at an adequate and acceptable distance from the real points requiring treatment.

Table 12.26 demonstrates that patients in Study F felt confident in both real and sham acupressure and that both approaches appeared to be logical. There was no difference in the perceived value of P6 or the sham acupressure point at the beginning of the study. Table 12.27 demonstrates that by the end of the study the women were significantly more confident in

the effectiveness of P6 acupressure, largely one can assume, because it was the more effective treatment. In other words, patients entering the study could not, at the outset, differentiate between real and sham treatment. This supports the claim that the study is of a "double-blind" nature in that the patients were clearly blind to the expected outcome. Furthermore, it provides additional evidence to support the validity of the placebo. The methodology used to evaluate the patient's perception of the placebo is the same as that described by Borkovec and Nau (1972) and previously used in the context of evaluating minimal acupuncture by Vincent (1990). This provides further validation for the claim that sham acupressure is acting as a true placebo in the context of this study, and for the claim that Study F represents the first attempt to create a randomised double-blind cross-over study in the context of evaluating acupressure as a treatment for nausea.

#### Overall results

The overall results of both these two studies are statistically significant. Unfortunately, the number of patients entered, particularly in Study F, was too small to give the study adequate statistical power. This was not for want of trying, but as always in clinical trials patient numbers tend to diminish rapidly when one begins the study. Furthermore, the time constraints of a fourth year project made it impossible for the period of data collection to be significantly extended.

Study E demonstrates that acupressure is a useful complementary or adjunctive therapy in the management of nausea associated with chemotherapy that has a high emetogenic potential. Many of the results in this group, particularly on the 2nd, 3rd and 4th days after chemotherapy had been given, are significant at the 0.01 level. It would be logical to consider

repeating this study, ideally with larger numbers. It would be sensible to concentrate only on chemotherapeutic agents that have a high emetogenic potential as it is in this group that the most impressive results are likely to be obtained. If a further study involving approximately 60 patients demonstrated equally impressive and significant results, it would then be logical to consider recommending P6 acupressure routinely in patients receiving chemotherapy with high emetogenic potential. It is important to remember that to date there have so far been no negative studies within the field of nausea and acupressure, acupuncture or TNS at P6. While, as has been discussed earlier, some of the studies may be methodologically flawed, even studies with more exacting methodology appeared to come to similar conclusions. Yet, in spite of the fact that P6 appears to be one of the most studied and best evaluated points within acupuncture, and that all these studies come to similar conclusions, P6 is not routinely used as an anti-emetic in departments of oncology.

It is interesting to speculate on this particular issue. A recent discussion with Professor John Dundee's department in Belfast elicited the response that the department was evaluating new chemical anti-emetic agents and had abandoned the use of Sea-Bands and other associated techniques which involved stimulation of P6. It is also interesting to note that in spite of this study no attempt has been made to repeat the study at the Department of Oncology at Southampton University and Sea-Bands are not routinely offered to patients having highly emetogenic chemotherapy. Conventional doctors have, quite rightly, called upon the complementary practitioners to produce evidence for their claims. The implied suggestion being that such evidence will act to change practice. The evidence is now available in relation to P6. The studies themselves are becoming more

refined methodologically and still demonstrate a clearly significant result. Why, therefore, are conventional doctors choosing not to make changes when the suggested therapies are cheap, simple and side-effect free? Perhaps this has far more to do with the conventional doctors' entrenched beliefs rather than a real desire to change practice based on hard clinical trial evidence.

Study F suffers much more obviously from a low statistical power because of the relatively small numbers of patients entered. However, when seen in context of all the studies within this field, it follows the same pattern of approximately 60% of patients perceiving real acupressure as beneficial as compared to a 30% placebo response with sham acupressure. While the results from Study F fall into a predictable response rate and provide further evidence pertaining the benefit of P6 acupressure in the treatment of nausea, the main advances relate to the methodology and the evaluation of placebo sham acupressure rather than any insights as to the clinical effectiveness of acupuncture. Fundamentally, this study repeats and further validates the work done by others. The results, while adding to our overall knowledge of the clinical effects of acupuncture, are less important than the development of better study methodology. The study's small patient numbers represent its primary weakness and it would certainly be advisable to repeat this study on a much larger group of patients. A definitive study of this nature should once and for all demonstrate that acupressure at P6 does provide an acceptable side-effect free treatment for EMS.

#### How do these studies fit into the overall picture?

When looking at the patient preference questionnaires, Study E demonstrates that 55% of patients found acupressure at P6 to be beneficial in nausea and



53% of patients found it to be beneficial in vomiting. When this was compared with the sham point, the results were 19% for nausea and 16% for vomiting. Similarly, in Study F, 66% of the patients found acupressure at P6 to be beneficial in the treatment of EMS induced nausea whereas only 30% found the sham acupressure helped as an anti-emetic. Both these results display a certain consistency in that one is dealing with a response rate of around 60% from acupressure and a placebo response from sham acupressure of between 15 and 30%. Study F demonstrates that patient expectation was that both sham and real acupressure points would produce the same result.

The mechanism of acupressure or indeed acupuncture as an anti-emetic is largely unknown. It is quite clear that acupuncture has a number of physiological effects on the body, the area that has been best studied involves its effects on chronic and acute pain. No-one has yet elucidated a mechanism to explain the anti-emetic effects of P6, but it is reasonable to hypothesise that this may not be totally endorphin mediated. It could well be mediated through a whole variety of autonomic effects which could in theory be very point specific.

The arguments outlined by Lewith and Machin (1983) with respect to the evaluation of acupuncture in painful conditions may not hold for the evaluation of acupuncture in non-painful conditions. Good circumstantial evidence is available to suggest that sham acupuncture has a physiological effect beyond that expected from a placebo in painful conditions (DNIC). These two studies, along with the other published literature, provide evidence to suggest that this is not the case in the use of P6 as an anti-emetic. It is possible that sham acupuncture or sham acupressure in this situation may elicit a true placebo response. Certainly the evidence from studies E and F would tend to support this conclusion and might indicate

that we need to consider different clinical trial methodology in studies that involve pain as opposed to studies that involve the treatment of non-painful conditions such as nausea.

### Conclusions

Studies E and F have added further data to support the hypothesis that P6 can act as a powerful anti-emetic in a variety of different conditions. Furthermore, these two studies have suggested clearer study methodology by which acupressure can be evaluated. It would be reasonable to suggest that similar approaches could be applied to the evaluation of acupuncture and TNS. Sham acupressure as a placebo has also been evaluated. Previous studies have analysed the effects of minimal acupuncture and mock TNS but Study F is the first attempt to evaluate the credibility of sham acupressure as a placebo. Furthermore, Study F represents the first attempt to design a credible, randomised, "double-blind", control model that has ever been used to evaluate an acupuncture-related technique. The underlying physiological mechanisms may differ depending on the type of condition that is treated by acupuncture. The physiological mechanism that underpins the treatment of chronic pain may be different to that which underpins the treatment of conditions such as nausea. Consequently, the expected response from sham acupressure or indeed sham acupuncture may differ depending on the type of illness being treated. This leads directly to the hypothesis that different illnesses may possibly need to be evaluated by different study methods.

**APPENDICES TO CHAPTER 12**

Patient Information Sheet for Sea-Band Study  
at Countess Mountbatten House

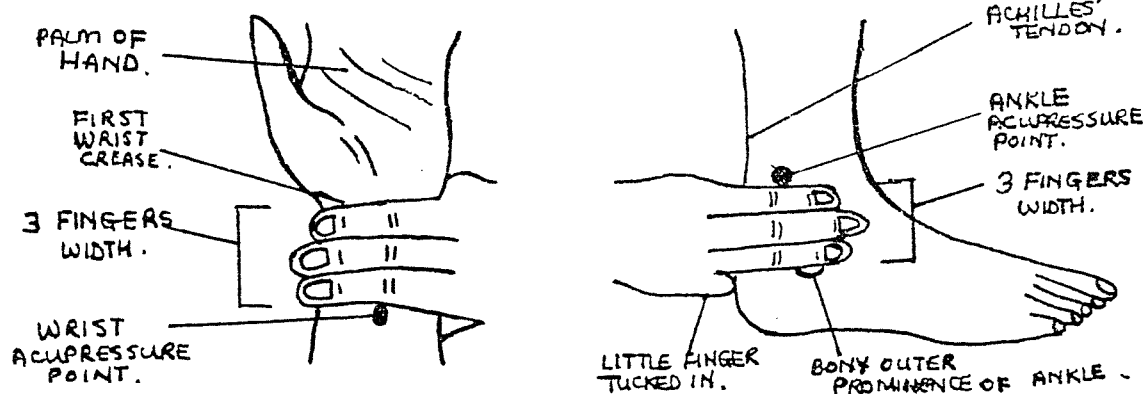
The Sea-Band uses acupressure to reduce nausea and vomiting. It may be helpful in controlling these symptoms, in addition to the drugs given against nausea and vomiting. There are no known side-effects of the Sea-Band.

The Sea-Band is an elasticated bracelet, with a button which exerts pressure on the acupressure point. In this study, two different acupressure points are being investigated. You will be asked to use each of them separately, with the button of the band accurately on the point. One point is on the middle of each wrist, three fingers width from the uppermost crease (see diagram). The other is on each ankle, in the soft tissue between the bony outer part and the Achilles' tendon at the back, three fingers width above the bony outer prominence (see diagram).

You will be given a pair of bands to wear continuously, either on both wrist points or both ankle points (you will be told which of these), for 7 days. It would be helpful if you could apply additional pressure to the points by pressing the buttons whenever you feel sick. After wearing the bands at one of the points for 7 days you will be asked to repeat exactly the same procedure, but this time with the band at the other point.

You will be asked to fill in a diary card for each day you wear the bands. There will also be a simple questionnaire to fill in, comparing the two acupressure points used in the study.

Your participation in this study will be very much appreciated.

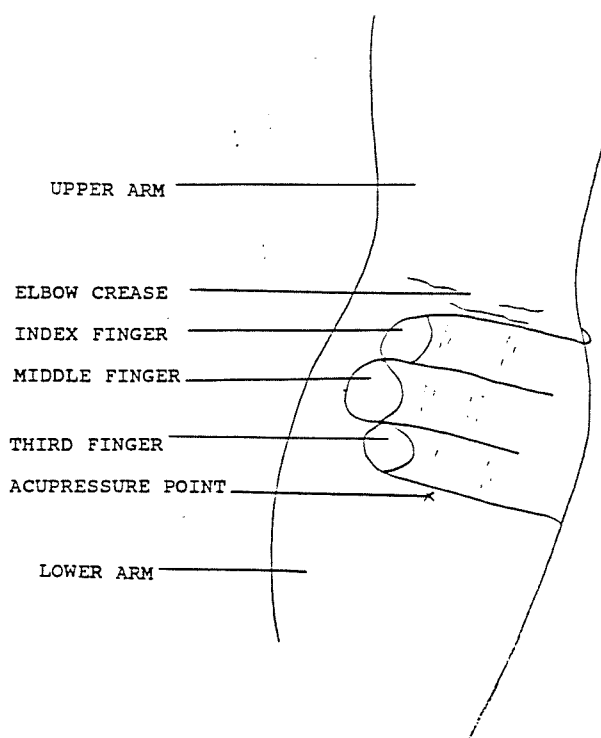


You have kindly agreed to participate in my study to test the relative effectiveness of acupressure in two separate positions, in the treatment of morning sickness. You have been shown how to wear the Sea-bands in both positions, and told to press the plastic button every few hours. It is of great importance that you wear the bands on your wrist and elbow for the week you are told to do so. I would like you to wear the bands just above your elbows for one week, then remove them for two days before wearing your second set of bands on your wrists for one week. I will be sending you a reminder to change your band position. I will visit you again in 16 days time, to collect the Sea-bands, your diary cards and your questionnaires. I will be happy to answer your questions at any time; you may leave a message for me on Southampton 334752.

Thank you for your help, Jane Bayreuther.

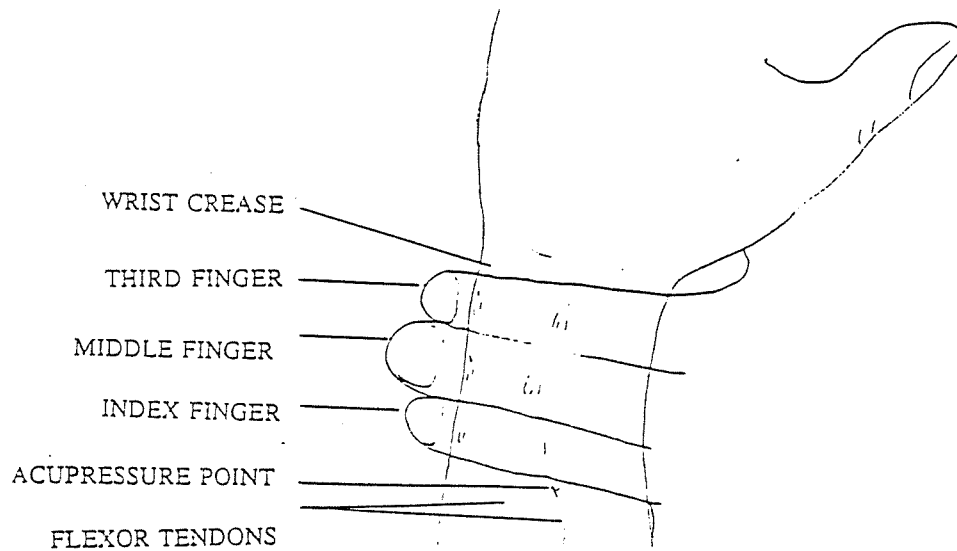
#### ELBOW POSITION. WEEK ONE.

This position is found by placing your middle three fingers on the inside of your elbow, with the edge of your index finger on the elbow crease. The button should be placed facing downwards, just under the edge of your third finger, in the midline, below your elbow. A band must be worn on each elbow.



WRIST POSITION. WEEK TWO.

This position is found by placing your middle three fingers on the inside of your wrist, with the edge of your index finger on the wrist crease. The button should be placed facing downwards, just under the edge of your third finger, in the midline, below your elbow. A band must be worn on each elbow.



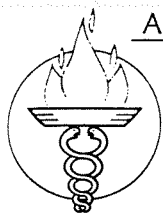
Appendix 12.3

Patient's Consent Form for Sea-Band Study

I have read and understood the attached information sheet about the Sea-Band study, and agree to participate in the study. I am aware that the Sea-Band is used in addition to the drugs used for controlling nausea and vomiting.

I understand that, if at any stage during the study I decline to take part in the research, it will not prejudice any further treatment.

Signed ..... Date .....



**THE CENTRE FOR  
THE STUDY OF COMPLEMENTARY MEDICINE**

51 Bedford Place, Southampton, Hampshire SO1 2DG  
Telephone Southampton: 0703 334752 Fax: 0703 231835

Also at: 6 Upper Harley Street, London NW1 4PS  
Telephone: 071-935-7848 Fax: 071-224-4159  
And: The Complementary Therapy Centre  
Arndale House, St. George's Esplanade,  
St. Peter Port, Guernsey, Channel Islands.  
Telephone: 0481-720708

A6

DR DAVID DOWSON M.B. Ch.B.

DR JULIAN N KENYON M.D. M.B. Ch.B.

DR GEORGE T LEWIS M.A. M.R.C.P. M.R.C.G.P.

**PATIENT INFORMATION SHEET FOR SEA-BAND STUDY.**

The sea-band is similar to a sweat band, with a button which exerts pressure on the acupressure point. They are used to reduce nausea and vomiting without any effect on your unborn baby. Acupressure may be used safely at any stage of pregnancy.

In this study two acupressure points are being investigated to see which has the greater effect. You will be asked to try each of these points for one week. I will not know in which position you will first be wearing the bands, the envelope which you have been provided with contains that information; you should not inform me of its contents.

One point is in the middle of your wrist, a distance equivalent to that of your middle three fingers above the uppermost crease. The second point is in the middle of your lower arm, the same distance below the crease of your elbow. I will demonstrate how to find both of these points.

You will be given two sets of bands, the larger pair are to be used on the upper arm. Both sets of bands are to be worn on both sides of the body. After wearing the bands in one position for 7 days you should remove them and after a break of 2 days, start wearing the other bands in the second position.

You will be asked to fill in a diary card for each day you wear the bands. There will also be a short questionnaire to fill, in comparing the two acupressure points used in this study.

Thank you for your help with this study.

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**PATIENT CONSENT FORM FOR SEA-BAND STUDY.**

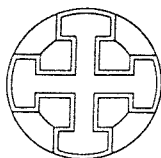
I have read and understood the attached information sheet about the sea-band study, and agree to participate in the study.

I understand that I am free to withdraw from the study at any stage.

Signed..... Date.....



CRC Wessex Regional Medical Oncology Unit  
University of Southampton



CF99, Southampton General Hospital  
Southampton SO9 4XY  
Telephone: (0703) 777222 Ext: 4296/7 & 4314/5  
(Clinical Secretaries) (0703) 634288 Ext: 2448  
FAX: (0703) 783839



Registered in England Charity 225838

Director: Professor J M A Whitehouse MA, MD, FRCP  
(0703) 783839 (direct line)

Dear Dr

Your patient has agreed to participate in a study using the Sea-Band. The Sea-Band utilizes acupuncture to alleviate nausea and vomiting, and may be helpful in controlling these symptoms, in addition to anti-emetic drugs given. There are no known side-effects of the Sea-Band.

The Sea-Band is an elasticated bracelet, with a button which exerts pressure on the acupuncture point. In this study, two acupuncture points are being investigated, and your patient will be asked to use each of them separately. One of the points is on the wrist, and the other on the ankle. The patient will be given a pair of Sea-Bands to wear on both wrists, or both ankles, continuously for the time instructed (this will be for no more than 7 days at each point). The patient will be asked to apply additional pressure by pressing the button himself. A diary card will be given to the patient to record sickness, nausea and general condition for each day the bands are worn. There will also be a simple questionnaire to fill in, comparing the two acupuncture points.

This study aims to evaluate the effectiveness of using the Sea-Band to control nausea and vomiting, since it is a potentially non-invasive, self-administered and inexpensive form of treatment. I am grateful for the help of your patient.

Yours sincerely

C J Williams, DM FRCP  
Senior Lecturer

- CODING
- SICKNESS (VOMITING):

1. None

2. Poor appetite

3. Felt sick but wasn't

4. Sick once

5. Sick more than once
- NAUSEA (FEELING SICK):

1. None

2. Transient nausea, not requiring treatment

3. Transient nausea, requiring treatment

4. Continuous nausea, responding to treatment

5. Continuous nausea, unresponsive to treatment
- MOOD:

1. Very happy

2. Happy

3. Average

4. Miserable

5. Very miserable
- ANXIETY:

1. Very calm

2. Calm

3. Average

4. Anxious

5. Very anxious
- OVERALL CONDITION:

1. Very well

2. Well

3. Fair

4. Poor

5. Very ill

Hospital number .....  
Doctor in charge.....  
Date of start of this card .....

	DAY						
	1	2	3	4	5	6	7
SICKNESS (Vomiting)							
NAUSEA							
MOOD							
ANXIETY							
OVERALL CONDITION							

INSTRUCTIONS

Please complete this card every evening after your last meal, to tell us how you have been feeling during the past 24 hours; this will help us to make a thorough assessment of your illness and any treatment that you may need. The codes to be used are shown.

Questionnaire for Sea-Band Study

Name: .....

Study Number: .....

Date: ...../...../.....

Please complete the following questionnaire about the two acupressure points you have recently used.

Please tick the relevant box in questions 1-8, and for 9 and 10 answer in the space underneath.

			OFFICIAL USE
1. Which acupressure point gave you better control of vomiting?	ankle	<input type="checkbox"/>	<input type="checkbox"/> 4
	wrist	<input type="checkbox"/>	<input type="checkbox"/> 5
	no difference	<input type="checkbox"/>	
2. Which acupressure point gave you better control of nausea?	ankle	<input type="checkbox"/>	<input type="checkbox"/> 6
	wrist	<input type="checkbox"/>	
	no difference	<input type="checkbox"/>	
3. Which acupressure point made you feel generally better?	ankle	<input type="checkbox"/>	<input type="checkbox"/> 7
	wrist	<input type="checkbox"/>	
	no difference	<input type="checkbox"/>	
4. Were you able to wear the bands continuously as instructed?	yes	<input type="checkbox"/>	<input type="checkbox"/> 8
	no	<input type="checkbox"/>	
5. Were you able to keep the bands in their correct positions?	yes	<input type="checkbox"/>	<input type="checkbox"/> 9
	no	<input type="checkbox"/>	
6. Did you apply pressure at the wrist points?	yes	<input type="checkbox"/>	<input type="checkbox"/> 10
	no	<input type="checkbox"/>	
7. Did you apply pressure at the ankle points?	yes	<input type="checkbox"/>	<input type="checkbox"/> 11
	no	<input type="checkbox"/>	
8. Would you use Sea-Bands again to control nausea and vomiting?	yes	<input type="checkbox"/>	<input type="checkbox"/> 12
	no	<input type="checkbox"/>	
9. What side-effects were you aware of from wearing the Sea-Band?	.....		
	.....		
10. Do you have any further comments about the use of Sea-Band in this study?	.....		
	.....		

THANK YOU FOR YOUR HELP.

SEA-BAND STUDY.

My name is Jane Bayreuther and I am a fourth year medical student at the University of Southampton. This year I am examining the effectiveness of Sea-Bands at two separate points, in the treatment of morning sickness. Previous studies have shown that Sea-Bands can prevent, or reduce morning sickness. You may already have heard about, or used, Sea-Bands; they resemble sweat bands and are worn in the same manner.

I am seeking the help of women between the ages of 18-35, in the first few weeks of pregnancy. You will be asked to wear the Sea-Bands on both wrists for one week and below both elbows for one week. The Sea-Bands should not cause you any discomfort and I will be supplying them to you. You will also be asked to make a note of how ill you feel for each day you wear the Sea-Bands. Sea-Bands may be worn with safety in pregnancy.

If you are interested in helping me in this study, or would just like more information about Sea-Bands, please complete the lower section of this leaflet and return it to your G.P.'s receptionist. I will contact you in the near future to arrange a convenient time and place to meet. This will not mean you are obliged to participate in the study.

If you wish to contact me directly, my telephone number is: Southampton 334752.

Thank you for your help.

Jane Bayreuther.

 -----  
SEA-BAND STUDY.

NAME: \_\_\_\_\_

ADDRESS: \_\_\_\_\_  
 \_\_\_\_\_  
 \_\_\_\_\_  
 \_\_\_\_\_

TELEPHONE: \_\_\_\_\_

QUESTIONS.

Please circle the appropriate answer.

for official  
use only.

1. Did you feel that the acupressure at the wrist point improved your morning sickness ?

YES/NO.

☐ ☐

2. Did you feel that the acupressure at the elbow point improved your morning sickness ?

YES/NO.

☐ ☐

3. Which position did you find most beneficial ?

WRIST/ELBOW.

☐ ☐

4. How confident would you be in recommending this treatment to a friend ?  
( 0 - would not recomend. )  
( 6 - would recomend very strongly. )

WRIST: 0---1---2---3---4---5---6

☐ ☐ ☐ ☐

ELBOW: 0---1---2---3---4---5---6

☐ ☐ ☐ ☐

5. How successful do you think this treatment would be in alleviating other complaints ?  
( 0 - not successful at all. )  
( 6 - completely successful. )

WRIST: 0---1---2---3---4---5---6

☐ ☐ ☐ ☐

ELBOW: 0---1---2---3---4---5---6

☐ ☐ ☐ ☐

DIARY CARD.

Please mark a cross on the line each day as an indication of how ill you felt over the whole day.

WEEK ONE.

DAY 1.

\_\_\_\_\_

no nausea. extreme nausea.

How many times were you sick today ? \_\_\_\_\_

DAY 2.

\_\_\_\_\_

no nausea. extreme nausea.

How many times were you sick today ? \_\_\_\_\_

DAY 3.

\_\_\_\_\_

no nausea. extreme nausea.

How many times were you sick today ? \_\_\_\_\_

DAY 4.

\_\_\_\_\_

no nausea. extreme nausea.

How many times were you sick today ? \_\_\_\_\_

PATIENT QUESTIONNAIRE.

1. Study number.		<input type="checkbox"/> <input type="checkbox"/>
2. Group.		<input type="checkbox"/> <input type="checkbox"/>
3. Age.	_____	<input type="checkbox"/> <input type="checkbox"/>
4. Parity.	_____	<input type="checkbox"/> <input type="checkbox"/>
5. Cohabiting.	YES/NO	<input type="checkbox"/> <input type="checkbox"/>
6. Gestation, in weeks.	_____	<input type="checkbox"/> <input type="checkbox"/>
7. Previously used Sea-Bands.	YES/NO	<input type="checkbox"/> <input type="checkbox"/>
8. Current knowledge of Sea-Bands.		<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>
9. How logical does this treatment seem.		
WRIST: 0---1---2---3---4---5---6		<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>
ELBOW: 0---1---2---3---4---5---6		<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>
10. Confidence in the treatment alleviating morning sickness.		
WRIST: 0---1---2---3---4---5---6		<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>
ELBOW: 0---1---2---3---4---5---6		<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>

**SECTION 4**  
**DISCUSSION**

**CHAPTER 13**



## CHAPTER 13

### DISCUSSION

#### Introduction

The overall objective of this thesis was to select relevant clinical trial methods in order to define and establish an appropriate methodology for clinical trials within the field of acupuncture. This necessarily includes an understanding of placebos, the adaption of current statistical techniques to clinical trials within the field of acupuncture and the evaluation of a variety of subjective and objective methods for assessing benefit and outcome in clinical trials involving acupuncture. Before the first objective can be fulfilled, it is essential to lay down an appropriate methodological framework so that both the method and application of acupuncture to a variety of clinical conditions can be adequately assessed. This therefore represents the first objective. Lewith and Machin (1983) laid down this initial framework for the evaluation of acupuncture in the treatment of painful conditions. This thesis has expanded the framework in order to allow for the evaluation of acupuncture in a variety of different clinical situations: pain, addiction (smoking withdrawal) and the treatment of nausea. Although nausea is a symptom, this particular therapeutic approach has been used as a model for the treatment of internal disease.

The second objective was to investigate the value of placebo control groups. As has already been discussed, the definition of appropriate control groups within acupuncture is a major methodological problem. Two main approaches have been outlined in trials concerned with pain; the use of mock TNS and minimal acupuncture. A detailed discussion of the

strengths and weaknesses of each of these approaches is found in chapter 5. While it is desirable to develop acupuncture trial methodology with the help of a true placebo control group, it is debatable whether this can ever be achieved. However, I have presented evidence which suggests that both mock TNS and minimal acupuncture provide relatively acceptable placebo control groups with which to compare real acupuncture. I have opted, in the context of studying pain, to look exclusively at mock TNS as a placebo controlled group. Minimal acupuncture may be triggering as yet unknown neurological and neurohumoral events which could, through DNIC and possibly other as yet unknown mechanisms, be providing analgesia. These concepts are fully elucidated in chapter 4.

In the context of smoking withdrawal, the only control group studied was that of sham acupuncture and it is clear that this does not represent a valid placebo control with which to compare real acupuncture. It is probable that sham acupuncture is having exactly the same physiological effect on the process of addiction as real acupuncture.

In the final group of studies, again a real versus sham acupuncture model was used, but this time to investigate the effect of acupressure on nausea. Here it appears that a sham versus real model may be appropriate in the context of this particular symptom and possibly, therefore, as a method for investigating the use of acupuncture in internal disease.

The third objective was to adapt currently available statistical techniques to clinical trials within the field of acupuncture. The study on headache went some way to fulfilling this aim as a survival curve technique was used to evaluate treatment outcome. This fits closely with observations from descriptive studies on acupuncture which suggest that acupuncture has a limited duration of action (Lewith et al, 1984).

Finally, a variety of different objective and subjective criteria have been developed to evaluate the outcome of acupuncture treatment. Lewith et al, 1984 developed a global score through which to assess outcome in a descriptive study on back pain. Study B used simple diary cards over prolonged periods of time in order to evaluate outcome in the treatment of headache. Study C used a variety of subjective measures of outcome building on the work of Machin et al (1988) when comparing the value of visual and verbal pain scales. Again in study C these were correlated carefully with a variety of objective measurements which relate to joint function.

While all the objectives have been addressed in each study, all 4 of the major objectives have been addressed by the body of the work presented within the 6 clinical trials. The body of work as a whole, particularly taken in context with other work published over the last decade, has allowed the definition of better study methodology for acupuncture as a whole. Appropriate controls have been established as far as studies A, B and C are concerned in the context of real acupuncture versus mock TNS for the treatment of pain. Appropriate controls appear to have been established in the 2 acupressure studies (E and F) in the treatment of nausea. Study B has certainly shown how our current knowledge of statistics can be adapted to trials on acupuncture and study C has used a range of objective and subjective methods in order to evaluate a painful condition (TMC joint OA).

One of the main problems in designing clinical trials on acupuncture is that the underlying mechanism is not completely understood. For instance, many of the early studies into painful conditions used a sham versus real acupuncture model (Richardson & Vincent, 1986) but now our current

understanding of DNIC (Le Bars et al, 1991) would suggest equating sham acupuncture with a placebo is unsustainable on physiological grounds when one considers how noxious stimuli may attenuate pain. Similarly, in the context of studies on nausea, while we understand much more about the mechanism of chemotherapeutically induced nausea (Leslie & Reynolds, 1992), we do not understand the mechanism of acupuncture and neither do we understand how acupuncture may be affecting the 5HT system implicated in chemotherapeutically induced nausea and vomiting. Similarly, our physiological understanding of the addiction process is limited and therefore the effects of acupuncture on this process are inadequately understood at a mechanistic level. While we may hypothesise that acupuncture may be working through the endorphin system (Clement-Jones et al, 1979), we cannot be certain that this is the case in smoking withdrawal.

Therefore, one of the major difficulties in designing more complete and detailed clinical studies is our current failure to understand the underlying mechanism. This has produced erroneous assumptions such as the view held by many clinical researchers during the early 1980s, that sham acupuncture was effectively a placebo.

This work has essentially been of a pathfinding nature and therefore some of the early studies, such as study A, appear in retrospect to have been particularly naive in their construction and methodology. The two best constructed studies (C and E) unfortunately suffer because far too few patients completed protocol treatment. In spite of this, both studies attained statistical significance but would have been much more powerful had they involved more patients.

As I shall discuss in this chapter, I believe I have been involved in the

development of a clear methodological model which unites traditional Chinese medicine, our limited neurophysiological understanding of acupuncture and our current understanding of clinical trial methodology. These studies have allowed me in effect to develop a unified hypothesis through which various aspects of acupuncture can be further evaluated.

### The clinical trials

Each of the 6 clinical trials outlined in this thesis have had their strengths and weaknesses highlighted in the discussion sections of Chapters 10, 11 and 12. These 3 chapters show an evolution in study methodology and critical thought in relation to evaluating acupuncture. The studies themselves were initiated in 1980 in the Department of Primary Medical Care at Southampton University. At that time it was thought reasonable that a descriptive evaluation of the effects of acupuncture in a variety of conditions would provide the basis for a DM thesis (Lewith & Machin, 1981). However, it became apparent that an exercise in data collection was too superficial to fulfil the requirements for a post-graduate research degree. While at the Department of Primary Medical Care a number of clinical trials were initiated. The first was the study on post-herpetic neuralgia. While planning and executing this study, it became apparent that clinical trials within the field of acupuncture were a complex undertaking. A thorough knowledge of conventional clinical trial methodology was required, as was a grasp of statistics and a clear understanding of the many different approaches to acupuncture. Claims from the traditional Chinese acupuncturists, those practising primarily auricular therapy (ear acupuncture) and those merely treating tender points in pain all needed to be taken into account and evaluated critically (Lewith & Machin, 1983). Chapter 10 analyses studies involving real acupuncture versus placebo in 3

painful conditions. The discussion at the end of this chapter shows how the study methodology has evolved in relation to the evaluation of pain. In Study A, the pain measurement methods employed were simple and unsophisticated. By contrast, Study C shows a much better understanding of how to evaluate treatments for chronic pain both subjective and objective. Study C involves multiple parameters for measuring pain and also includes measurements of functional disability.

Study A used simple statistics whereas in Study B the statistical sophistication improved and involved the use of survival curve analysis for the first time in the evaluation of acupuncture. The overall evolution of the study methods in Chapter 10 demonstrates an ability to learn from previous errors and to overcome them. Chapter 12 demonstrates a similar evolution; study E utilised a cross-over model although it was a single-blind study, whereas in Study F the cross-over model was developed further so that it became "double-blind". Study F also included a validation of sham acupressure for the first time. There have been attempts at validating both minimal acupuncture and mock TNS (vide supra), but so far no published attempt at the validation of sham acupressure.

Study D, the smoking study, represented an attempt to introduce proper guidelines into acupuncture studies within the field of addiction. Prior to the early 80s, claims for acupuncture as a treatment for smoking and hard drugs were based largely on descriptive studies. There had been little attempt to orchestrate properly controlled randomised trials with appropriate periods of follow-up.

Each study built on the previous experience and mistakes encountered in earlier investigations. Suggestions in relation to the statistical handling of data were outlined in the early 80s and have been reproduced in

full in chapter 9. The published investigations have also suggested a number of faults, difficulties and problems that can occur in attempting to measure the subjective phenomenon of pain. Again these issues were addressed by Machin and Lewith (1988).

The major problems relating to these studies, particularly studies C and F, are the limited number of patients entered. While this does not necessarily devalue the study methodology employed, it does (for statistical reasons) make it difficult to draw definitive conclusions. It is probable that with larger patient numbers (particularly in these 2 studies), it would have been possible to draw further more detailed conclusions pertaining to study methodology.

#### The story so far

Many of the earlier clinical studies involving acupuncture investigated its use as an analgesic for chronic pain. As has already been outlined the major studies involved clinical trials in which real acupuncture was compared with sham acupuncture (Leewith & Machin, 1983). Even though many of the sham versus real acupuncture studies have substantial statistical weaknesses, sham acupuncture seems to provide an effect greater than that which would be expected from a true placebo (Leewith & Machin, 1983; Richardson & Vincent, 1986). The studies reviewed in Chapter 9 and upon which the first theoretical model for evaluating acupuncture was based, concentrated exclusively on the management of chronic pain. Consequently, studies A, B and C have used different trial methodology and attempted to compare real acupuncture with a true placebo, rather than using sham acupuncture which, in any event, appears to represent an ineffective form of acupuncture (see Table 6.4).

By contrast, chapter 11 reviews studies involved in the treatment of

smoking with acupuncture. These studies suggest that there is little to choose between real and sham acupuncture as a treatment for addiction. An excellent review by Schwartz (1987) has examined the detailed evidence within this particular field. Eight studies are reported including the study outlined in chapter 11 (see Table 13.1). All of these studies look at the effect of acupuncture on a sham versus real basis. Two of them have very limited periods of follow-up, Steiner et al (1982) and Lagrue et al (1983) analyse the number of patients who have ceased to smoke either at the end of treatment or within one week of treatment having been completed. Parker and Mok (1977) look at smoking cessation at the end of 6 weeks and Gilbey and Neumann (1977) examine smoking cessation at the end of 3 months. Three of the other 4 studies analyse smoking cessation at the end of 6 months (MacHovec & Mann, 1978; Lamontagne et al, 1980 and Gillams et al, 1984). Vandevenne et al (1985) look at cessation rates at the end of 1 year.

The first point to make is that smoking cessation rates in these studies average 25%. The studies all use acupuncture exclusively and there appears to be little difference in smoking cessation in those with fairly short-term follow-up and those with much longer follow-up. This argues strongly against Ter Reit et al's (1990) conclusion that acupuncture has no effect on smoking cessation. The overall cessation rate suggests that acupuncture can be classed as a good treatment designed to promote smoking cessation. However, the conclusion reached by these 8 studies is that only in one of them is there anything to choose between sham and real acupuncture. MacHovec and Mann (1978) showed a clear difference in acupuncture performed at the correct site as compared with acupuncture performed at an incorrect site, but had the smallest number of patients



entered. Only 12 patients were entered into this study whereas in all the other studies, over 20 patients were entered into each group and in the Vandevenne study, over 100 patients were entered into each group. This would tend to support the conclusion that acupuncture produces an increased smoking cessation rate. However, overall there is little to choose between using a real and sham acupuncture point.

The third group of studies involved using acupuncture as a treatment for internal disease where it is appropriate to use P6/nausea model as an experimental tool (see Table 13.2). Here we have clear evidence to suggest that real acupuncture and acupressure provided a therapeutic benefit in between 50% to 70% of patients whereas sham acupuncture and acupressure provided benefit for only 20% to 30% of patients.

Consequently, we have 3 different groups of diseases all showing slightly different responses to a real versus sham model.

1. In chronic pain it appears that sham treatment provides an ineffective form of acupuncture, benefiting 45-50% of patients. Real acupuncture provides significant pain relief in 60-65% of individuals in these situations (Lewith & Machin, 1983; Richardson & Vincent, 1986).
2. In the treatment of addiction, there appears to be very little difference between the real and sham points. While acupuncture seemed to help the treatment of smoking addiction, putting needles into "inappropriate points" appears to be just as effective as putting needles into "appropriate points" (Schwartz, 1987).
3. Finally, we have a group of internal illnesses, the best studied acupuncture point being the use of P6 in nausea. In this group of studies, it is clear that a sham versus real model engenders a

placebo response (20%-30%) when using acupuncture placed in an inappropriate point. Real acupuncture or acupressure appears to provide a significant clinical response in 50-70% of patients (Dundee et al, 1991).

### Neurophysiology

Chapter 4 outlined the neurophysiological basis for acupuncture. The vast majority of the research work completed is within the field of pain. Many of the studies which show that naloxone can completely reverse the effect of acupuncture have been carried on acute experimental pain in rodents (Cheng & Pomeranz, 1980). Furthermore, the experimental work on DNIC leads one to believe that many of the non-specific effects of needle puncture may in fact be endorphin mediated and naloxone reversible (Le Bars et al, 1991).

Chronic pain is certainly a different phenomenon to common laboratory models used to investigate acute experimental pain. It is apparent that in many instances patients with chronic pain (such as those who present with sympathetic dystrophies) will respond to empirical manipulation of the autonomic nervous system. For instance, guanethidine blocks, a technique widely used and commonly available within pain clinics, will specifically alter local autonomic function and is reported to have a significant and dramatic effect on autonomically mediated pain syndromes.

The mechanism of acupuncture's effect in heroin addiction is clearly mediated through the endorphin system (Clement-Jones et al, 1979). While many mechanisms may be invoked to explain the effect of acupuncture on addiction, few of them have been clearly supported by hard experimental evidence. However, the available evidence suggests that some addictive processes, and the subsequent withdrawal from the addiction, may be

endorphin mediated and therefore naloxone reversible.

It is apparent that any noxious stimulus will trigger release of endorphins and this, in itself, will have an analgesic effect. It is likely that chronic pain has a larger autonomic input than acute pain. This would be supported by the empirical experience of those who have worked within pain clinics. Consequently, it is reasonable to suppose that acupuncture in chronic pain will be at least partially endorphin mediated. Therefore sham acupuncture, which stimulates endorphin release through diffuse noxious inhibitory control, will have some effect in alleviating chronic pain. However, there may be other effects gained from acupuncture's autonomic stimulus which do not act through DNIC.

In addictive processes it is reasonable to suggest that the major underlying mechanism of the acupuncture response is probably endorphin mediated. Consequently, one might not expect too much difference between real versus sham acupuncture in the treatment of smoking cessation (table 13.1). Natural opiates may underpin, equally, the effects of real and sham acupuncture in the treatment of this condition (Pomeranz 1991).

The final group of studies involved an acupuncture related technique in the treatment of nausea. It is possible, perhaps probable, that acupuncture's effect in internal diseases is largely autonomically mediated (Mann, 1977). This would be supported by some of the very limited physiological research that we have in this field. However it must be understood that the mechanism of acupuncture as an anti-emetic effect is as yet unclear. Equally, the physiological basis which underpins the effect of acupuncture in asthma, irritable bowel syndrome, psoriasis and eczema is undefined. The endorphins have not been invoked as a putative mechanism to explain acupuncture's effect in these internal conditions. It is therefore

reasonable to hypothesize that acupuncture may be working through non-endorphin possibly autonomically mediated mechanisms, in these conditions. If this is the case then point selection may be of vital importance in the treatment of internal disease. Traditional Chinese medicine attributes very specific functions to each acupuncture point and this is certainly compatible with an autonomically mediated mechanism. Furthermore, the clear clinical differences that exist between real and sham acupuncture in the treatment of nausea strongly support the claim that this condition may be responding differently possibly because there are different underlying mechanisms than those involved in the treatment of pain and addiction (table 13.2).

#### The way forward

From the 3 groups of illnesses studied in this thesis, it would seem that 3 different acupuncture models might emerge. In Chapter 9, the arguments for a real versus sham acupuncture model in chronic pain were shown to provide a limited assessment of the real effects of acupuncture. It is therefore reasonable to suggest a real versus placebo model rather than a real versus sham acupuncture model when attempting to evaluate the effects of acupuncture in a chronically painful condition. It is obvious that further evaluation of appropriate placebos is required. Perhaps the placebo used in studies A, B and C (mock TNS) is not the most appropriate and a better approach might be found. However, the clinical response within studies on chronic pain ties in closely with the information outlined in Chapter 5 and would imply that in chronic pain a combined endorphin and autonomic effect is occurring. This may explain the observation that sham acupuncture represents a poor form of acupuncture, one that is probably endorphin mediated through a range of physiological

mechanisms including DNIC.

The opposite situation would appear to be occurring in the studies on smoking cessation. Here we have consistent reports that suggest that smoking does respond to acupuncture and acupuncture-related techniques, but that it makes little difference as to whether a real or sham point is used. Therefore, in studies on addiction, we might assume that the mechanism is completely endorphin mediated, and that appropriate clinical trials should be based on a real versus placebo model or a model involving comparative treatment methods. It should not be based on a real versus sham acupuncture model as this does not fit with the clinical trial evidence we have available, neither does it fit with our neurophysiological understanding of what might be happening.

The final group of studies involves looking at internal disease. The best and most clearly evaluated example of this is the treatment of nausea with P6. Here we are unclear about the mechanism involved but suspect that it is autonomic and not endorphin mediated. Furthermore, the available evidence demonstrates unequivocally that sham stimulation of P6 results in a placebo type response. In a sense this allows us to return full circle to a traditional Chinese approach.

Acupuncture was developed as a system of preventative medicine, largely targeted at balancing the body's energy in order to allow the individual to remain in good health. The primary focus within traditional Chinese medicine is not in the management of pain, but rather in the treatment of a whole range of internal diseases, frequently in conjunction with traditional Chinese herbal remedies (Lewith & Lewith, 1980). The selection and prescription of points for non-painful conditions, such as the treatment of nausea, is firmly rooted in traditional Chinese theory.

Consequently, it is interesting to note that in the treatment model which makes most use of traditional Chinese concepts, it appears that a sham versus real acupuncture model is applicable. This is probably the least endorphin mediated of the 3 acupuncture treatment models evaluated in the context of this thesis, and yet it appears to totally contradict the hypotheses set out in chapter 9 which deal exclusively with the management of painful conditions. It would, therefore, be reasonable to put forward a hypothesis based on these observations.

#### The hypothesis

It seems that the closer one comes to the treatment of a purely endorphin mediated mechanism, as in smoking cessation, the less difference there will be between real and sham acupuncture (Schwartz 1987). Conversely, specific point selection, based largely on traditional Chinese theory, appears to be more important in the treatment of internal conditions such as nausea (Dundee 1991). Chronic pain falls between these two, having both endorphin and possibly an autonomically mediated mechanisms (Lewith & Machin, 1983)

The hypothesis generated by this thesis would suggest that there are three main models for acupuncture studies.

1. It is probable that addictive processes are mediated through the natural opiate system. It is therefore possible that the clinical effects of real acupuncture in addictive processes may be exclusively opiate mediated. We can observe that there is no difference between sham and real acupuncture in the treatment of smoking cessation (13.1). Therefore, non-specific needling may be having as great a clinical effect as specific needling techniques. Non-specific needling techniques may be releasing endorphins through DNIC.

Therefore, if researchers wish to design studies to test the efficacy of acupuncture in addictive processes, it is reasonable to suggest that they compare acupuncture with non-invasive placebos such as mock TNS, or other ethically acceptable treatments such as hypnosis, group therapy or nicotine patches and/or nicotine gum. Further studies using a sham versus real model would only serve to confound rather than elucidate the issue of whether acupuncture is effective in the treatment of addiction. This aspect of our hypothesis unifies the putative underlying mechanism for acupuncture in addiction and consistent observations of a number of clinical trials.

2. If the P6/nausea model can be used as an effective method for evaluating the effects of acupuncture in internal disease, then this too has a great deal to tell us about future studies. It is possible that the effect of acupuncture in internal disease is mediated through the autonomic system. If the P6/nausea model holds true for a whole variety of internal diseases, then it is reasonable to suggest that the real versus sham acupuncture model may be an appropriate mechanism through which acupuncture could be evaluated in the treatment of internal disease. It appears that sham acupuncture might be a true placebo in this situation because of its very specific effects on the body's neurophysiology. Further studies would conceivably use a sham versus real acupuncture model with some likelihood that sham acupuncture would produce no more than a placebo response. However, it would be advisable to validate this hypothesis concerning internal disease much more comprehensively in at least one other condition, for instance asthma.
3. It appears that in chronic pain, both these above mechanisms may be

operating. Sham acupuncture represents a poor form of acupuncture as has already been discussed at length (Lewith & Machin, 1983). Therefore, in chronic painful conditions, appropriate clinical trial methodology will involve either using some sort of placebo control group, such as mock TNS or minimal acupuncture, or comparing acupuncture with a well validated conventional treatment.

What has clearly emerged from this thesis and the decade of work which it covers, is that the exact nature of the questions asked within any particular study are of vital importance. These questions must be placed in the context of a good understanding of the underlying neurophysiology involved in acupuncture and how that may impinge on the suggested study model. It is very clear that many of the early studies involving real versus sham acupuncture models in the treatment of chronic pain failed to grasp the true clinical and neurophysiological implications of the study model employed. It is also likely that if the P6/nausea model holds for the treatment of all internal diseases, that we may now have a much more effective way of testing the validity of many of the assumptions within traditional Chinese medicine. For instance, a study involving the real versus sham acupuncture model for asthma may use classical traditional Chinese theory as the basis for point selection. While this may fail to "prove" the philosophical concepts that underpin traditional Chinese medicine, as a body of work it might validate the use of these concepts empirically.

### Conclusion

The objective of this thesis was to provide a strategic approach to research methodology in order to develop better methods of assessing the clinical effects of acupuncture. It was to involve elements of



traditional Chinese medicine, the development of appropriate outcome measures, statistics, the physiological mechanism that lay behind acupuncture and our current understanding of placebos. These principles were to be firmly grounded in current clinical trial methodology. The thesis has achieved all its objectives. In spite of the fact that some of the clinical trials in themselves are individually weak because of small patient numbers, it has been possible to integrate both modern physiology and traditional Chinese medicine into one coherent and unified model pertaining to clinical studies in acupuncture.

Furthermore, this model can be tested by the use of more detailed clinical trials in a number of simple painful, addictive and non painful conditions. Our current understanding of statistics has been used to great advantage in developing better and more realistic methods of evaluating chronic symptomatology. This was demonstrated clearly in study B. The effect of placebos was looked at critically, both in the studies involving chronic pain and in the studies on acupressure. It is, however, apparent that far more work is required in the general field of placebos to enable us to understand them better. Such studies are required both from complementary and conventional medical practitioners and may help us improve our understanding of disease processes and consultation technique. This thesis has drawn together a number of very diverse disciplines, including philosophy, neurophysiology and statistics. It is something of an achievement to have even begun to develop a model that could possibly be used to bind these diverse areas into a coherent whole which in its turn will allow us to begin to evaluate and understand acupuncture in a more complete manner.

**TABLES FOR CHAPTER 13**

TABLE 13.1 Summary of clinical trials involving real versus sham treatment for smoking

Authors	Total	Acupuncture Technique	Follow up	Study Model	Cessation rates	
					Real Acupuncture	Sham Acupuncture
Vandevenne et al 1985	200	Classical Body	1 year	Blind Randomized Control Trial (RCT)	40%	32%
MacHovec & Man 1978	58	Auricular. Lung Point	6 months	Comparative RCT including Untreated group	25%	0%
Gillams & Lewith 1984	87	Auricular. Lung Point	6 months	Comparative RCT, including Group Therapy	18%	15%
Lamontagne et al 1980	75	Auricular. Lung Point	6 months	Single Blind RCT including Advice Group	8%	16%
Gilbey & Neumann 1977	93	Auricular. Lung Point	3 months	Randomized RCT Single Blind	21%	15%
Parker & Mok 1977	41	Auricular. Lung Point	6 weeks	Randomized RCT Single Blind	14%	15%
Lagruet et al 1983	154	Auricular. Lung Point	1 week	Randomized RCT Single Blind	44%	40%
Steiner et al 1982	23	Auricular. Lung Point	End of Treatment	Randomized RCT Single Blind	9%	8%

If we exclude the MacHovec & Man study, which appears to be the only one showing sham acupuncture has no effect at all, then the average response to real acupuncture is 22.5%, and the average response to sham acupuncture is 20%.

TABLE 13.2 Summary of clinical trials involving real versus sham treatment for nausea

Authors	Number	Condition	Acupuncture Technique	Study Model	Results
					Real Acupuncture (Acupressure) Sham Acupuncture (Acupressure)
Price & Lewith 1991	53	Chemotherapeutically induced nausea	Acupressure	Randomized Single Blind Crossover Study	54% 18%
Bayreuther & Lewith 1994	23	Early Morning Sickness	Acupressure	Randomized Double Blind Crossover Study	69% 31%
Aloysio & Penachioni 1992	66	Early Morning Sickness	Acupressure	Randomized Controlled Study Comparing 4 Groups of Patients	60% 30%
Dundee et al 1988	120	Early Morning Sickness	Acupressure	Randomized Controlled Study with no Crossover	58% 24%
Dundee et al 1991	62	Post Operative Nausea	Acupuncture and Acupressure	Comparative Randomized Study involving Comparative Groups	Real Acupressure 60% Real Acupuncture 80% 30%

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