

DO SIMPLIFIED DRUG REGIMENS IMPROVE COMPLIANCE?

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By

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ABSTRACT

A PROTOCOL FOR THE DESIGN OF A RANDOMIZED CLINICAL TRIAL IN A FAMILY PRACTICE SETTING IS DESCRIBED. THE TRIAL IS DESIGNED TO TEST IF TWICE A DAY (B.I.D.) ANTIBIOTICS PRODUCED BETTER COMPLIANCE THAN THE STANDARD FOUR TIMES A DAY (Q.I.D.) REGIMENS. THE DISEASE MODELS OF STREPTOCOCCAL PHARYNGITIS AND UNCOMPLICATED URINARY TRACT INFECTION ARE USED BECAUSE OF THEIR SIMILARITY, AND BECAUSE THEY ARE COMMON IN THE FAMILY PRACTICE SETTING. COMPLIANCE MEASURES INCLUDE URINE ASSAY FOR ANTIBIOTIC PILL COUNTS AND DROP OUT RATES. COMPLIANCE WILL BE ANALYZED IN RELATIONSHIP TO THE TYPE OF REGIMEN, SIDE EFFECTS AND DISEASE OUTCOME.

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I. INTRODUCTION

Compliance has become an important word in every day medical care as evidenced both by its recent inclusion in the Index Medicus and in the drug advertisements of medical journals. A clear definition of compliance is essential to the understanding of this thesis. Compliance in its clinical sense is *the extent to which patients follow the recommendations of their physicians*. This definition does not take into consideration the point at which partial compliance is equivalent to non-compliance as this will be discussed in the analysis section.

Compliance is often the last step in the successful solution of the health problem. Once an efficacious therapeutic regimen is found for a specific problem, then the only obstacle standing in the way of a successful outcome is whether the patient will follow the regimen i.e. patient compliance. The classic example is hypertension. Pharmacologists in the 1960's made it possible to control blood pressure and subsequent trials showed treatment to be effective i.e. patients taking these drugs had less morbidity and mortality than those on no treatment(1). Unfortunately, this advance has not had as great an impact as expected due to poor compliance with long-term anti-hypertensive drug therapy(2). As will be discussed below, similar evidence of non-compliance has been found for short-term regimens and other long-term regimens. With this realization of the extent of non-compliance, the importance and relevance of research

into factors affecting compliance become clear.

It seems logical that patients would be more likely to adhere to a simple rather than to a complex regimen. In fact, as far back as 1954(3), it was suggested that reducing dosages to the fewest possible per day would increase compliance. Today, physicians are urged both by the editors of medical journals(4) and by their advertisers to use once a day or twice a day regimens because they are "easy to remember", "easy to comply with".(Diag. 1) One may reasonably ask that if a simple regimen is as efficacious as a more complex one; why not choose the simplest one. Unfortunately, the relationship between complexity and compliance is far from clear. In fact, several studies have shown that compliance is better with more complex regimens(5,6). It would therefore seem a matter of some importance to determine whether simplifying drug regimens actually reduces compliance before the current wave of popularity for simplified regimens progresses to the extent where a controlled trial would be deemed unethical.

twice-a-day

for maintenance therapy

easy to
remember



easy to
comply
with



Diag. 1

II. REVIEW OF THE LITERATURE

This review of the literature was done as a prelude to the actual design of the trial. It was considerably simplified by the annotated bibliography of Haynes & Sackett(7) and by computerized searches of the literature. The following outline will be followed:

- A. The magnitude and importance of non-compliance both with short-term and long-term regimens will be discussed. This discussion will include both the direct and indirect benefits of a compliance improving strategy.
- B. The present state of knowledge relating to factors known to affect compliance will be reviewed.
- C. Studies that have dealt with some aspect of the simplification manoeuvre will be reviewed with some emphasis on methodologic soundness.
- D. Studies testing other compliance improving strategies will be reviewed.
- E. Standards will be developed for the design of a compliance trial.

A. Magnitude and Importance of Non-Compliance

Poor compliance with long-term drug therapy has been well documented in such groups as hypertensives(2), patients with tuberculosis(8) and patients with rheumatic fever(9). Perhaps because the long-term burden on society is less, short-term illnesses have attracted less attention. Nevertheless, a similar problem of poor compliance seems to apply to short-term illnesses. Charney(10) studying ten-day penicillin treatment in children found that by the ninth day only 56% were still taking their penicillin as measured by urine assay. Bergman, again in a pediatric population with streptococcal infections using a urine assay, found only half taking their penicillin by day three, 29% by day six and 18% by day nine(11). Similarly, Porter in a British general practice setting found overall compliance with antibiotics as measured by pill counts to be approximately 60% (12). It seems clear therefore, if a complete course of antibiotic therapy is necessary to eradicate an infection, considerable numbers of patients do not benefit from treatment.

It is well known that the ineffective treatment of streptococcal infections may lead to rheumatic carditis with the severe sequelae of heart failure, bacterial endocarditis or cardiac surgery(13). It is clear that despite the availability of an efficacious treatment regimen, rheumatic carditis is still a major cause of cardiac disease(14). Although there is no direct evidence to show what proportion of rheumatic carditis is

due to non-compliance, we do know from the studies of Charney(10) and Bergman(11) that only between 18-56% of patients seeking treatment complete their prescribed regimen. Therefore, it would seem reasonable to expect a compliance improving strategy to reduce the incidence of rheumatic fever among those seeking treatment. The enormous cost of rheumatic carditis both to the victim in terms of chronic ill health and loss of productivity and to society in terms of the funding of rheumatic fever programs, chronic medical care and cardiac surgery can be easily appreciated. The benefits of a compliance improving strategy are not limited just to the improvement of disease outcome but there is some recent evidence that improving compliance results is an improvement in the patient's perceptions of his health and subsequently fewer days off work. This contrasts sharply with the large increase in number of days off work by those who know they are ill and are non-compliant(15). The cost of poor compliance with the therapy for urinary tract infections is less clear cut and there is no good evidence that a simple cystitis may lead to chronic renal disease. Urinary tract infection however does provide a convenient model for 10 day antibiotic treatment in an adult population similar to streptococcal infection in children. In any case, the major impact of a compliance improving strategy would be in the area of chronic illnesses like hypertension. If simplified drug regimens were shown to improve compliance for short-term therapy, it would be reasonable to expect they might have a similar effect on long-term regimens.

B. Factors Affecting Compliance

A multitude of factors have been proposed as variables affecting compliance(7). The studies are of mixed methodologic soundness and the results are often conflictual. The generalized confusion obscuring our understanding of the determinants of compliance has been clarified by Haynes(16). Patient characteristics such as age(17,18), sex(19,20), intelligence(21), social class(22) and religion(23) do not appear to be important variables in the determination of patient compliance. Similarly, and surprisingly enough, there does not seem to be any relationship between the patients' knowledge of their disease, its therapy or its seriousness, and their compliance with the treatment plan(11,22,24).

Non-compliance has been associated with a psychiatric diagnosis(25,26), patients who have had inappropriate beliefs about their health(10,27,28), patients who have shown themselves to be non-compliant with other aspects of a regimen(29,30) and patients in an unstable family setting(31,18). Some characteristics of the source of health care and the doctor-patient relationships have also been associated with non-compliance such as inconvenient or poorly run clinics(32,33), inadequate supervision by the physician(34) and patient dissatisfaction with the physician(23).

The nature of the treatment regimen and its relationship to compliance is one of the central issues of this thesis. Here

again there are contradictory studies. It seems, that the greater the change in the patient's behaviour, the less the compliance. For example, Donabedian(17) interviewing chronically ill patients three months after hospital discharge found compliance decreased with regimens that required more behavioural changes. This finding has been verified by others(35,36). Similarly, Davis in a study of farm workers(29) found compliance lower with the medical regimens requiring the most behavioural change but interestingly enough, he found higher compliance in those on two regimens rather than those on one regimen. This seems to reinforce the previous discussion that possibly a treatment regimen must be complex enough to impress the patient that it is not trivial, without being too difficult as to make it impossible for the patient to actually adhere to it. The number and type of side effects also may have some negative effect on compliance. In ambulatory neurotic patients studied in a general practice setting Rickels found compliance fell in patients experiencing side effects from various tranquilizers(37). This finding was confirmed by Wintraub in his study of outpatient digoxin therapy (38); but Willcox in a study of psychiatric outpatients found no relationship between compliance and side effects(39). Willcox's study is supported by the finding that side effects are not highly rated by patients as a reason for non-compliance(40). The fact, that several studies have shown the frequency of side effects in treatment and placebo groups are essentially the same(41,42) seems to suggest that side effects are often not due

to the drugs themselves but rather due to some psychological reaction to being under treatment. Therefore, it would seem reasonable to conclude that side effects do not play a major role in the determinance of compliance.

The dosage of the drug ie. the amount of drug taken at one time has not been shown to have any relationship to compliance(12,43). If we interpret this in the light of our knowledge that side effects usually increase with the dose of the drug, these findings support the previous discussion that side effects have little relationship to compliance. The effects of the cost of therapy on compliance has been studied by Alpert in a pediatric outpatient setting(25) and Donabedian in chronically ill patients (17). Both found a negative effect of cost. Maddock in outpatients with tuberculosis(44) found no association between cost and compliance. This factor may be of less importance in the Canadian setting with universal health care particularly in provinces having programs that pay for prescribed drugs. An interesting sidelight of the compliance literature is the effect safety lock pill containers have on compliance. Originally designed to keep children from taking their elders' pills, they have been shown to have a similar effect on their elders ie. safety bottles decrease compliance(45).

The relationship between the type of medication and compliance is not clear. Unfortunately, in all the studies done to date, it is impossible to isolate the effect of the drug from

other aspects of the treatment regimen. For example, Porter found compliance with short-term antibiotics to be less than that for long-term digoxin and thyroid(12). It is easy to appreciate that the two groups are not comparable. The short-term antibiotic regimen is almost certainly to be more complex than the once-a-day digoxin or thyroid regimens. There is also the effect of long-term treatment versus short-term treatment which will be discussed below. If one accepts the previously discussed evidence that side effects do not have any important result on compliance, then it is difficult to explain why the type of drug should by itself have any effect on compliance. It seems more likely that the difference between the drugs is really due to a difference in convenience or complexity of their associated regimen.

The length of the therapy appears to have a definite effect on compliance. In previously cited studies with 10 day oral penicillin Charney and Bergman both found a consistent fall in patient compliance over time(10,11). Their findings have been supported by others in patients with tuberculosis(46) and in hypertensive patients(47). Porter's(12) finding of no association is upheld by the findings of others in tuberculosis patients(40) and in ulcer patients(43). This discrepancy has been explained by Haynes(16) on the basis that, studies showing no relationship consist of groups of patients already undergoing treatment and as such they had already identified themselves as

compliant. Those studies showing that compliance decreases with the increasing duration of treatment were done with groups of patients at the start of treatment (inception cohorts) and thus, give a more realistic reflection of overall compliance. It therefore seems justifiable to state that compliance does indeed fall with the length of therapy and some studies have already been done testing the effectiveness of shortening traditional regimens(49).

In summary then, the following factors have been associated with non-compliance: a psychiatric diagnosis, non-compliance with some other aspect of the regimen, inappropriate health beliefs, an unstable family setting, inconvenient clinics, inadequate supervision, patient dissatisfaction, excessive behavioural change, increasing length of treatment and safety lock pill containers. Little or no relationship has been found between compliance and socio-demographic factors, the nature of the disease, patient knowledge of the disease, type of drug, dosage, side effects or cost.

C. Studies Relating to a Simple versus Complex Question

The most important studies relating to this thesis are those that have already examined some aspect of the relationship between regimen complexity and patient compliance. Drug regimens may be simplified in three basic ways. First, the length of treatment may be shortened. As has been shown in previously cited studies, compliance decreases over time. It would therefore seem reasonable to expect the numbers of patients complying with regimens to increase if the regimen was shortened, thus becoming a self-fulfilling prophecy. It is, as yet, unclear whether efficacious short-term regimens would actually change the compliance distribution. It is conceivable that patients might be sufficiently unimpressed by a two-day course of treatment to ignore treatment completely and hence short-term regimens might actually reduce compliance.

The second way drug regimens could be simplified would be to reduce the total number of pills taken. This could be done by increasing the dosage ie. one 5 gm. tablet for two 2.5 gm. tablets or by combining several agents into one pill. To date, there have been no compliance trials on combination therapy. There have been two studies in hypertensive patients comparing combination with regular treatment, one showing better control with combination(50) and the other showing no difference(51). Further use of combination drugs awaits the appropriate compliance trials and the development of new knowledge with respect

to the interactions and the bio-availability of drug combination.

The third simplification method would be to reduce the frequency of the doses say from four times a day to once a day or, if suitably long acting preparations were found, to once a month or longer. In situations where long-term therapy is already available eg. depo-penicillin and depo-phenothiazines, compliance has been shown to be better than self-administered oral therapy (52,53,54,55). Further utilization of this knowledge awaits the production of long acting oral preparations and trials of self-administered long acting drugs. Until these long-term drugs are developed we must focus our attention on improving compliance with those drugs we do have.

In many of the studies dealing with regimen complexity and compliance it is difficult, if not impossible to determine if less complex means less frequent doses, fewer numbers of drugs or fewer numbers of pills per dose. In most studies complexity seems to be equated with the total numbers of medications. This may not be true for it could be argued that someone taking two medications, both in the morning, has a simpler regimen than someone taking one medication at four different times of the day. Only those studies including at least a partial description of the regimen will be reviewed.

Weintraub studying out-patients on digoxin therapy found compliance to be less if the patient was also on a diuretic(38). Digoxin is usually taken once a day but a diuretic can be taken

once or twice daily. No attempt was made in this study to identify the total number of pill taking episodes and their relationship to compliance. It is possible that if most of the patients were on twice-a-day diuretics then the fall in compliance was due to the more frequent dosing rather than the extra medication. This study is basically descriptive and deals with an out-patient population who have been under treatment for some time and as discussed previously, is devoid of patients who have expressed their non-compliance by dropping out. Neely in a random sample of the "over-sixty" users of an American health care plan found the number of medication omissions increased with the number of medications the patient was supposed to take(56). Again, it is unclear as to how the numbers of medications actually related to the frequency of doses. The patients in this study are suffering from many different diseases and thus are unlikely to be comparable in other compliance determinants eg. length of therapy. The measure of patient compliance by interview, as used in this study, has also been shown to be unreliable(57). In a similar study Schwartz, again using interviews with an over sixty age group, found an overall trend of increasing errors with increasing numbers of medications(58). It is not really clear how errors actually relate to the potential number of medication errors or to compliance. For example, if a patient taking one drug per day forgets that dose he commits one error but has zero compliance, whereas someone on a four times a day routine making two errors is

actually more compliant. This is further confounded by her finding that patients on four to nine drugs per day made fewer errors than those on two to three drugs, suggesting we can improve compliance by making drug regimens so complex as to take over the patient's life completely.

In a group of neurotic out-patients, Rickels randomly assigned them to one of four regimens(5). In the first group, he found one pill three times a day and two at bedtime to be better than one four times a day as measured by interview and pill count. In the second group, he found two pills four times a day better than one pill four times a day. In both cases the frequency of the dosing is the same ie. four times a day, but the total number of pills taken is higher in the group that had more pills to take. The relationship between this and actual compliance is not clear. Although the study was well designed, unfortunately those not returning their pills were dropped from the study and there is no indication as to which regimen had the most dropouts. It is also clear that pill counts cannot accurately determine the number of pills that actually make it into the patient's bloodstream versus those pills making it into the local sewage system or into other people's bloodstreams.

Hulka in her recent study of private patients with diabetes and heart failure found greater numbers of errors both in patients on more drugs and in patients with more complex scheduling (59). Again, interviewing was used as a method of identifying

errors and misconceptions and there was no direct measure of compliance. This group was not an inception cohort. Non-prescriptive drugs were excluded despite the fact that regular consumption of these drugs may be an important aspect of the older patient's daily medication regimen. This study did find that errors of commission or "the proportion of the drugs the patient was taking which the physician had not prescribed" increased with the complexity of scheduling which could be interpreted as meaning increasing complexity increases compliance past the 100% level to the point where patients are paradoxically not "compliant" by consuming more drugs than necessary. Errors in dose scheduling actually were quite low. This has been confirmed by several others(56,58). This implies that patients know when they must take their pills and that it is not confusion about the regimen by the patient that produces non-compliance but perhaps inconvenience or some other, as yet, unidentified factor.

Gatley, in a British general practice convenience sample of patients on a variety of regimens varying from one pill per day to two pills four times a day found compliance (as measured by pill counts) decreased with increasing frequency of dosage(60). Unfortunately, his sample size was small and encompassed several different disease entities. His finding that compliance increased with the length of treatment also suggests that his sample was not an inception cohort. He did find that there was a little difference between the one pill four times a day and the two pills four times a day regimens. This along with the previously cited study

of Rickels(5) suggests that it is the frequency of dosages rather than the total number of pills that is the important variable.

In summary then, it appears that the most effective compliance improving regimen is a one dose, one time medication given by injection. Unfortunately, this type of treatment is not available for many diseases as yet. It appears from the review of the literature that actually reducing the number of pills taken per day is less important than reducing the frequency of doses per day. This is further supported by the evidence that it is not so much that patients forget the more complicated dose schedules but rather that they find it impossible to fit them into their daily rituals. This does not however mean simplest is best. Several of the studies have indicated higher compliance in those regimens of intermediate complexity. The omission of one dose in a less frequent dosage schedule becomes an increasingly important factor and must be regarded as a definite risk of over simplification. The objective therefore of compliance research in this area will be to define the regimen of optimum complexity or optimum simplicity.

D. Other Compliance Strategies

Compliance improving manoeuvres, other than regimen simplification are also under study. These will be reviewed to further expand the discussion on compliance and to identify those strategies that may relate to the design of the present study. Most strategies have focused on three broad areas, the patient; patient education and behavioural modification, other aspects of the regimen; free pills, pill calendars and special packaging, and the type of medical care; comprehensive versus speciality care, continuity of care and increased supervision.

The education of patients seems to be an obvious means of increasing their compliance. It is very difficult to define what actually constitutes "education", which makes both the evaluation and the design of educational strategies problematic. For, if one could communicate the benefits of treatment and the risks of non treatment one would reasonably expect compliance to improve. This does not seem to be the case. A large experimental study of hypertensive steel workers(61) found that despite the men learning more about high blood pressure, it did not affect their compliance, although it did make them more likely to receive treatment from their physicians. The educational area of major interest to this thesis is patient counselling. Unfortunately, most of the studies in this area do not carefully define what is meant by counselling and it is impossible to separate counselling from other compliance variables like

attention. For example, Colcher(52) in a study of oral penicillin treatment for streptococcal pharyngitis found that specific counselling of parents combined with written instructions improved compliance. It is doubtful if the control group received as much attention and possibly because of investigator bias they may have received less than the usual information. The contamination of the educational manoeuvre by also giving written instructions serves to obscure the interpretation of this study. Similarly, the affect of education on the therapeutic outcome is frequently ignored. Significant improvements in compliance were found in a diabetic education program (62) and in a predischage pharmacist consultation (63), but the counselling of coronary high risk business men had no affect (54). This area has been discussed in detail by Neufeld and Rosenberg (65). As yet, the role of patient education is not clear although the best evidence available to date suggests it has only a minor role as a compliance improving strategy.

Behavioural strategies have shown to be effective in several settings. Using health volunteers Azrin (66) found timer-alarm pill containers improved compliance with a half-hourly schedule. A token reward system was found to be successful in improving dental hygiene in second grade students(67). The previously cited study of Meyer(64) found role modelling and selective reinforcement successful in reducing coronary risk factors. Haynes(68) in non compliant hypertensive steel-workers found several behavioural manoeuvres, including reinforce-

ment and reward, tailoring of medication to daily rituals, day charting and home blood pressure measurement improved compliance. It is not clear which of these manoeuvres may be the most important or whether the supervision given by the twice weekly visits to a high school graduate constitute the most important factor. In any case, the study was designed for use of those who have already been identified as non compliant and therefore may have restricted use as a primary strategy for improving compliance. Overall though it would appear that behaviourally oriented strategies seem to have a high proportion of successes in improving compliance.

Strategies revolving around the dispensing and consumption of medication other than just simplifying the regimens have been examined. The costs of medication may have some effect. Bonnar (69) studying prenatal iron supplementation found those given their iron tablets slightly more likely to take them than those who obtained it at their local chemists; but the difference was not statistically significant. This is the only study that looks at this factor directly. There is some indirect evidence in the review done by Colcher(52) that there is no relationship between compliance and the free dispensing of drugs. At present then, reducing the cost does not appear to be an important factor especially when viewed in the light of the evidence that there is no relationship between socio-economic status or income and compliance(31). Modification of the actual packaging of medication has also been studied. Linkewich(70) using four times

a day penicillin prescriptions found that specially packaged tablets improved patient compliance as measured by pill counts. In the same study, he found that a pill calendar was not helpful as the majority did not use it, but in those using the calendar 88% were deemed compliant. Written instructions were also studied and were not found useful. This contradicts the study of Colcher which did find written instructions useful although they were combined with counselling(52). It seems therefore that special packaging may have a definite role to play in improving compliance.

The last area to be examined is the source of medical care. In a well-controlled study, Gordis(71) found no difference between comprehensive care and specialty care given to a pediatric population with rheumatic fever. In a similar study, continuity of care did not seem to be an important factor(72). Several studies have shown some effective continuity but they were both confounded by other factors like convenience (the St. Anthony's dining hall effect), extra attention or home visits(32,73). Increasing the amount of supervision either by home visits, family involvement or more frequent office visits seems to have a definite compliance improving effect. This has been demonstrated in tuberculosis patients(32,73), in hypertensives(68) and in epileptics(74). The improvement in compliance produced by increased supervision does not necessarily seem to be related to the content

of the encounter but more so to the amount of time actually spent with the patient(75). The effect that attention or increased time with the patient has on compliance becomes a critical factor in the design of compliance trials that will be discussed further in the methodology section. It is quite difficult to decide whether a convenience of care is an important variable. In the hypertensive steelworkers study Sackett(61) found no difference between patients receiving their care at the plant and those receiving standard community care. In the studies of Curry (32) and Onstad(73), convenience did seem to have some affect. In the latter two studies, most of the patients were already labelled as non compliant and other strategies like home visits and extra attention confound their interpretation. It may be possible that convenience may be an important secondary strategy for those already identified as non compliant.

In summary then, it would appear that special pill packs, behavioural modification, extra supervision and extra attention are all manoeuvres that improve compliance. Patient education, written instructions and improved convenience may have some role but the type of care whether continuous, specialist, comprehensive or reducing the cost of care appear to have no major influence on compliance.

E. Methodologic Standards

The contradictory outcomes of the various studies included in the literature review can be attributed in part to differences in the way these studies were executed or their methodology. The purpose of defining methodologic criteria in advance allows for the avoidance of these flaws and increases the probability of finding a definitive answer to the study question. The crux of methodologic criteria is the insurance of similarity between the control and experimental groups. In reality, it is impossible to insure that the groups are identical for all factors except for one receiving the experimental manoeuvre. A compromise is reached by insuring that the two groups are equivalent for factors that are known to affect the outcome. For example, if one was testing a new anti-stroke drug in a group of patients without hypertension and the control group all had hypertension, the results would certainly show the experimental group to have fewer strokes and one might conclude that the drug was efficacious, if one did not realize that hypertension is an important etiologic factor in the development of strokes. Similar principles apply to the experimental manoeuvre. It is of critical importance that the only difference in what is done to the two groups is the experimental manoeuvre itself. In some studies, the experimental manoeuvre may be confounded by some other related activity. For example, if a trial was being undertaken to see if an exercise program would reduce blood pressure and an enthusiastic therapist put all the exercise group on a weight-loss program, then it

might be falsely concluded that exercise lowers blood pressure when in fact the weight loss was responsible. This type of error is termed co-intervention(76). The last important area for "equality - insurance" is the measurement of outcome. If the person measuring the outcome knows the manoeuvre each subject has undergone then this may bias his measurement depending on his opinion of the manoeuvre. For similar reasons, having the two groups undergo different outcome measures is also unacceptable. These basic methodologic criteria are further discussed by Hill (77), Feinstein(78), and Armitage(79). The specific problems of the design of a compliance trial are discussed by Sackett(16). In the following sections, the specific criteria for the design of this trial will be described.

The first step in any trial is the selection of the sample. In order to enable others to replicate the trial and also to have some idea as to what type of patients the strategy might be applied (generalizability), the population from which the sample is to be selected must be carefully described. A factor of crucial importance in the design and the compliance trial is the selection of an inception cohort ie. knowledge of when treatment began must be known for all subjects if an accurate idea of overall compliance with treatment is to be obtained. An attempt should be made to discuss any selection biases that may be operating on the population itself. For example, patients with coronary heart disease attending a referral cardiology clinic would be unlikely to have similar

severity of disease as those patients being seen in the office of their family physician. The criteria for someone being labelled with the illness and subsequently included or excluded from the trial must be unambiguous and subject to objective verification ie. isolated as much as possible from observer variability. The eligible subjects must be stratified for important outcome and compliance determining variables before randomization. The randomization process must be clearly defined and must insure allocation is free from investigator control. In compliance trials, the groups should enter the trial at the initiation of therapy to avoid the falsely high estimates of compliance given in those trials that have excluded dropouts from treatment. In order to maximize the chance of finding a real difference between the two groups, the choice of sample size must take into consideration the known distributions of compliance and the expected clinically significant difference between the control and experimental groups.

The compliance improving strategy must be clearly described. The manoeuvre being tested must be isolated from contamination with other strategies, particularly those known to affect compliance like extra attention. If possible, the investigators should remain unaware of which patients are receiving which manoeuvre. This becomes mandatory for those who are actually measuring disease outcomes, compliance and other parameters if bias is to be controlled. As in all trials involving humans,

the patient must be reasonably informed as to the purpose of the trial and the risks, both of the treatment regimen and the compliance improving strategy. In a compliance trial, this informed consent should not sensitize the patient to the fact that his adherence to a regimen is to be measured, as this may in itself change the observed compliance. It would also be important to assure that information about patients' non-compliance was kept confidential to prevent it from being used to embarrass or harm the patient. Those trials undertaking modification of long-term behaviour should include measures of the patients' perceptions of their health. This will help to monitor the adverse effects the manoeuvre may have on the patient and would be an important factor of the cost/benefit evaluation of any manoeuvre.

The outcome measures both of compliance and disease outcome, if subject to observer variability, must be done by those who are unaware of subject allocation. Criteria for successful outcome must be clearly defined in advance and have clinical as well as statistical significance. Similarly, the definition of what constitutes compliance must be clearly spelled out and must be correlated to the disease outcome. For example, it would be pointless to define compliance as consumption of 90% of prescribed doses if only 50% were needed to effect a clinical cure. Compliance, if possible, should be measured directly as in a blood or urine assay. Preferably, two or more methods should be used

until more is known about the characteristics of the methods available at the present time. Dropouts must be monitored as an indication of non-compliance and/or toxicity. For the same reason, side effects should be monitored, although in the majority of studies to date they do not seem to be related to compliance. Perhaps by increasing compliance, one may also increase the number of serious side effects as more medication is consumed.

Now that the methodologic criteria have been detailed, the challenge lies in the application of these standards in a clinical setting.

III. CLINICAL SETTING


The setting for the execution of this trial is unique to the compliance field and as such will be discussed in some detail. This trial will be designed to be carried out in the offices of urban Canadian family doctors. Most of the compliance studies to date have been carried out in hospital out-patient populations(44,39,11, 31), a few in private pediatric practices(10,52), some in industrial groups (61,80) and some in solo British general practice (12,60). This is an important step not only because it meets the call for more research at the primary care level(81) but also because it meets a need for more compliance trials at the grass roots of medical care i.e. the private physician's office(82).

It is very difficult to define the special attributes of family doctors and the patients they see. The type of practice varies immensely, depending on the individual's interest, training and location. Some general principles can be abstracted from several studies done to date (83,84,85). Family doctors are more likely to see a larger number of patients than specialists who derive much of their income from the care of in-hospital patients or from consultations on complex problems. It is also clear that family practice is primarily oriented to ambulatory non-hospital care (83). As most family doctors do not limit the type of patients they see to the extent specialists do, they are more likely to see a broader range of diseases, at an earlier stage, in all age groups and in both sexes.

Recent studies indicate that despite family physicians' opposition(83), more patients are using the Emergency Room as a source of primary medical care(86). This would suggest that family practitioners may be less likely to see acutely ill patients unless they actually do part-time work in an Emergency room. Several studies comparing family doctors with specialists in the consultation process have found family doctors ask fewer questions for the same amount of information and seem to ask more mental status and life situation questions(87,88). This may be interpreted to mean the family doctor is more practical and "more person oriented". This practical bent may result in a bias for simple medical regimens. In fact, one of the first calls for simplification of medical regimens as a compliance improving strategy came from a family doctor(89). Part of the study group of physicians will be drawn from an academic department of family medicine. Rudneck(90) has described the change from private to academic practice. He found practice volume dropped, there was a shift to younger patients but the profiles of compliants and diagnoses remained similar. Academic practices might also have important differences in major compliance determinants such as convenience and increased supervision because of learner involvement. These factors will be taken into consideration in the estimation of the number of study physicians and in the analysis (to determine if there is an academic effect on compliance).

How does this information relate to the design of a compliance trial? A knowledge of the incidence of various diseases in

family practice is critical for the selection of disease models that are common enough to produce the large numbers of subjects needed for a clinical trial. With a universal Canadian health care plan, the important variables of convenience and availability are largely due to the preference of the practitioner. These characteristics will have to be determined for each participating physician. This will be primarily for the estimation of disease frequencies as any inter-practice differences that might affect compliance would be controlled by separate randomization within each practice. A major area of interest is whether the characteristics of family practice affect the compliance proportions used for sample size determination. As Gordis(71,72) has demonstrated, continuity and comprehensive care, as a family doctor would be expected to provide, does not seem to improve compliance. Perhaps the only reason a family physician might have higher compliance is because he may act as a more "personal" physician as reflected by the study of Smith and McWhinney(87). This long-term involvement combined with interactions with other members of the family may act as a type of cumulative attention placebo resulting in higher compliance. This has not been borne out by the studies of Gatley and Porter(12,60). These factors as they relate to the design of the present study will be discussed further in the sample selection and sample size areas.



IV. DESIGN

A. Sample

1. Description of Patient and Physician Participants

The study will be undertaken in Winnipeg, a city of 500,000 located in the centre of southern Manitoba, a province with a population of approximately one million. The city is the provincial capital and its economy is derived from light industry, communications, transport and activities related to grain production. All residents of Manitoba are covered by universal health care and there is also a provincial pharmacare program allowing for reimbursement of 80% of drug costs greater than \$50 per year. Winnipeg has a total of 1,200 licenced doctors, 600 non-specialists, of these 200 belong to the College of Family Physicians of Canada and of these only 50 have written exams leading to certification(91). It is difficult to say if College members or certificants have any different characteristics than those who are not; but it would seem safe to say that those certified have at least met some standard and are likely to be practising family medicine. It would seem that the majority of the research done by Canadian family doctors has been done by certificants of the College.

The primary reasons for using the physicians who are certified in Family Medicine is because they are a definable

group, because they are likely to have some commitment to the practice of Family Medicine and because many have had some experience with research. A substantial proportion of the participating physicians will be part of an academic teaching unit. As Rudneck's(90) study has demonstrated these practices are about two-thirds as large as community practices. This will be taken into consideration in the determining of the number of practices needed to complete the study. The following criteria must be met for a physician to participate.

CRITERIA FOR PRACTICE SELECTION

- i. The physician must be a certificant of the College of Family Physicians of Canada.

This will help to ensure that the physician population included those with some commitment to family medicine and to research. It may also be possible to obtain financial support from the College of Family Physicians of Canada if the study is being done by its members.

- ii. The physicians must be in active open practice.

This is again necessary to ensure that the physician is spending the majority of his time in active office practice ie. a minimum of five half days per week. An open practice means the physician does not limit his practice ie. exclude obstetrics or pediatrics. This will help ensure adequate patient volume to generate

study subjects and will help to define the generalizability of the patient population.

- iii. The physician must have a method of seeing patients with acute illnesses.

If a physician is operating a practice that is geared to seeing only those patients that can wait 4-6 weeks for an appointment, he is obviously excluding those with acute illnesses like streptococcal pharyngitis and urinary tract infections. Therefore, it will be necessary for a study physician to demonstrate that he does have a system for seeing acutely ill patients.

- iv. The physicians must be adequately informed about and agree to abide by the study protocol.

It is essential that the physicians understand the purpose of the trial and agree that it is worthwhile if the physicians' enthusiasm is to be maintained to avoid physician dropouts.

When selecting a model to test a compliance improving strategy in any primary care setting, the frequency of the disease model is a primary consideration. It would appear that streptococcal pharyngitis and acute uncomplicated cystitis are ideal models as they are frequent enough and similar enough in nature and length of treatment (antibiotics four times a day for 10 days) to provide a testing ground for the

simple versus complex trial.

In Hart's(92) study done in Winnipeg, it appears that most community physicians see about 14 cases of streptococcal pharyngitis per year with a range from 7 - 21 (10% of all patients seen with pharyngitis). The number of cases would depend on the physician's practice size and the proportion of his practice that was pediatric, as the majority of streptococcal pharyngitis is found in that age group. The only other information available in the incidence of streptococcal illness in a primary care setting is Fry's(93) statistic of 21 - 23 cases per year, or 43% of all patients seen with pharyngitis. This discrepancy, in proportion of positives, may be explained by the fact that Fry's study is older and strep illness is less prevalent now and by the fact that Hart's study likely included more throat swabbing than is usual because of the nature of the study itself. The data for urinary tract infections are somewhat better. For adults both Fry(93) and Hodgkin(94) saw about 25 - 30 cases per year in a practice size of 2500. In the Canadian academic setting Dickie(95) found a rate of 12 per 1,000 patients. 80% of these were women over 14 years of age. This rate is remarkably similar to the two British studies but as Dickie's setting was an academic Family Practice Unit the practices were smaller, ie. about 1500 patients. Using Rudneck's estimate that academic practices are about a third smaller than

community practices, the following incidence data are derived:

i. Urinary tract infections

	<u>Community Practice</u>	<u>Academic Practice</u>
Total per year	27	18
% women	21	14

ii. Streptococcal pharyngitis

	<u>Community Practice</u>	<u>Academic Practice</u>
Total per year	14	9

2. Sample Size Estimation

As was discussed in the methodologic standards section, the specification of the sample size needed to maximize the chances of detecting a real-difference between the two regimens is of critical importance. This will be done in the following steps:

- i. Compliance will be defined and related to clinical outcome.
- ii. Estimates of patient compliance with four times daily Q.I.D. regimens will be made.
- iii. Estimates of what constitutes an important clinical difference between Q.I.D. and twice daily B.I.D. regimens will be discussed.
- iv. Using these estimates sample size will be sought.
- v. A compromise between what is available and what is statistically desirable will be calculated.

i. Definition of Compliance

The standards described in the methodologic criteria ask for a clear definition of what constitutes compliance in relationship to clinical outcome or "how much medicine has to be taken over what period of time to produce the desired result". The length of treatment, ie. ten days will be justified in the section dealing with the individual regimens. Assuming then that all ten days of treatment are necessary, one would

need to determine that the medication was being consumed each day over the ten day period. This of course is unrealistic. We do know however, that compliance does fall with time, and from the studies of Charney(10) and Bergman(11) we can see that compliance falls most after days 5 - 6 from about 81% to 56% and from 29% to 18% or approximately thirty percent. The estimates of Bergman are likely underestimates of the expected compliance as the study was done on a small sample of children from an outpatient and emergency room setting (known for their inconvenience and hence poorer compliance) with a mixture of strep pharyngitis, skin infections and otitis media. Knowing that there is this progressive fall in compliance to be lowest on days 9 and 10, this then would seem the ideal time to obtain a measure of compliance to determine if a compliance improving manoeuvre was having any effect. This time has been used by most of the authors working with the strep model(10,11,96,97,98,52). There is no comparable information for the urinary tract infection model but because the length of treatment, drug regimen and type of illness are quite similar, it will be assumed throughout this section that this model is similar to the streptococcal pharyngitis model. Therefore, some measures of whether the patient has taken his medication in the last

few days of treatment will be obtained. The most convincing measure of drug consumption is an assay that detects the presence of the drug in the patient's body fluids. Depending on the pharmaco-kinetics of the drug involved, most methods detect drugs consumed in the last 12 to 16 hours. This means an assay done on samples collected in the afternoon will detect medication consumed that morning or the previous evening. The assay techniques in this study will be described in the outcome section.

It is not clear how the measurement of the drug on the last few days of therapy related to the actual consumption over the preceding days. If the patient knows in advance of the collection day, it is possible he may suspect why the samples are being obtained and this of course could have a substantial effect on the number of positive results. Measuring the amount of medication remaining in the bottle near the end of therapy would give some estimate of what had been consumed over the time previous to the drug assay being done. This assumes that those doses missing from the bottle were actually consumed by the patient which is not necessarily true. It would be useful to know how pill count and drug assays correlate as measures of compliance. Only Bergman(11) does this. He found that pill counts give higher estimates of compliance

than urine assays. This is probably partially due to his low criteria for adequate consumption, ie. 66% of expected consumption. As we know, compliance is still high by day 6 and many patients would be labelled compliant by his criteria even if they had stopped taking their penicillin on day 7. What then is a reasonable expectation for pill consumption by day 9? It is necessary not only to estimate what is a reasonable consumption but also to relate this consumption to disease outcome, if clinical relevance is to be maintained.

Green(98), using the strep model, found that in those compliant as defined by urine assay at day 9 on a three times a day penicillin regimen had a recurrence rate at three weeks of 12% in contrast to a recurrence rate of 30% in those who had no penicillin in their urine. It would seem reasonable therefore to define compliance as having a positive drug assay on day 9, ie. indicating medication consumption in the past twelve hours. In order to increase the probability that this direct measure actually represents medication consumption over the previous eight days, pill counts will also be used. If 100% compliant, an individual would be expected to have consumed 80-90% of the prescribed doses by day 9 depending on when the pill count was performed and when the treatment regimen was begun.

This variability of start and measurement time could account for approximately $\frac{1}{2}$ -1 day's amount or 5-10% of a ten day course. Similarly, allowing for the fact that the subjects are human, forgetting 10% of the dosages would not seem unreasonable, ie. four pills on the Q.I.D. regimen or two pills on the B.I.D. regimen. This means therefore that by day 9 one would expect a compliant patient to have consumed 80% of his expected doses as measured from the start of treatment to the time of pill counts. Thus, a compliant patient would be defined as *having a positive drug assay on day 9 and having consumed 80% of the expected doses*. If a smaller amount of drug consumption, for example 60%, gave as good disease outcomes than this arbitrary 80% level of consumption could be lowered to this clinically important level. For the reasons described above both the streptococcal pharyngitis and urinary tract infection models will be treated in the same way.

ii. Estimates for Compliance With a Q.I.D. Regimen

As the discussion above has indicated, the definition of what constitutes compliance varies from study to study. If one accepts the 9 day urine assay in the strep model as a reasonable reflection of compliance with the standard ten day three times a day (T.I.D.) regimens, remarkably similar compliance levels

are achieved, 56%(10), 68%(98) and 58%(52). This suggests an overall compliance rate of 60% with T.I.D. penicillin regimens. The Q.I.D. regimens would be expected to be lower. Gatley in his study found Q.I.D. compliance to be only 25% by pill counts which usually overestimate compliance. Rosenstein(97) again with a strep model and a B.I.D. penicillin regimen and some other compliance improving manoeuvres achieved 90% compliance by urine assay on day 8-10. This seems to suggest a simple linear relationship between compliance and frequency of dosages, ie. B.I.D. - 90%, T.I.D. - 60% and Q.I.D. - 30%. As such a relationship is unlikely and because too low an estimate for a control compliance would result in a small sample size, ie. reducing the probability of finding a real difference, an intermediate value of 45% will be set for control group compliance for both urinary tract and streptococcal pharyngitis, Q.I.D. regimens.

iii. What is a Clinically Important Change?

As the study of Green(98) demonstrated, those who do not comply with penicillin have a 32% chance of recurrence at day 28 and a 12% chance of recurrence if they are compliant. This means that a Q.I.D. regimen with a compliance level of 45% would yield a recurrence rate of 23%. This is probably an over-

estimate as Breese's(99) larger study found an overall recurrence-relapse rate at 28 days with Q.I.D. penicillin (no compliance measured) to be about 14%. This would suggest an intermediate value of approximately 18% recurrence-relapse rate for the control regimen. A clinically significant fall in recurrences would be about 50% ie. to about 10% and is about what one would expect if Green's(98) data is correct. This is more in line with the 5% recurrence rates for the best form of treatment, ie. intramuscular penicillin. This means that compliance must be increased by at least 50%, from 45% to 67.5% or 70% with a B.I.D. regimen. This is consistent with the study by Colcher who showed that at an 80% compliance level intramuscular penicillin and oral penicillin had equal success in preventing recurrences. Therefore the expected compliance level for the simplified group will be set at 70% in order to achieve a significant improvement.

iv. Calculation of sample size

Using the high estimate of expected compliance
in the treatment group:

Proportion compliant in central group $p_c = .45$

Proportion compliant in treatment group $p_t = .70$

Expected difference in proportion $d = .25$

N = Sample Size

Z_a = Z value two tailed normal test for
 α error level.

Z_B = Z value one tailed normal test for
 β error level.

Using the calculation for N for two independent
proportions

$$N = \left[\frac{Z_a \sqrt{2 p_c (1-p_c)} - Z_B \sqrt{p_t (1-p_t) + p_c (1-p_c)}}{d} \right]^2$$

The appropriate substitutions yield a

$$N = 99 \quad \alpha = .05$$

$$\beta = .05$$

The total number of subjects for 2 groups would then
be 200 for each disease model.

$$N = 65 \quad \alpha = .10$$

$$\beta = .10$$

The total number of subjects for 2 groups would then
be 130 for each disease model.

v. The Compromise

Now that the number of subjects that are statistically important and the number of cases expected to be seen per physician per year are known, it is possible to achieve a compromise between the statistical desirability and availability. Four academic practices would meet the criteria for physician selection. They would provide 46 cases for the urinary tract infection trials and 36 cases for the strep trials. This leaves 144 patients for the urinary tract infection for $N = 100$ and 74 for $N = 65$. At 21 patients per non-academic practice, this yields a total of 7 and 4 practices respectively. For the strep trials, non-academic practices would be expected to provide 164 cases for $N = 100$ and 94 cases for $N = 65$. At 14 cases per year this yields a total of 12 and 8 practices respectively. Because of the small numbers of certified family physicians in Winnipeg only 10 non-academic practices could be recruited. This would mean a total of 14 participating physicians. These estimates do not take into consideration those patients who may not fit the inclusion criteria and who may be lost to follow-up. At any rate, there appears to be a good chance of achieving the more powerful sample size, ie. $\alpha = \beta = .05$ at least for the urinary tract infection model and a sample of intermediate power ie. between $\alpha = \beta = .10$ and $\alpha = \beta = .05$ for the strep model.

3. Inclusion/Exclusion Criteria and Stratifications

a. Streptococcal Pharyngitis

1. The patient must have a sore throat or purulent nasopharyngitis. (92)

This is to insure that all patients are symptomatic and that asymptomatic carriers are excluded. This will insure at least some similarity in motivation to seek and comply with treatment.

- ii. The patient must belong to the physician's practice or the practice of another study physician.

Belong is defined as having a chart in the study physician's files.

- iii. The patient must be seen in the physician's office.

This is to control the types of patients seen and to insure that they are patients of the family physician selected for the trial, not patients of other physicians. This serves to maintain homogeneity and generalizability of the sample and would exclude patients seen in other settings eg. Emergency Room. It also is a must from a practical point for randomization and medication dispensing.

- iv. The patient must have a Group A beta hemolytic streptococcus grown from the throat swab.

This serves to specify the illness carefully. It is essential as many sore throats are not streptococcal and the clinical criteria are inaccurate.

- v. The patient must be able to swallow liquid if under age 12 and able to swallow pills if age 12 or over.

It is essential that the patient be physically able to take the medication before compliance can be measured. It is also necessary for the patient to be able to take the form of medication assigned to his age group to prevent mixing of the manoeuvres.

- vi. The patient must not be allergic to penicillin or any penicillin derivative.
- vii. The patient must not be on any other medication.

This will prevent contamination of the complexity issue.

- viii. The patient or legal guardian must give consent.

This is morally necessary and must include information regarding risks and benefits of treatment, the follow-up expectations and be free from coercion.

The nature of the consent will be detailed in the following sections. Appendix I.

- ix. The patient must be between the ages of 2 and 30.

The lower age was chosen for the practical limitations of obtaining blood and urine specimens on those less than 2 years of age. There would also be an increasing probability of unacceptable side effects from the penicillin dosages for those under 2. The upper age limit of 30 was chosen because streptococcal infections are unusual in those over 30(100) and because of the increasing likelihood that those over 30 may be on some other medication.

- x. The patient must be available for follow-up.

This will serve to minimize the amounts of missing data and will exclude those who live out of access to home visitation or who are planning to be away during the observation period.

- xi. No subject may be entered into the trial more than once.

Entering a subject into the trial more than once increases the probability that the subject may become aware that his compliance is being

measured. It is also possible that if a subject was allocated to a regimen different from his first regimen, his bias towards the first regimen would affect his compliance and his perceptions of side effects.

Stratifications

The only stratification will be into liquid and pill groups. This stratification was chosen because the administration of liquid medicine to young children is generally accepted as more difficult than the administration of pills to adolescents and young adults. There is also some evidence from Bergman(11) that pills are associated with better compliance irrespective of the child's age.

b. Urinary Tract Infections

- i. The patient must be symptomatic ie. have at least one of the following: dysuria, frequency or urgency but not pyelonephritis.

This, as in the inclusion/exclusion criteria for streptococcal pharyngitis, is to ensure that asymptomatic bacteriuria is excluded, that is, patients must have similar motivation to seek and comply with treatment. ~~Pyelonephritis is defined~~ *as having symptoms of frequency and dysuria but associated with high fever, chills, general*

malaise and severe renal tenderness. These patients will be excluded because sulpha drugs are not appropriate for the treatment of pyelonephritis.

- ii. The patient must belong to the physician's practice.

This has been discussed above.

- iii. The patient must be seen in the study physician's office.

This also has been discussed above.

- iv. The patient must have a midstream urinalysis culture of greater than 10^5 bacteria sensitive to sulfa.

The symptoms of urinary tract infection are non-specific and culture is essential to determine which of those with symptoms have an infection.

- v. The patient must not be allergic to sulfa drugs.
- vi. The patient must not be on any other drug regimen other than oral contraceptives.

As most urinary tract infections occur in young women in the reproductive age group and

because many of these women are on oral contraceptives, excluding those on oral contraceptives would reduce the number of subjects considerably. Those taking oral contraceptives will be stratified into a separate group. Those taking medications other than oral contraceptives will be excluded for the reasons described in the streptococcal inclusion/exclusion criteria.

- vii. The patient's consent will be obtained.
- viii. The subjects will be women between the ages of 18 and 65.

As previously stated, the majority of urinary tract infections occur in women in the reproductive age group. Men therefore have been excluded from the study. The age of 18 was chosen to coincide with the patients entering the reproductive age category and with the patients' ability to give consent. Although age 65 is well beyond the reproductive age, urinary tract infections are still moderately common in women of this age. Those women over 65 were excluded because of the increasing likelihood that a substantial number of these women would be on other medications.

- ix. The patient must not be pregnant.

Urinary frequency is often associated with pregnancy. This combined with an increase of asymptomatic bacteriuria of pregnancy(101) serves to confound the labelling of patients. This would also form a very small section of those patients with urinary tract infections. The compliance characteristics of a pregnant woman are unlikely to be the same as a non-pregnant woman due to the fears relating to harm the taking or not taking of pills may do to the baby.

- x. The patient must have no known urinary tract abnormalities or have had more than one urinary tract infection within the past twelve months.

It is well accepted that urinary tract abnormalities are related to persistence of the infection(102). Therefore women with known urinary tract abnormalities should be excluded as their outcomes would be different from those with normal urinary tracts. Similarly, women with chronic urinary tract infections would likely have a high incidence of bacteria resistant to sulfa drugs and by definition, a higher than average rate of recurrence. For this reason, women having had more than one urinary tract infection in the past twelve months will be excluded.

- xi. The patient must be available for follow-up.
- xii. The patient can only be entered into the trial once.

Stratifications

Women will be stratified into two groups, those on oral contraceptives and those not on oral contraceptives.

B. Regimens

1. Description and Justification of Regimens for Streptococcal Pharyngitis

As was alluded to in the Review of Literature, Group A beta hemolytic streptococcal pharyngitis must be treated if one is to reduce the risk of the patient developing rheumatic carditis. This has been demonstrated in a controlled clinical trial by Siegel(103). It is also clear that rheumatic fever although on the decline is still responsible for a large proportion of cardiac disease(14). It is therefore clinically important to identify those sore throats that are of Group A beta-hemolytic etiology. Unfortunately, this can only be done by culture techniques as clinical criteria have been shown to be unreliable(92). This leads to the dilemma of whether to treat all sore throats with penicillin and risk penicillin allergy and any other problems associated with unnecessary treatment or whether to wait 3 or 4 days for a culture report and risk an attack of rheumatic fever. A compromise has been reached in many cases by waiting 24 hours for a preliminary report ie. whether there is beta hemolysis, before starting treatment; if the patient is acutely ill, starting a partial course of treatment while awaiting the report and depending on the report, continuing or discontinuing treatment.

The regimens used to treat streptococcal infections are quite variable. The American Heart Association has

recommended penicillin G 200,000 units three times a day for 10 days(104) but many physicians prescribe penicillin four times a day because of penicillin's pharmacologic properties(105). Although a single injection of benzathine penicillin has been shown to be the most effective regimen(106), few physicians use this because: there is a higher incidence of anaphylactic reactions with injected penicillin, a distaste for inflicting pain particularly on children, problems with storage and because a prescription is more suitable for the culture-confirmation problem. In a large study, Breese found that twice daily doses of 400,000 units of penicillin for 10 days were as effective as the standard four doses of 200,000 units for 10 days(99). Unfortunately, there was no compliance measure included in this study so the effect of compliance on outcome is unclear. From an ethical viewpoint then, there would be no problem in prescribing twice daily penicillin or four times daily penicillin provided the total daily dose was the same.

Penicillin V has often been substituted for penicillin G because it is better absorbed from the stomach. The trials of Bergman(11), Charney(10) and Colcher(52) all use penicillin V. It is generally accepted that the dosages are equivalent. The derivation of the dose for the under 12 age group is detailed in Appendix A. In the under 12 age group the simple regimen consists of 5 ml. or 500,000 units of penicillin V twice a day and the complex regimen of 5 ml. or

250,000 units of penicillin V four times a day. Those 12 years of age and over will be assigned to 1,000,000 units (1 tablet) twice a day or 500,000 units (1 tablet) four times a day. It is certainly possible that the higher, dose twice a day regimen may have a higher incidence of side effects like diarrhea, particularly in the younger age group, but this did not appear to be a problem in the previously cited study of Breese(99). In any case, side effects will have to be closely monitored throughout the study.

Ideally a drug manufacturer would be able to supply the penicillin V in similar volume and form. This would minimize any effect the color or taste of the medication might have on compliance or side effects. If this is not possible, then the commercially available suspension 250,000 units per 5 ml. (banana colored) and 500,000 units per 5 ml. (orange colored) will have to be used. The tablets are supplied commercially in 500,000 strength. This means that those on the B.I.D. regimen would be taking two pills for each dose. The higher number of pills per individual dose may increase compliance as shown by Gatley(60) and Rickels(5) ie. this would be a bias towards the hypothesis.

2. Description and Justification of Regimens for Urinary Tract Infections

As was shown in the description of the patient population, urinary tract infections are common in the primary care setting. They are responsible for much short-term morbidity but there is no good evidence to indicate that they produce any long-term morbidity or mortality(107). Because dysuria is such a common symptom in women in the 20 - 60 age group, up to 22% of women experience one episode per year(108). Of those women who visit a physician complaining of dysuria, only about 50% have significant bacteria in their urine(109). Significant bacteriuria has been defined and is well accepted as greater than 100,000 bacteria per ml. of clean midstream urine(110). As a culture is necessary to confirm the presence of a urinary tract infection, the physician is faced with the dilemma of whether to prescribe immediately and risk overtreatment and drug sensitization or withhold a possibly beneficial treatment for 24 hours in the symptomatic patient. Fortunately, there are now available simple dip slide tests that give the physician a good indication of whether there is a urinary tract infection or not. The test relies on the fact that bacteria in urine produce nitrites. When a culture-indicator pad is dipped into a freshly voided specimen of infected urine it turns pink. This test has been shown to be 90.7% sensitive and 99.1% specific in a series of 1,000 cases (111). A few bacterial strains do not turn the pad pink but they are not sensitive to the antibiotic being used in this

trial. Once the pads have been dipped in the urine they may then be incubated for colony count and subsequently sent to a central laboratory for further bacterial identification and antibiotic sensitivity determinations.

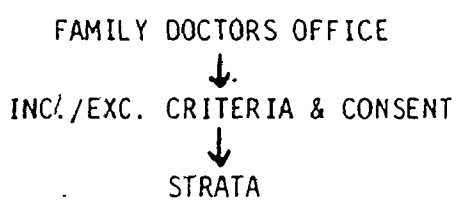
The majority of uncomplicated urinary tract infections, ie. simple cystitis, still respond to sulfonamides(112, 113). There is presently no agreement as to whether a seven or ten day regimen is best(114); but for the purposes of this study a ten day regimen will be used, as it is similar to the regimen being used for streptococcal pharyngitis. Two forms of sulfonamides will be used. They are not clinically different but do have different half-lives. Sulfisoxazole is more rapidly excreted and must be given four times a day. Sulfamethoxazole is more slowly excreted and is given twice a day(115). Most sulfa drugs have the potential danger of crystallizing in the urinary tract so fluid intake is usually increased during treatment. Here, as for the penicillin regimens, an attempt will be made to have the pills of identical size and shape (1 containing 1 gm. of sulfa-methaxazole and 1 containing 500 mg. of sulfisoxazole). If this is not possible, commercially available sulfisoxazole (500 mg. white tablet) and sulfamethoxazole (500 mg. green tablet) will be used. This means those on B.I.D. regimens will be taking two pills per dose, a bias discussed in the description of the penicillin regimens.

C. Manoeuvre

1. Streptococcal Pharyngitis

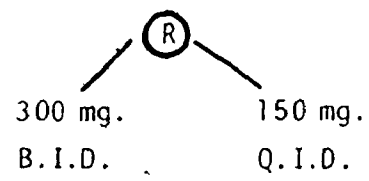
The patient with a sore throat would be seen in the office of a participating physician (Fig. 1). If the patient fit the inclusion criteria, the patient would be asked without coercion to participate in a trial to see which form of penicillin worked best for the treatment of sore throats. The patient would also be informed that a nurse would be visiting the home sometime while the patient was on treatment to see how things were progressing. If the patient or guardian was agreeable a signed consent would be obtained. Basic identifying data would also be obtained including age, sex, home address and phone number. The back of the patient's throat would be carefully swabbed and the swab directly plated onto a blood agar plate and incubated in the physician's office. The swab would then be sent in transport media to a central laboratory. Blood, approximately 1 cc., would be drawn for an antistreptolysin O titre (ASOT). The physician would then have two options. First, he could tell the patient to start penicillin that day if the patient was very ill or if the physician would not be available the next day to read the culture. Secondly, it would be explained to the patient that the majority of sore throats are viral and it is safe to wait 24 hours for a preliminary report on the throat swab. All discussion of the illness and the importance of taking the medicine if the culture is positive would be done before the

STREP PHARYNGITIS (Fig. 1)



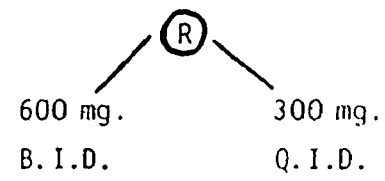
LIQUID

2 yrs. ≤ pt. < 12 yrs.



PILLS

12 yrs. ≤ pt. ≤ 30 yrs.



START TREATMENT DAY 1

IF T/S (+)

IF T/S (-)

DROPPED & RETURN MEDICINE

TREATMENT DAY 9 - HOME

1. AMOUNT MEDICINE CONSUMED
2. URINE ASSAY

DAY 11 - 18

PHONE CALL RE SIDE EFFECTS

DAY 21 - DR.'S OFFICE

T/S + ASOT

drug was dispensed, to control any bias the physician might introduce if he knew the regimen the patient was to be assigned to.

The patient would then be asked to go to the office nurse or receptionist to receive his medication. Although the evidence in the Review of Literature suggests that the cost of medicine is not an important factor, by dispensing the medication free to both groups this will insure cost - equivalence and minimize even a small effect the costs of the different regimens might have on compliance. The medication will be in a sealed box labelled DO NOT OPEN UNLESS INSTRUCTED BY YOUR PHYSICIAN. This will be done to minimize the chance of a patient starting the regimen before culture confirmation which would make it difficult to specify the actual time consumption of the medication began (for home visit date) and also make it impossible to obtain an accurate estimate of indirect compliance as measured by medication consumption. Patients having negative initial cultures will be asked to return the medication as will those who initially showed beta hemolysis but are not Group A. For the age group 12 and under, the box will contain a clear plastic bottle graduated for easy measurement of amount consumed when the nurse makes her follow-up visit. The bottle will contain an eleven day supply of medicine to allow for wastage. A clear plastic 5 ml. spoon will be included to insure standardization

of individual dosage amount, as household spoons are quite variable in their size(96). The bottles will be labelled as follows:

- i. Penicillin V - take one tsp. twice a day (mornings and evenings) for 10 days for strep throat. Please use enclosed plastic spoon.
- ii. Penicillin V - take one tsp. four times a day (morning, noon, supper and at bedtime) for 10 days for strep throat. Please use enclosed plastic spoon.

The time specifications are in accordance with what is feasible and with standard clinical practice. Those subjects over 12 years of age will receive a similar package similarly labelled, but containing bottles of pills with only enough for 10 days. They will be labelled in the following way:

- i. Penicillin V - take one pill four times a day (morning, noon, supper and at bedtime) for 10 days for strep throat.
- ii. Penicillin V - take one pill twice a day (morning and evening) for 10 days for strep throat.

The medication would be randomly allocated. Each practice would be separately randomized by using random number tables and by balancing each fourth allocation. This will minimize the effect each individual physician and his practice style might have on compliance. The age group strati-

fications will be separately randomized to control the effect the form of the medication may have on compliance.

Those patients awaiting culture confirmation would be telephoned by the physician's office the next day. If the blood agar plate showed beta hemolysis ie. a clear zone around the colonies, they would be instructed to start their medication. If there was no beta hemolysis, those patients would be asked to return their medication. The date and time the patient was informed would be noted for both those starting their medication, the day they saw the physician and for the group awaiting the preliminary culture report. This is necessary to establish the amount of medication that should have been consumed by the time the nurse makes her follow-up home visit. The patients will be unaware of what day the nurse will make her visit as this awareness may have a definite affect on medication consumption that day. All patients will be given a follow-up appointment three weeks after the start of treatment for the measurements of the outcome criteria.

2. Urinary Tract Infection

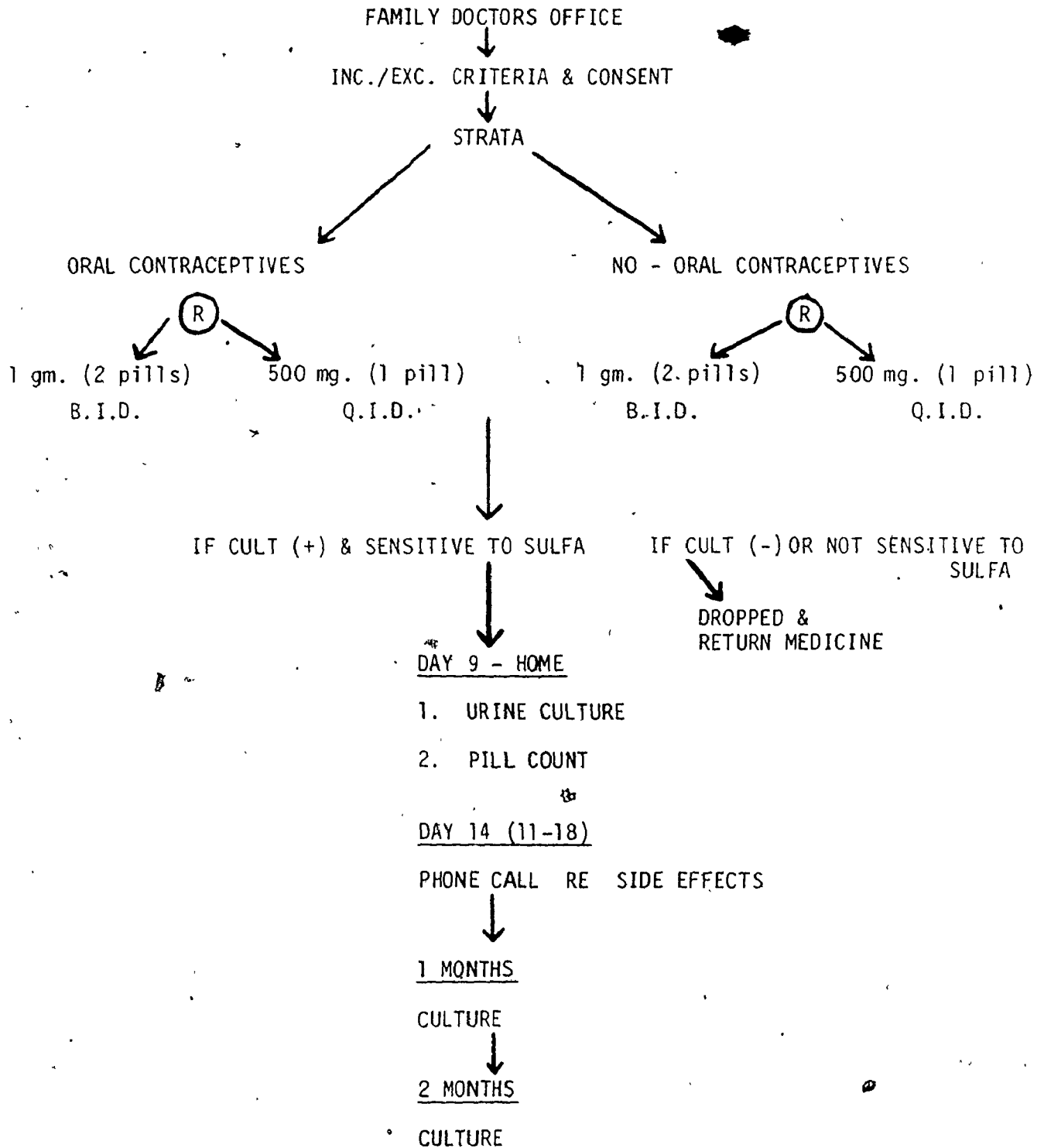
The patient with an uncomplicated urinary tract infection would be seen in the office of a participating physician, Fig. 2. Application of the inclusion criteria and consent would be similar to the previously described protocol for streptococcal pharyngitis. A midstream urinalysis after perineal cleansing would be obtained. If the microstix indicated urinary tract infection the physician would discuss the illness and the importance of therapy before the medication was dispensed.

The medication would be dispensed by the office nurse or receptionist in sealed boxes. The boxes will contain ten days' supply of each regimen and will be labelled as follows:

- i. Sulfa - Take one tablet twice a day, mornings and evenings for ten days for urinary infection. Drink four extra cups of fluid per day while taking the medication.
- ii. Sulfa - Take one tablet four times a day, morning, noon, supper and at bedtime for ten days for urinary infection. Drink four extra cups of fluid per day while taking the medication.

The medication would be randomly allocated after stratification for oral contraceptives or non-oral contraceptives. As for the streptococcal protocol, separate randomization would be applied for patients within each practice.

U.T.I. (Fig. 2)



The microstix would be incubated then sent for sensitivity testing and typing. If the colony count was less than 10^5 or the bacteria isolated were not sensitive to sulfa, patients would be asked to return their medication. The date and time the medication was dispensed would be recorded as would the time the patients were asked to return their medication. The patients would be unaware of what day the nurse would make her visit. All patients would be given a follow-up appointment one month after the start of treatment for the measurement of outcome criteria.

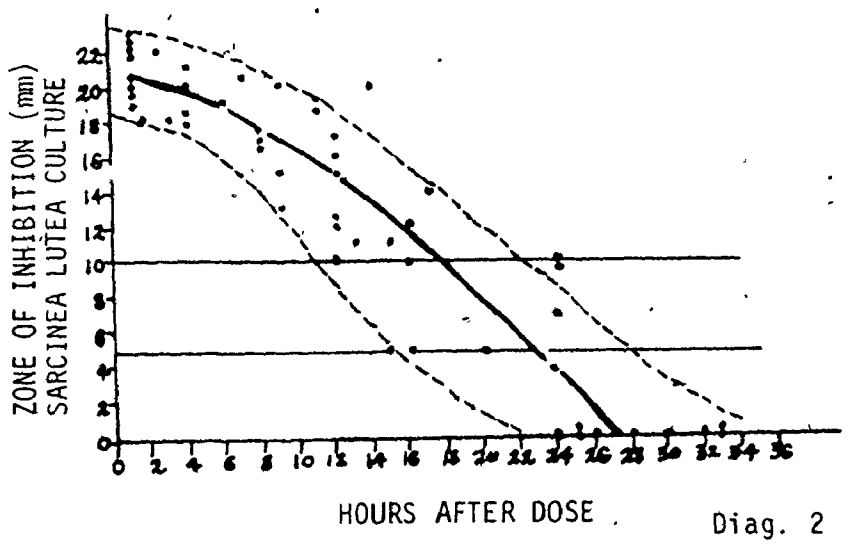
D. Measurements

i. Compliance

The patient will be visited by a nurse on the ninth day of treatment. The only warning the patient will have of the visit will be a phone call from the nurse approximately one hour before the visit. This is necessary to reduce the number of patients not at home when the home visit is made. It is not felt that this short a warning will have any detectable effect on the compliance measures. Visits will be done in the late afternoon or early evening in an attempt to maximize the number of patients at home and to insure that the urine samples collected reflect drug consumption that day. Those not at home on day 9 or day 10 will be labelled as dropouts. The interpretation of the compliance measures done on day 10 will be discussed in the Analysis section. During the visit the nurse will ask to see the patient's medication, then ask the patient to provide a urine sample. While the patient is doing this, a pill count or measurement of the liquid left in the graduated bottle will be done. The urine samples will be frozen immediately and analysed weekly for the presence of sulfa or penicillin.

The Sarcinea Lutea test as described by Charney(10) will be used for the detection of penicillin. Briefly, it relies on penicillin present in the urine of patients taking

penicillin to inhibit the growth of the sarcinea lutea bacteria. It has been shown to be very sensitive and quite specific. Because the regimens used in this study are different than Charney's, some preliminary standardization would have to be done for the dosages used. The excretion curves for B.I.D. penicillin would be expected to be different from the Q.I.D. excretion pattern. For example, if a nurse obtained a late afternoon specimen from a patient on each regimen and a positive test is interpreted as the patient having taken a dose of penicillin the last 16 hours, it is possible that those taking a larger B.I.D. dose may still have an inhibition zone at 24 hours after the last dose, ie. shifting the curve of the diagram below to the right. It would be important to determine this before the study was begun. This would be done on healthy volunteers.



Diag. 2

The Bratton Marshall test(116) for the detection of sulfa has not been used in compliance trials as yet. It depends on a colorometric reaction with sulfonamides and can measure up to one part per million ie. is quite sensitive. It will also give a positive reaction with drugs similar to sulfonamides, for example P.A.S., but not with any common household drugs. The exclusion of patients taking other drugs should avoid false positives. The original assay was described for use on whole blood but it can also be done on urine. Again a pre-trial determination of what range of urine levels would represent drug consumption in the past sixteen hours would be necessary.

The measurement of the amount of medication consumed would be fairly straightforward. A compliance level has been defined as a pill count equivalent to 80% of the expected consumption. The total expected doses would be calculated from the first dosage time after the medication was dispensed to the dosage time before the pill count was done. For example, if the medication was dispensed at noon, the start of medication consumption would be expected to be supper time for Q.I.D. regimens or evening for B.I.D. regimens; and if the patient was seen in the mid-afternoon at home the last expected dose would be noon for the Q.I.D. regimen and that morning for the B.I.D. regimen.

Dropping out of treatment is an emphatic express-

tion of non-compliance. The regimens under consideration in this study are short-term and occur in symptomatic patients, dropouts therefore are likely to be less frequent. Patients could be labelled as dropouts if they are not available for home visit, if they fail to return for their follow-up appointments or if they refuse to participate in any other aspect of the trial. Throughout the study the numbers of patients failing to keep appointments, those not at home, and those refusing to report side effects will be monitored for each regimen to see if this might represent some variation of the dropout phenomenon. This does not mean that those failing to keep follow-up appointments will be dropped from the study. A vigorous attempt will be made to insure that patients are followed, both because it is clinically important and because it is necessary to minimize the amounts of missing data. The information concerning the patient's compliance will not be given to their family physician in order to protect them from embarrassment or harassment.

ii. Disease outcomes

The primary goal of antistreptococcal therapy is to remove streptococci from the patient's throat and hence prevent secondary complications like rheumatic fever. The throat is usually swabbed about one week after the patient has finished therapy or about three weeks after the initial

office visit. This is because earlier throat swabs don't seem to reflect the recurrence rate accurately, possibly because residual penicillin may inhibit the growth of streptococci. The body's immune response to a streptococcal infection can be measured by the antistreptolysin O titre (ASOT). It has been shown that when streptococcal infections are treated adequately this titre does not rise(114). A significant rise in titre is accepted as two dilutions and is indicative of a strep infection(100). It is the actual change in ASOT that is important as pre-infection levels are quite variable. The technique is freely available and requires approximately 1 ml. of blood for the micro determination method(117). This is a distinct advantage when the majority of specimens will be taken from children. The ASOT's will be drawn on the first office visit and on the three week follow-up visit as this is when the rise in titre would be expected for those not being effectively treated.

Those with a positive B hemolytic strep throat swab with or without symptoms would be regarded as treatment failures. Those with an ASOT rise of two dilutions or more would also be regarded as treatment failures. There will be no follow-up longer than three weeks because of the difficulty in determining whether positive cultures after this time are due to re-emergence of latent streptococci.

Those patients with positive cultures at three weeks will be treated as their physician wishes.

The rarity of rheumatic fever and glomerulonephritis as outcomes of streptococcal pharyngitis preclude their use as sensitive outcome measures. Nevertheless, their occurrence would be monitored throughout the study both because they are important clinically and because this monitoring would help to insure that the application of both regimens was of equal effectiveness. Incidence would be monitored by clinical detection only. These unusual outcomes like the ASOT and throat swab results would be interpreted in the light of measured compliance.

The outcome measures of the urinary tract group will be urine cultures. In the study of Mabeck(102) it appears that antibiotics cause a good immediate cure rate as defined by urine cultures less than 10^5 bacteria. The recurrence rates were highest in the first two months post-treatment, 6% at 1 month and 12% at 2 months. This study also found that more than 50% of recurrences were really re-infections with a new organism rather than a recrudescence of the old organism. In this study therefore, urine cultures would be obtained on day 9 at home and in a physician's office at one month and two months post-treatment. The microstix method will be used. All cultures will have to be carefully identified and typed by a central laboratory

if patients are to be labelled as recrudescences or re-infections. A treatment failure will be defined as having a positive culture with the same organism as the original infection. A recurrence will be defined as a culture positive with a bacteria other than the original one. Any patient having a positive culture on day 9 or at the first or second month would have a serum creatinine and intravenous pyelogram. Those patients with positive cultures would be treated as their physician sees fit. Those patients having a culture positive on day 9 or at one month will not be followed further. Those patients with abnormal creatinine levels and/or abnormal I.V.P.'s would be excluded from the study for the reasons described in the inclusion/exclusion criteria.

iii. Side Effects

The necessity for the monitoring of side effects was detailed in the methodologic standards. The principal reason for determining side effects is to see if the compliance improving strategy is inflicting unwarranted toxicity on the patient. This is particularly important in this situation because of high doses used for the B.I.D. regimens. The monitoring of side effects will also detect those who may have had to drop out of treatment because of toxicity, for example sulfa sensitivity. This will be done by telephone from the coordinating centre. During the first week after treatment the caller, unaware of which regi-

men the patient was assigned to, will determine:

- 1) If the patient noted any serious side effects?
- 2) Did the patient feel these side effects interfered with his taking of the drug?
- 3) Did the patient experience any of the following common side effects;

Penicillin & Sulfa

- a) nausea
- b) diarrhea
- c) vomiting
- d) rash
- e) other (specify)

This order was chosen to prevent the caller from inadvertently increasing the patient's perceptions of side effects.

V. ANALYSIS

The main purpose of the analysis is to detect statistically significant differences in the outcome measures between the B.I.D. and Q.I.D. regimens. As the actual distribution of compliance is unknown(118), this can be obviated by transformation to a binomial distribution. This is done by setting the level of compliance (in relationship to clinical outcome) and designating those at or above this level as compliant and those below this level as non-compliant. This transformation of an unknown distribution to a binomial distribution allows the application of an appropriate parametric test. The data will be arranged in 2×2 tables and a chi-square test will be applied. A summary chi-square or Mantel-Henszel(119) will be used to assess the overall effect the manoeuvre has, independent of the stratifications. The overall interactions between the regimen and the outcome measures can be clarified by log linear analysis of multidimensional contingency tables(120). The two disease models will be analyzed separately. In the derivation of the sample size, the two models were assumed to be equivalent because there was no information on urinary tract infections and because of regimen similarity; but in the analysis area, it would be logically and statistically unsound to assume this equivalence and analyze data summarized from both models.

i. Compliance

- a) The proportion of patients deemed compliant by urine assay in each stratification will be analyzed for both disease models. (Sample calculation Appendix III).

- b) The proportion of patients deemed compliant by pill count in each stratification would be analyzed.
- c) The proportion of patients deemed compliant by both pill count and urine assay would be analyzed in a similar fashion.
- d) The proportion of patients lost to follow-up would be analyzed (as a reflection of drop outs).

ii. Disease Outcomes

- a) Outcome would be related first to the treatment group to determine if one group was more successful than the other.

Then summary chi-square would be applied. Similarly the other outcome measures, ie. culture at one and two months and throat swab and ASOT.

- b) Outcome would then be compared with compliance. As there are four measures of compliance and three measures of outcome for urinary tract infections and two for streptococcal pharyngitis, calculations would be considerably simplified if only one measure was chosen for compliance. The measure that probably reflects compliance best is; those that have consumed 80% of their medication and have a positive urine test on day 9.

iii. Side Effects

- a) The most important relationship is between the regimens and the three measures of side effects.
- b) The data would also be analyzed to see if there is a relationship between compliance and side effects.

iv. Secondary Analyses

The compliance measures done on day 10 will be analyzed to see if they are significantly different from those done on day 9. If they are different, data from day 10 measurements will be analyzed separately. If they are the same, data obtained on day 10 will be added to the day 9 data. An analysis will be done comparing academic practices with community practices to see if there is any effect on compliance.

Interpretation of Results

The primary motive behind this thesis is to test the Null Hypothesis that simplified regimens have no effect on compliance. In order for this hypothesis to be rejected, the importance of both a statistically and clinically significant difference has been discussed above. The minimal statistical level of significance would be $p \leq .05$, as has achieved wide acceptance. Ideally, the relationship between regimen and compliance would be shown in both disease models and for all parameters of compliance. The minimum of evidence for acceptance of the hypothesis would be a statistically and clinically important difference in compliance as measured by urine assay in one disease model. The urine assay was chosen because it is a direct method, it has been used in many previous studies and because the parameter of 80% medication consumption is untested.

The study would be expected to show that those completing their regimen had a better outcome than those who did not. This is necessary if clinical credibility is to be maintained. It would also be important to confirm the expectation that the disease outcome is the same for compliers in both regimens. For if there was a difference in regimen efficacy it would be difficult to relate compliance directly to outcome. Overall then, assuming equal efficacy, simple regimens would be expected to show better outcomes if they had an important effect on compliance. Because this study was designed using compliance-related outcome measures derived from a strep study, the strep model would be judged as reflecting the most reliable results in this compliance-outcome area.

Side effects would not be expected to differ between the two groups.

(99) If there was no difference the analysis could be stopped at that point. If there was a difference it would be important to see if it had any effect on compliance. If there were more side effects with one regimen and this was shown to decrease compliance, it would be necessary to re-test the thesis hypothesis with less toxic regimens.

If simplification was found to be an effective manoeuvre to increase compliance, trials could be undertaken in the long-term regimens like epilepsy, hypertension, tuberculosis, etc. If no difference was found, or paradoxically, if more complex regimens were shown to increase compliance the present rush to simplify could be stopped before it became an established practice.

VI. BUDGET

1. Personnel

One full-time research assistant for 1 year	\$13,000.00
One part-time registered nurse ½ time for 1 year	3,250.00
Part-time secretary - peak periods pre-study and post-study	<u>500.00</u>
	\$16,750.00
Fringe benefits 15%	<u>1,642.00</u>
Total	\$18,392.00

2. Travel

Mileage @ 16¢ per mile - house calls (2,000)	\$ 320.00
Investigator	<u>500.00</u>
Total	\$ 820.00

3. Material and Supplies

a) Office space rent - 1 year	\$ 3,600.00
Office equipment rent - 1 year	1,500.00
Paper, postage, copying, miscellaneous	200.00
b) Microstix	400.00
Incubators	500.00
Blood agar plates and throat swabs (2,000)	600.00
c) Antibiotic assays	
Bratton-Marshall	
initial test period	\$ 1,500.00

assays	\$ 500.00
Sarcinea lutea	100.00
d. Medication	
penicillin	900.00
sulfa	1,000.00
bottles - spoons	<u>100.00</u>
Total	\$10,900.00
Total cost	<u><u>\$30,112.00</u></u>

VII. BUDGET JUSTIFICATION

1. Personnel

A full-time research assistant would be needed to coordinate the day-to-day running of the study. This person would be responsible for insuring adherence to the research protocol and for the follow-up phone calls concerning side effects. A part-time registered nurse would make the home visits needed for the day 9 compliance measures. This has been estimated using a total of 400 (including dropouts) subjects in the study, or approximately eight subjects per week at one hour per subject including travelling time, yielding approximately 80 hours or one-quarter of a 40 hour week. A part-time secretary would be employed for the peak periods before the study started and in the pre-publication stage. This person would type the labels for the medications, letters to the study physicians and the write-up of the study.

2. Travel

The nurse would be expected to make approximately a five mile round trip per patient or 2,000 miles for 400 subjects at a rate of 16¢ per mile. The investigator's travel to a scientific meeting for a presentation of the results is also included as a travel cost.

3. Material & Supplies

A small office would be rented at commercial rates for one year. Office equipment including a desk, chair, type-

writer, calculator and telephone would be rented at commercial rates for one year. Paper, postage, copying and miscellaneous office supplies have also been accounted for.

The urine dip sticks cost approximately \$20 per 25. It is expected that to achieve 200 subjects when less than 50% of symptomatic females have positive cultures would mean that at least 500 of these would be needed at a cost of \$400. Incubators would be needed for each setting at \$45 per incubator and in 11 settings. Blood agar plates cost 25¢ per plate and throat swabs, 5¢ per swab. Knowing that only 10% of swabs are positive, a total of 2,000 of each would be needed.

Antibiotic assays would be contracted out. The Department of Pharmacology at the University of Manitoba has supplied the costs given in the budget. The initial test period includes equipment costs and the determination of the "compliance level" of antibiotic in the urine. The trial assays have been estimated for 200 subjects. The *Sarcinea Lutea* assay has been undertaken by the Department of Microbiology, St. Boniface Hospital at an approximate cost of 50¢ per assay for 200 assays.

It is hoped that the medication will be obtained from a pharmaceutical supplier free of charge. If this is not possible, the wholesale prices of penicillin and sulpha, dispensing bottles and spoons have been included.

VIII. SUMMARY

A protocol for a randomized trial designed to answer the question, Do Simplified Drug Regimens Improve Compliance? The literature has been reviewed as a background to the study question and as a means of developing methodologic criteria for the design of the study. The study will be done in the offices of urban family doctors including some academic family physicians. The disease models, streptococcal pharyngitis and uncomplicated urinary tract infection, were chosen because they are similar and because they are common in the family practice setting. Sample sizes of 200 were calculated for each disease model. This would involve 14 individual practices. Inclusion/exclusion criteria and stratifications were described and explained. The regimens would consist of 10 days of B.I.D. penicillin versus 10 days Q.I.D. penicillin for streptococcal pharyngitis and 10 days of B.I.D. sulfa versus 10 days of Q.I.D. sulfa for urinary tract infection. The application of the manoeuvre in the family practice setting was described in the context of the methodologic criteria. The measurement of compliance both direct and indirect, the assessment of disease outcomes and the monitoring of side effects were also detailed. The analysis would clarify the relationship between regimens, compliance, disease outcomes and side effects. The interpretation of these results would include the concept of clinical as well as statistical significance. A budget of \$30,000 was described and justified.

APPENDIX I.

<u>Age</u>	<u>Weight</u>	<u>25,000 u/Kg.</u>	<u>Q. I. D. dose</u>	<u>100,000 u/Kg.</u>	<u>Q. I. D. dose</u>
2	12 Kg.	300,000	75,000	1,200,000	300,000
4	17 Kg.	425,000	106,000	1,700,000	425,000
6	22 Kg.	550,000	137,000	2,200,000	550,000
8	27 Kg.	675,000	169,000	1,700,000	675,000
10	32 Kg.	800,000	200,000	3,200,000	800,000
12	39 Kg.	975,000	244,000	3,900,000	975,000

The table given above was derived from the 50th percentile weights for each age group(121). The maximum dosage being 100,000 u/Kg./day and the minimum effective dose being 25,000 u/Kg./day of Penicillin V(122). As one can see the minimum effective dose for age 12 is about 250,000 units four times a day (Q.I.D.) or 500,000 units twice a day (B.I.D.). This does not exceed the maximum dose for age 2.

APPENDIX II.

CONSENT FORM

SUBJECT NO. _____

Name _____

Date of Birth _____

Parent or Guardian if under 18 years _____

Home Address _____

Home Phone No. _____

Date of Office Visit _____

I agree to participate in a trial testing the effectiveness of penicillin in the treatment of sore throat. This has been explained to me and I understand the risks and benefits of treatment. I also understand that a nurse will visit my home during the treatment.

Date _____

Witness

Patient or Parent/Guardian

APPENDIX III.

U.T.I. ORAL CONTRACEPTIVES

Regimen	Compliance	
	+	-
B.I.D.	45	5
Q.I.D.	20	30

$$\chi^2 = 27$$

$$p < .005$$

Summary $\chi^2 = 33$

$$p < .005$$

U.T.I. - NO ORAL CONTRACEPTIVES

Regimen	Compliance	
	+	-
B.I.D.	40	10
	25	25

$$\chi^2 = 13.2$$

$$p < .005$$

BIBLIOGRAPHY

1. Veterans Administration Cooperative Study Group on Antihypertensive Agents. Effects of treatment on morbidity in hypertension: results in patients with diastolic blood pressures averaging 115 through 129 mm. Hg. J. Am. Med. Ass., 202:1028-1034, 1967.
2. Abernethy, J.D. The Problem of NonCompliance in Long-Term Anti-hypertensive Therapy, Drugs 11(1):86-90, 1976.
3. Jenkins, B.W. Are patients true to T.I.D. and Q.I.D. doses? G.P., 9:66-69, 1954.
4. Komaroff, A.L. Editorial. The Practitioner and the Compliant Patient. Am. J. Public Health, 66:833-835, 1976.
5. Rickels, K. and Briscoe, E. Assessment of dosage deviation in outpatient drug research. J. Clin. Pharm. J. New Drug, 10: 153-160, 1970.
6. McInnis, J.K. Do patients take antituberculosis drugs? Amer. J. Nurs., 70:2152-2153, 1970.
7. Haynes, R.B., and Sackett, D.L. An Annotated Bibliography on the Compliance of Patients with Therapeutic Regimens, McMaster Medical School, Hamilton, Ontario, 1974.
8. Preston, D.F. and Miller, F.L. The tuberculosis outpatient's defection from therapy. Amer. J. Med. Sci., 247:21-25, 1964.
9. Gordis, L., Markowitz, M. and Lilienfeld, A.M. Studies in the epidemiology and preventability of rheumatic fever. IV. A quantitative determination of compliance in children on oral penicillin prophylaxis. Pediatrics, 49:188-195, 1967.
10. Charney, E., Bynum, R., Eldredge, D., Frank, D., MacWhinney, J.F., McNabb, N., Scheiner, A., Sumpter, E. and Iker, H. How well do patients take oral penicillin? A collaborative study in private practice. Pediatrics, 40:188-195, 1967.
11. Bergman, A.B. and Werner, R.J. Failure of children to receive penicillin by mouth. New Eng. J. Med., 268:1334-1338, 1963.
12. Porter, A.M.W. Drug defaulting in a general practice. Brit. Med. J., 1:218-222, 1969.
13. Seigal, A.C., Johnson, E.E., Stollerman, G.H. Controlled Studies of Streptococcal Pharyngitis in a Pediatric Population. New Eng. J. Med., 268:1334-1338, 1963.

14. Taranta, A., Gordis, L. The Prevention of Rheumatic Fever, Opportunities, Frustration and Challenges. Cardiovascular Clinics, Vol. 4, No. 3, 2-10, 1972.
15. Sackett, D.L., "Private Communication from Dr. D.L. Sackett"
16. Haynes, R.B. Chapter 3 - Determinants of Compliance in Compliance with Therapeutic Regimens. ed. by D.L. Sackett and R.B. Haynes, Johns Hopkins, Baltimore, 1976.
17. Donabedian, A. and Rosenfeld, L.S. Follow-up study of chronically ill patients discharged from hospital. J. Chron. Dis., 17:847-862, 1964.
18. Macdonald, M.E., Hagberg, K.L. and Grossman, B.J. Social factors in relation to participation in follow-up care of rheumatic fever. J. Pediat., 62:503-513, 1963.
19. Fink, D., Malloy, M.J., Cohen, M., Greycloud, M.A. and Martin, F. Effective patient care in the pediatric ambulatory setting: A study of the acute care clinic. Pediatrics, 43:927-935, 1969.
20. Latiolais, C.J. and Berry, C.C. Misuse of prescription medications by outpatients. Drug Intell. Clin. Pharmacy, 3:270-277, 1969.
21. Lund, M., Jorgenson, R.S. & Kuhl, V. Serum diphenylhydantoin (Phenytoin) in ambulant patients with epilepsy. Epilepsia, 5:51-58, 1964.
22. Gordis, L., Markowitz, M. and Lilienfeld, A.M. Why patients don't follow medical advice: A study of children on long-term antistreptococcal prophylaxis. J. Pediat., 75:957-968, 1969.
23. Diamond, M.D., Weiss, A.J. and Grynbaum, B. The unmotivated patient. Arch. Physical Med. Rehab., 49:281-284, 1968.
24. Rae, J.B. The influence of the wives on the treatment outcome of alcoholics: A follow-up study of two years. Brit. J. Psychiat., 120:601-613, 1972.
25. Alpert, J.J. Broken appointments. Pediatrics, 34:127-132, 1964.
26. Atkinson, R.M. AMA and AWOL discharges: A six-year comparative study. Hosp. Comm. Psychiat., 22:293-296, 1971.
27. Becker, M.H., Drachman, R.H. and Kirscht, J.P. Predicting mothers' compliance with pediatric medical regimens. J. Pediat., 81:843-854, 1972.

28. Rosenstock, I., Patients' Compliance with Health Regimens. JAMA, 234:402, 1975.
29. Davis, M.S. Predicting non-compliant behaviour. J. Health and Soc. Behav., 8:265-271, 1967.
30. Roth, H.P., Caron, H.S., Hsi, B.P. Estimating a patient's cooperation with his regimen. Am. J. Med. Sci., 262:269-273, 1971.
31. Elling, R., Whittmore, R. and Green, M. Patient participation in a pediatric program. J. Health Human Behav., 1:183-189, 1960.
32. Curry, F.J. Neighborhood clinics for more effective outpatient treatment of tuberculosis. N. Eng. J. Med., 279:1262-1267, 1968.
33. Finnerty, F.A., Jr., Mattie, E.C. and Finnerty, F.A. III. Hypertension in the inner city. I. Analysis of clinic dropouts. Circulation, 47:73-75, 1973.
34. Zaki, M.H., Edelstein, S., Josephson, R.A. and Weisberg, S.R. Regularity of drug administration among hospitalized and ambulatory tuberculosis patients. Amer. Rev. Respir. Dis., 97:136-139, 1968.
35. Johannsen, W.J., Hellmuth, G.A. and Sorauf, T. On accepting medical recommendations. Arch. Envir. Health, 12:63-69, 1966.
36. Collette, J. and Ludwig, E.G. Patient compliance with medical advice. J. Nat. Med. Ass., 61:408-411, 1969.
37. Rickels, K., Boren, R. and Stuart, H.M. Controlled psychopharmacological research in general practice. J. New Drugs, 4:138-147, 1964.
38. Weintraub, M., Au, W.Y.W. & Lasagna, L. Compliance as a determinant of serum digoxin concentration. JAMA, 224:481-485, 1973.
39. Willcox, D.R.C., Gillan, R. and Hare, E.H. Do psychiatric outpatients take their drugs? Brit. Med. J., 2:790-792, 1965.
40. Glick, B.S. Dropout in an outpatient, double-blind drug study. Psychosomatics, 6:44-48, 1965.
41. Lipman, R.S., Rickels, K., Uhlenhuth, E.H., Park, L.C. and Fisher, S. Neurotics who fail to take their drugs. Brit. J. Psychiat., III:1043-1049, 1965.

42. Feinstein, A.R., Spagnuolo, M., Jonas, S., Levitt, M. and Tursky, E. Discontinuation of antistreptococcal prophylaxis. JAMA, 197:949-952, 1966.
43. Roth, H.P. and Berger, D.G. Studies on patient cooperation in ulcer treatment I. Observation of actual as compared to prescribed antacid intake on a hospital ward. Gastroent., 38:630-633, 1960.
44. Maddock, R.K. Patient cooperation in taking medicines. A study involving isoniazid and aminosalicylic acid. JAMA, 199:137-140, 1967.
45. Lane, M.F., Barbarite, R.V., Bergner, L. and Harris, D. Child-resistant medicine containers: Experience in the Home. A.J.P.H., 61:1861-8, 1971.
46. Ireland, H.D. Outpatient chemotherapy for tuberculosis. Am. Rev. Respir. Dis., 82:378-383, 1960.
47. McKenny, J.M., Slining, J.M., Henderson, H.R., Devins, D. and Barr, M. The effect of clinical pharmacy services on patients with essential hypertension. Circulation, 48:1104-1111.
48. Dixon, W.M., Stradling, P. and Wotton, I.D.P. Outpatient P.A.S. therapy. Lancet, 2:871-2, 1957.
49. Charlton, C.A.C., Crowther, A., Davies, J.G., Dynes, J., Howard, M.W.A., Mann, P.G., Rye, S. Three-day and ten-day chemotherapy for urinary tract infections in general practice. Br. Med. J., 1:124-126, 1976.
50. Clark, G.M., Troop, R.C. One-tablet combination drug therapy in the treatment of hypertension, J. Chron. Dis., 25:57-64, 1972.
51. David, N.A., Welborn, W.S., Pierce, H.I. Comparison of multiple and combination tablet drug therapy in hypertension. Curr. Ther. Res., 18:741-754, 1975.
52. Colcher, I.S., Bass, J.W. Penicillin treatment of streptococcal pharyngitis: A comparison of schedules and the role of specific counselling, JAMA, 222:657-659, 1972.
53. Feinstein, A.R., Wood, H.F., Epstein, J.A., et al, A Controlled study of three methods of prophylaxis against streptococcal infection in a population of rheumatic children. II. Results of the first three years of study, including methods for evaluating the maintenance of oral prophylaxis. N. Eng. J. Med., 260:697-702, 1959.
54. Feinstein, A.R., Spagnuolo, M., Jonas, S., et al, Prophylaxis against rheumatic fever, JAMA, 206:565-568, 1968.

55. Johnson, D.A.W., Freeman, H. Long-acting tranquilizers. Practitioner, 208:395-400, 1972.
56. Neely, E. and Patrick, M.L. Problems of aged persons taking medications at home. Nurs. Res., 17:52-55, 1968.
57. Gordis, L., Markowitz, M. and Lilienfeld, A.M.. The inaccuracy of using interviews to estimate patient reliability in taking medications at home. Med. Care, 7:49-54, 1969.
58. Schwartz, D., Wang, M., Zeitz, L., Goss, M.E.W. Medication errors made by elderly, chronically ill patients. A.J.P.H., 52:2018-2029, 1962.
59. Hulka, B.S., Cassel, J.C., Kupper, L.L. and Burdette, J.A. Communication, Compliance, and Concordance between Physicians and Patients with Prescribed Medications. A.J.P.H., 66:847-853.
60. Gatley, M.S. To be taken as directed. J. Roy. Coll. Gen. Practiti., 16:39-44, 1968.
61. Sackett, D.L., Gibson, E.S., Taylor, D.W., Haynes, R.B., Hackett, B.C., Roberts, R.S., Johnson, A.L. Randomized Clinical Trial of Strategies for Improving Medication Compliance in Primary Hypertension. Lancet, 1205-1207, 31 May 1975.
62. Stone, D.B. A study of the incidence and causes of poor control in patients with diabetes mellitus. Amer. J. Med. Sci., 241:436-442, 1961.
63. Cole, P. and Emmanuel, S. Drug consultation: Its significance to the discharged hospital patient and its relevance as a role for the pharmacist. Am. J. Hosp. Pharm., 28:954-960, 1971.
64. Meyer, A.J. and Henderson, J.B. Multiple risk factor reduction in subjects at high risk for cardiovascular disease. Paper presented at the Cardiovascular Epidemiology Meetings of the American Heart Association, March 13, 1973.
65. Neufeld, V.R. Patient Education: A Critique, Rosenberg, S.G. Patient Education: An Educator's View in: Compliance with Therapeutic Regimens. ed. by D.L. Sackett and R.B. Haynes. Baltimore, Johns Hopkins University Press, 1976, Ch. 7 & 8:
66. Azrin, N.H. and Powell, J. Behavioral engineering: The use of response priming to improve prescribed self-medication. J. Applied Behav. Anal., 2:39-42, 1969.

67. Martens, L.V., Fracier, P.J., Hirt, K.J., Meskin, L.H. and Proshek, J. Developing brushing performance in second graders through behaviour modification. Health Serv. Rep., 88:181-823, 1973.
68. Haynes, R.B., Gibson, E.S., Hackett, B.C., Johnson, A.L., Sackett, D.L., Taylor, D.W., Roberts, R.S. Improvement of Medication Compliance in Uncontrolled Hypertension. Lancet, 1265-1268, 12 June 1976.
69. Bonnar, J., Goldberg, A. and Smith, J.A. Do pregnant women take their iron? Lancet, 457-458, 1969.
70. Linkewich, J.A., Catalano, R.B. and Flack, H.L. The effect of packaging and instruction on outpatient compliance with medication regimens. Drug Intell. Clin. Pharmacy, 8:10-15, 1974.
71. Gordis, L. and Markowitz, M. Evaluation of the effectiveness of comprehensive and continuous pediatric care. II. Effectiveness of continuous care in influencing patient compliance. Pediatrics, 48:766-776, 1971.
72. Gordis, L. and Markowitz, M. Evaluation of the effectiveness of comprehensive and continuous pediatric care. I. Effectiveness of comprehensive care in influencing infant health. Pediatrics, 48:766-776, 1971.
73. Onstad, G.D., Sbarbaro, J.A. and Rotenberg, L. Post-hospital chemotherapy of the unreliable patient. Amer. Rev. Respir. Dis., 101:258-264, 1970.
74. Gibbard, F.B., Dunne, J.F., Handley, A.J. and Hazleman, B.L. Supervision of epileptic patients taking phenytoin. Brit. Med. J., 1:147-149, 1970.
75. Korsch, B.M. and Negrete, V.F. Doctor-patient communication. Scientific American, 227:66-74, 1972.
76. Sackett, D.L. Design, measurement and analysis in clinical trials. In: Hirsh, J., ed., Platelets, Drugs and Thrombosis. Basel: S. Karger, 1975, 219-225.
77. Hill, A.B. Principles of Medical Statistics, 9th ed. London: Lancet, 1971, 254-257.
78. Feinstein, A.R. Clinical Judgment. Huntington, N.Y., Krieger, 1974.
79. Armitage, P. The construction of comparable groups. In Controlled Clinical Trials. Oxford: Blackwell, 14-18, 1960.
80. Biener, K.J. The Influence of Health Education on the Use of Alcohol and Tobacco in Adolescence. Prev. Med. 4:252-257, 1975.

81. White, K.L. Primary Care Research and New Epidemiology, J. Fam. Prac., 3:579-580, 1976.
82. White, K.L. The Ecology of Medical Care. New Eng. J. Med., 265:885-892, 1961.
83. Bass, M. A Profile of Family Practice in London, Ontario. Can. Fam. Phys., 113-120, September 1975.
84. Labelle, C. Alberta Workload Study. Can. Fam. Phys., 99-108, May 1973.
85. Valentine, A.S. What Is Family Practice? Maybe the E Book Can Tell You. Can. Fam. Phys., 10:29-35, October 1975.
86. Kunian, L. Role of the Emergency Unit in a Community Hospital. New Eng. J. Med., 283:1367-1370, 1970.
87. Smith, D.H., McWhinney, I.R. Comparison of the Diagnostic Methods of Family Physicians and Internists. J. Med. Educ., 50:264-269, March 1975.
88. Feightner, J.W., Barrows, H.S., Neufeld, V.R., Norman, G.R. Solving Problems: How Does the Family Physician Do It.?. Can. Fam. Phys., 67-71, April 1977.
89. Jenkins, B.W. Are patients true to T.I.D. and Q.I.D. doses? G.P., 9:66-69, 1954.
90. Rudneck, K.V., Spitzer, W.O., Pierce, J. Comparison of a private family practice and a university teaching practice. J. Med. Educ., 51(5):395-402, May 1976.
91. College of Physicians and Surgeons of Manitoba and Manitoba Chapter, College of Family Physicians of Canada Registry Statistics.
92. Hart, W.J., Streptococcal Pharyngitis, Can. Fam. Phys., 22:516-521, 1976.
93. Fry, J. Acute Urinary Infections. Common Diseases: Their Nature, Incidence and Care, 15:164-173, 1974.
94. Hodgkin, K. Towards Earlier Diagnosis, 3:21-23, 1973.
95. Dickie, G.L. Symptomatology of Urinary Tract Infections. Can. Fam. Phys. 51-56, December 1975.
96. Leistyna, J.A., Macaulay, J.C. Therapy of streptococcal infections, Amer. J. Dis. Child, 111:22-26, 1966.

97. Rosenstein, B.J., Markowitz, M., Goldstein, E., et al. Factors involved in treatment failures following oral penicillin therapy of streptococcal pharyngitis, J. Pediat., 73:513-520, 1968.
98. Green, J.L., Ray, S.P., Charney, E. Recurrence rate of streptococcal pharyngitis related to oral penicillin, J. Pediat., 75:292-294, 1969.
99. Breese, B.B., Disney, F.A., Talpey, W.B., Penicillin in Streptococcal Infections, Total Dose and Frequency of Administration, Amer. J. Dis. Child, 110:125-130, August 1965.
100. Stollerman, G.H. Rheumatic Fever and Streptococcal Infection, Clinical Cardiology Monographs, 3:47-62, 1975.
101. Little, P.J. The incidence of urinary infections in 5,000 pregnant women, Lancet, 2:925, 1966.
102. Mabeck, C.E., Treatment of uncomplicated urinary tract infection in non-pregnant women, Postgraduate Med. J., 48:69-75, 1972.
103. Siegel, E., Thomas, D., Coulter, E., Tuthill, R. and Chipman, S. Continuation of contraception by low income women: A one-year follow-up. A.J.P.H., 61:1886-1898, 1971.
104. Committee report on prevention of rheumatic fever and bacterial endocarditis through control of streptococcal infections. Circulation, 21:151-155, 1960.
105. Weinstein, L. Antimicrobial Agents; Penicillins and Cephalosporins, The Pharmacological Basis of Therapeutics, ed. Goodman, L.S., Gilman, A., 5th Ed., 57:1130-1166, 1975.
106. Breese, B.B., Disney, F.A., Penicillin in the Treatment of Streptococcal Infections, A comparison of Effectiveness of Five Different Oral and One Parenteral Form, N. Eng. J. Med., 259:2:57-62, 10 July 1958.
107. Sanford, J.P. Urinary Tract Symptoms and Infection. Ann. Rev. Med., 26:485-98, 1975.
108. Waters, W.E., Prevalence of Symptoms of Urinary Tract Infection In Women. Brit. J. Prev. Soc. Med., 23:263, 1969.
109. Gallagher, D.J.A., Montgomerie, J.Z., North, J.D.K., Acute Infections of the Urinary Tract and the Urethral Syndrome in General Practice. Brit. Med. J., 1:622, 1965.
110. Craig, W.A. et al, Appl. Microbiol., 26:196-201, 1973.

111. Microstix and Other Office Tests for the Detection of Urinary Tract Infection, Medical Letter, Vol. 16, 3:3, 1 Feb. 1974.
112. Turck, M. The problem of Infections by Gram Negative Organisms, Antimicrobiol. Agents Chemother, 6:265, 1966.
113. Choice of Drugs for Treatment of Urinary Tract Infections, Medical Letter, Vol. 18, 1:3, 2 Jan. 1976.
114. Turck, M. Therapeutic Guidelines in the Management of Urinary Tract Infections and Pyelonephritis, Urol. Clinics of N. America, 2:3:443-451, 1975.
115. Weinstein, L. Antimicrobial Agents, Sulfonamides and Trimethoprim-Sulfamethoxazole, The Pharmacological Basis of Therapeutics, ed. Goodman, L.S., Gilman, A., 5th Ed., 56:1113-1129, 1975.
116. Bratton, A.C., Marshall, E.K., Jr. A New Coupling Component for Sulfonamide Determinations, J. Biol. Chem., 128:537, 1939.
117. Klein, D.C., Moody, M.D., Baker, C.N., Addison, B.V., Appl. Microbiol., 16:184, 1968.
118. Goldsmith, C.H. The Effect of Differing Compliance Distributions on the Planning and Statistical Analysis of Therapeutic Trials, Compliance with Therapeutic Regimens, ed. by D.L. Sackett and R.B. Haynes, Johns Hopkins, Baltimore, 1976, 13:137-151.
119. Mantel, N., Haenszel, W. Statistical Aspects of the Analysis of Data from Retrospective Studies of Disease, J. Nat. Canc. Instit., 22:719-748, 1959.
120. Feinberg, S.E., The Analysis of Multidimensional Contingency Tables, Ecology, 51:2:419-433, late Spring 1970.
121. Nelson Textbook of Pediatrics, 10th Ed.
122. Handbook of Antimicrobial Therapy, Medical Letter, Rev. Ed. 1976.