COMPLIANCE IN THE R.R.P.C.E. STUDY
COMPLIANCE
IN THE STUDY OF
RECENT RECURRENT PRESUMED
CEREBRAL EMBOLI

By

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ABSTRACT

The measurement of compliance is essential in clinical trials to assess the efficacy and side effects of treatment. Multiple methods of measuring compliance and several predictors of it are recognized. However, noncompliance has been defined using arbitrary "cutting points" on scales measuring compliance. Such "cutting points" should be validated against an external measurement.

In the Study of Recent Recurrent Presumed Cerebral Emboli, multiple measurements affected by the drugs (which are meant to prevent such events) are available on multiple occasions in the same subjects. This thesis explores ways in which one can assess the extent to which these measurements agree as indices of the intake of those drugs. Furthermore, it explores how such measurements can be validated against an external measurement, the outcome desired (i.e. the control of cerebral emboli) in order to choose a valid "cutting point" to define compliance and non-compliance. Finally, it suggests methodologies to predict whether a subject will be compliant or non-compliant and to study whether compliance
is a constant characteristic of certain subjects or varies through time, being affected by time or various events in the course of therapy. Thus, this thesis proposes a methodology to obtain a valid index of compliance which will predict outcomes and a methodology to study the factors which predict such compliance.
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INTRODUCTION

The R.R.P.G.E. Study

The purpose of this study is to determine whether sulfinpyrazone, acetylsalicylic acid or combinations of these drugs which suppress platelet adhesiveness are effective in significantly reducing the number of transient ischemic attacks, and if so, preventing strokes or increasing life expectancy.

The design is essentially a between-patient, double-blind study to assess the efficacy of these drugs. It employs a factorial arrangement in which patients are allocated to one of four treatments, placebo, acetylsalicylic acid, sulfinpyrazone, or acetylsalicylic acid and sulfinpyrazone according to a prescribed randomized arrangement.

Extensive clinical assessments are available at the initial visit, at intervals, and at exit from the study. Laboratory investigations are used to monitor the effects of the drugs on platelet reactivity. These are the platelet collagen and epinephrine aggregation reactions, platelet glass adhesiveness and platelet turnover studies in some cases. In addition, other measures relevant to patients' compliance with the therapeutic regimen have been included: record of dropouts, patients' reports of intake of other medications and pill counts (1).
Objectives of the Study of Compliance in the R.R.P.C.E. Study

The objectives of this thesis are:
1. to study the extent to which the various measurements of compliance employed in the R.R.P.C.E. Study agree;
2. to attempt to derive a clinically meaningful operational definition of compliance in this study based on the ability of measurements of compliance to predict outcome;
3. to study the determinants of compliance in the setting of the R.R.P.C.E. Study.

This paper will deal with the following issues:
i. the importance of the measurement of compliance;
ii. the need for an operational definition of compliance which is clinically meaningful;
iii. a review of the current methods of measuring compliance;
iv. a review of the currently accepted predictors of compliance;
v. limitations of the data set available in the R.R.P.C.E. Study;
vi. the methods of measurement of compliance and outcomes employed in the R.R.P.C.E. Study;
vii. the methodology of analyzing the agreement among the measurements of compliance employed in the R.R.P.C.E. Study;
viii. the methodology of obtaining a clinically meaningful definition of compliance in the R.R.P.C.E. Study;
ix. the methodology of determining the predictors of compliance in the R.R.P.C.E. Study.
Compliance may be defined as the measurement of congruence between a therapeutic intent and the action of a patient. A patient falls ill, is advised to undertake a series of manoeuvres by his physician and follows these manoeuvres to a varying extent. He may be asked to restrict some of his activities, to partake in others, to follow a diet, and finally to take medication. The patient may follow some or all of this advice.

In this study, the patient is advised to take medications four times a day. Various indices of compliance will be utilized to determine to what extent he follows that advice.

Insofar as this study is a subset of a controlled clinical trial, the major importance of compliance relates to the results of that trial. If sufficient patients fail to take a sufficient amount of the medication, the medication may be deemed to be without efficacy when indeed it might have proven efficacious if taken (2,3,4,5). In addition, the frequency of side effects could be grossly underestimated if patients were failing to take the medication and this were not detected.

However, compliance is obviously essential for a therapeutic result to be seen in any clinical situation. Moreover, although of lesser concern, noncompliance results in stockpiling of potentially dangerous drugs in patients' homes and in needless expense.
THE OPERATIONAL DEFINITION OF COMPLIANCE

The literature contains many studies dealing with compliance which have produced confusing and often conflicting results. The rates at which patients are stated to comply with their medication vary widely. Part of this variation is related to the different populations studied, their diseases, their therapists, and the therapeutic manoeuvre employed. However, in addition, different operational definitions of compliance also result in different rates. Multiple methodologies of studying medication intake have been employed. Then, convenient values which arise from these measurements have been chosen as division points to decide whether the patient is compliant or noncompliant. Insofar as such a decision remains arbitrary, different authors choose different decision points and observe widely varying rates of compliance.

The operational definition of compliance should not be an arbitrary one. The extent of deviation from a regimen which is tolerable should depend on the effects of such deviation. Pill-taking is not an end in itself. It is meant to be a means by which one can achieve a specific goal, either the prevention of a disease or the attainment of improved health. Accordingly, compliance would be most appropriately defined as congruence between the prescribed intent and the action of the patient to such an extent that the desired therapeutic results would be seen. This definition gives clinical meaning to the
concept of compliance and allows one to assess the validity of any definition of compliance as a predictor of a clinical outcome.

Thus defined, a measurement of compliance becomes a test which is predictive of a therapeutic result. Such an index is useful to a physician as an aid to deciding upon the correct dosage of a medication to prescribe. Physicians have been demonstrated to be unable to predict which patients will comply or to what extent they will comply with a prescribed regimen (2,6,7,8,9,10,11,12). Accordingly, currently, a physician must prescribe a dose which is sufficiently greater than the minimal effective dose so that a therapeutic result will be seen in noncompliers and yet not excessively in excess of the therapeutic dose lest toxicity result in compliers. This may not be a problem in cases where there is a wide margin of safety with regards to the drug, for example, with penicillin. However, with drugs having a relatively narrow margin of safety, this may be an exceedingly hazardous practice, for example, with digitalis or anti-convulsants. Thus, a measurement that indicates that the patient is ingesting a sufficient amount of the medication to achieve a desired therapeutic result would be most useful.

**METHODS OF MEASUREMENT OF COMPLIANCE**

Multiple ways of measuring compliance have been attempted. These are summarized in Table I.
Interview of Patient

Asking the patient directly concerning his compliance with medication is a relatively simple way of obtaining information. Moreover, it allows one to determine relatively easily the exact pattern of missed medication and the patient's perception of its cause.

Several studies employing this technique have been fruitful concerning patients' stated reasons for not taking the medication. Two studies concerned acute illness in children. Mohler et al (13) found that the commonest reasons for not completing a course of prescribed penicillin were that the patient felt well, or the parent was careless or had insufficient money. Francis (14) found that if the patient's expectations of a visit to an Emergency Room were unmet, compliance was less likely to occur.

Of more relevance to this study are two studies dealing with chronic disease in adults. Both of these dealt with P.A.S. in tuberculosis. Luntz (15) found that patients stated that P.A.S. was unpleasant, that they ran out of a supply of medicine, that there was staining of underwear or linen, that with time or the belief that they were cured, they tended to decrease their medication, and finally that some patients were simply uncooperative. On the other hand, a study in Madras (16) revealed that few patients would give a spontaneous reason for their lapse. However, a very few did have minor side effects, some
complained of hunger, some related minor unassociated complaints and some put forward religious reasons such as fast days or inauspicious days for drug-taking. Nevertheless, even on probing, many offered no explanation. Accordingly, it is perhaps not surprising that relatively few studies have relied on patients to provide reasons for their lapses in drug-taking. Authors have tended to concentrate on more objective methods of obtaining measurements which might predict such behaviour.

The main disadvantage of obtaining information concerning compliance directly from the patient is that such an approach involves all the problems of interviewing so that the results are affected by the interviewer, the types of questions asked, the setting, the patient's memory, and the motivation of the patient (e.g. fear of the doctor, desire to please). Accordingly, in comparison with pill counts or direct measurements of the drug in the blood or excreta, this method tends to be a relatively insensitive one to detect noncompliance (12,17,18,19,20,21,22,23).

**Interview of Physician or Other Health Professional**

Interviewing of a physician or other health professional who is involved in the care of a patient is perhaps the simplest way of obtaining an index of compliance. However, this methodology has proven to be extremely inaccurate (2,6,7,8,9,10,11,12).
Dispensing of Medication

Determining whether the patient obtains dispensed medication remains a relatively simple way of obtaining a measure of compliance. If the patient does not obtain the medication at a study pharmacy, one then assumes that he did not consume the medication. However, if the patient knew the content of the medication and it were sufficiently inexpensive, he might obtain it elsewhere. On the other hand, if the patient does obtain the medication, he may simply store it, give it to his friends, or dispose of it. Moreover, this methodology yields only the total amount of medication which may not have been taken and does not reveal the pattern of missed doses. Nevertheless, this method has been used in several studies of chronic illness (24, 25, 26).

Pill Counts

The measurement of residual medication has been widely used (3, 5, 17, 18, 19, 21, 27, 28, 29, 30). This may involve a pill count or an estimate of the volume of medication remaining in the case of liquid medication. This method is relatively objective, avoiding the problems of interviewing, and may detect patients who obtain medication from the dispensary but do not ingest it.

It is less simple than the previous methods. Moreover, the patient may dispose of the medication in ways other than ingesting it and
may forget to return the remaining medication. While this method provides an index of the total medication ingested over a relatively long period of time, it remains a global estimate of that intake and does not reveal the pattern of medication errors which may occur through time.

Roth (31) compared an estimate of compliance derived from counting empty bottles of antacid with an estimate provided by a bromide marker. He found that the bottle count overestimated compliance in 23 of 105 patients and overestimated total consumption by 20%. This may be partly explained by a high intake of chloride which would yield a falsely low measurement of his marker. However, low levels of the marker may have been related to true noncompliance with intake of the antacid and disposal of it in other ways.

Measurement of Drug or Marker

A much more sophisticated method of determining drug intake is to measure the drug presence or concentration in blood or excreta (2, 4, 8, 10, 12, 15, 16, 17, 20, 22, 23, 29, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 47).

A variant on this technique is to measure a marker (e.g. riboflavin) which is added to the drug and then measured (3, 31, 32, 40, 42, 43, 44, 45, 46). These types of measurement are probably the most direct determinations of the intake of a drug. The use of a marker has the advantage of simplicity over the direct measurement of the drug. On the other
hand, these tests tend to be qualitative and indicate only that the patient has taken his medication recently. (The bromide marker is perhaps an exception of this rule due to the relatively long half-life of bromide and allows some extrapolation backwards to determine what amount of medication may have been missed. Nevertheless, the result tends to indicate only if the patient has taken the medication during a short time prior to the test.)

Some authors have considered whether patients might be more likely to take medication prior to the time of a check of compliance. It has been suggested that as long as the purpose of the test is unknown to the patient, he is unlikely to comply only to "pass the test", and objective evidence in this regard has been obtained. Gordis, studying penicillin prophylaxis against rheumatic fever in children, tested their urine for penicillin at scheduled clinic visits and also on random weekly specimens. He found that there tended to be good agreement between scheduled and non-scheduled checks for those whose scheduled specimens were positive either greater than 75% of the time or less than 25% of the time. Thus, the scheduled tests would identify 81.5% of "true noncompliers" and 96% of "true compliers". However, in those who had negative tests between 25 and 74% of the time, agreement was less satisfactory (39). Morrow and Rabin used a riboflavin marker of INH in tuberculous patients and compared urines tested at clinic visits and at unannounced home visits. They studied 350 patients' urines at a series of clinic visits and performed four
unannounced home visits on one-third of these patients. Of the patients tested at the clinic, 31.7% failed to demonstrate the label in their urine on at least 50% of the tests. In the sub-group tested at home, 36.5% showed the same index of the noncompliance. The increase in this evidence of noncompliance was attributable to decreased compliance of working-aged males when tested at home (42). Maddock also obtained similar results for P.A.S. and INH compliance by testing urine at surprise home visits and at scheduled clinic visits (4). Thus, it would appear that testing for a drug at scheduled visits will identify most true compliers and severe non-compliers, particularly regular non-compliers (as compared to the random visit).

The detection or measurement of drugs or markers require the obtaining of samples. Accordingly, they tend to be done at various points in time and do not reveal what the patient does during other times. Luntz and Austin had patients test their urine with Phenistix to detect P.A.S. without being aware of the rationale of the test. This clever approach was limited to few patients. However, they found that patients tended to miss their medications more frequently on weekends when their usual pattern of life was changed (15).

Outcome

A further method of assessing compliance is to measure some predictable
outcome of taking the drug. For example, one may perform throat cultures in those receiving penicillin for streptococcal infection (13). This methodology indicates that the patient has taken sufficient medication to achieve the therapeutic end desired and is probably an ideal methodology. However, as a measure of medication intake, this approach requires the assumption that compliance with a therapeutic regimen is both necessary and sufficient to ensure the outcome. Few drugs are as uniformly efficacious as penicillin in oral streptococcal infection. Accordingly, it would be possible to classify some compliers as noncompliers. Moreover, many noncompliers may still have a good therapeutic outcome. Thus, this approach can lead to errors in the estimate of compliance.

A further limitation to the direct assessment of outcomes as a measure of compliance occurs in preventive medicine or the treatment of chronic disease. In these cases, one often wishes to predict outcomes which will occur at some time in the future. On the other hand, if one is attempting to alter these, one wishes to have an index of the patient's compliance at the present. Obviously, if one wished to prevent a stroke, one would wish to know prior to the occurrence of a stroke that the patient was failing to ingest the necessary preventive medication.

**Predictor of Outcome**

A further methodology to obtain an index of compliance is to measure
some intermediate outcome (some biochemical or physiologic effect) of taking the drug. If this intermediate effect can be related both to the ingestion of the drug and also to a final outcome measure, it provides a most useful clinical index. For example, the prothrombin time is used in gauging the appropriate amount of anticoagulants to prescribe and is used to predict a decreased risk of thromboembolism. Accordingly, such an index provides a predictor of outcome which can be related to drug ingestion and ensures that therapy is adequate.

Such measures may impose difficulties. First, it is necessary to validate the measurement against other indices of compliance and as a predictor of outcome. The methodology of determining such biochemical or physiologic parameters may be complex (e.g. platelet survival studies in the R.R.P.C.E. Study). Finally, factors other than compliance may affect the predictor or outcome, making it difficult to observe the desired correlation.

Perhaps, the most widely used such index in the past was the determination of sugar in the blood or urine in diabetes. In multiple studies, this was correlated with outcomes in diabetes mellitus (48, 49, 50). However, the major difficult in these studies is that the blood sugar has not been adequately correlated with other measures of compliance. Accordingly, it is not possible to assess whether the blood sugar reflects compliance or other aspects of the disease or patient. On the other hand, the U.G.D.P. Study (51) attempted to study some of these parameters directly. For example, they were able to demonstrate that there was no significant long-term difference in blood sugar
levels between patients in groups who were prescribed Tolbutamide as compared to a placebo. In addition, they studied compliance as measured by the prescription record and the physician's evaluation of the patient's adherence to that prescription (51). (It is recognized that this is a poor method of measuring compliance as discussed above). Employing this methodology, there appeared to be a correlation between the level of adherence and an increased incidence of adverse events (death, cardiovascular death) (52).

Conclusion

The different methods of measurement of compliance are of varying accuracy. They are summarized in Table 1. In essence, the different methodologies measure different aspects of compliance. The decision point concerning whether a patient is compliant or noncompliant is often arbitrary. To obtain clinically useful indices of compliance, it is highly desirable to correlate any measurement of compliance employed with other measurements of compliance and with outcome measures.

PREDICTORS OF COMPLIANCE

Compliant behaviour may be considered to be the result of an interaction between the patient, his illness, the therapist, and the therapeutic
manoeuvre (including the milieu) desired. Many factors are embodied under each of these headings and the various factors interact and correlate among themselves. Accordingly, it is not surprising that any one factor does not appear to have an overriding effect. In addition, as discussed previously, the operational definition of compliance varies widely in different studies. Accordingly, in this complex field there are many contradictory findings and the quality of studies varies greatly.

The Patient

Demographic data on patients is readily available, objective, and has been considered on many occasions. The majority of studies have reported no effect of age, at least in the adult age group (4, 23, 37, 47, 53, 54, 55, 56, 57, 58, 59). However, several studies concerning tuberculosis have revealed a lower compliance rate in younger adults or adolescents with the effect being more marked in females (2, 15, 37, 40, 42). These were all based on biochemical measurement of the drug or a marker in the urine so that the data is relatively firm. One of these studies reported a similar fall-off for males of the age of 55. [This was based on 104 patients in that age group and while it has not been confirmed in other studies, this is an unusually large number for such investigations (15).] Schwartz, using patient interview in clinic patients of a New York hospital, showed that with advancing age beyond 60, there was a mild
increase in error-making (60). However, the effect was neither linear nor marked. Obviously, multiple variables are associated with advancing age in this age group including multiple disease, complex medical regimens, failing mental faculties and increasing supervision of the patient. The interaction of these with age per se was not investigated. In any case, it would appear that compliance tends to decrease at the extremes of life, although the reasons for this have not been entirely delineated.

In several studies concerning not only tuberculosis, but other diseases as well, sex per se has not been observed to have an appreciable effect (4,23,53,57,59,61).

The effect of marital status on compliance may be reflecting an influence of social supervision as well as other factors. Separated and divorced patients have been shown to take less INH than married patients (using riboflavin-tagged INH) (42). Schwartz in her study of the elderly found that widowed, divorced or separated patients made more errors than those who were single or married (60); although Neeley (53) did not confirm this effect. However, Neeley's patient population was smaller and was drawn from a pre-paid partly rural practice rather than a clinic of a New York Hospital. Accordingly, it appears that marital status does predict compliance to some degree, although the effect may not be marked and may be attributable to social supervision.
Several studies have considered the effect of social supervision more directly. Porter (24) found that social isolation was the most significant contribution to a step-wise multiple regression used to predict compliance in 58 patients on various long-term treatments. Schwartz observed that living alone created errors in elderly patients (60). This effect was again not confirmed by Neeley (53). In depressed and schizophrenic patients living alone has been associated with increased drug defaulting (23). Supervision of drug intake by relatives or friends in schizophrenics has similarly been shown to increase compliance (26). More directly, social supervision as exemplified by supervision in a closed ward, open ward, or clinic have been seen to be associated with decreasing compliance in that order (38). Thus, it would appear that living with others or some direct supervision of medication intake will increase compliance, at least in elderly or psychiatric patients. This appears to be a fairly strong and consistent predictor of compliance although no individual study is outstanding in the power of its methodology.

Socioeconomic status, when studied, has tended to be relatively weakly associated with compliance and results have been conflicting. Being unemployed has been associated with less intake of P.A.S. (2), but family income, source of income or employment status prior to the diagnosis of tuberculosis was not related to the intake of INH (42). Davis observed no effect of education or occupation among patients in a general medical clinic with a wide variety of diseases using a global
index of compliance (59) and Bonnar observed 'no effect among pregnant women taking prophylactic iron during pregnancy using a chemical test for iron in the stool (47). However, among neurotic patients, there is a slight but not statistically significantly greater compliance rate among whites with eight grades of education or more than among negroes or those with less education. [This study was based partly on pill counts with noncompliance being defined as failure to keep appointments, taking less than 75% of the prescribed medication or taking other psychotropic medications. Being based on 248 patients with 110 noncompliers while 25 hypotheses were tested, the study design was most likely very sensitive to minor differences (27). Moreover, white educated neurotics may be especially likely to take psychotropic medications.] Porter found that antenatal patients were more likely to take iron tablets if they belonged to a higher social class. He employed pill counts to obtain his estimate of compliance and found that social class was correlated with the duration of observation, parity, and whether the pregnancy was planned. When the effect of these latter factors was removed in his multiple regression model, social class accounted for only 11.8% of the variation and this was not statistically significant (24). Accordingly, it would appear that socioeconomic status has a mild effect or no effect on compliance.

Certain limitations of these studies might be borne in mind. It must be recognized that neither the definition of compliance nor the criteria used to assess social class are consistent. The samples
studied were samples of convenience and tended to demonstrate rather narrow ranges of social class. Accordingly, any lack of a demonstrable effect of socioeconomic status cannot be considered to be conclusively demonstrated.

Formal education has been found to have little influence on compliance. One study showed a slightly increased compliance rate with more education (42) while a second showed a similarly weak opposite effect (40). Davis, among clinic outpatients observed no effect of education (59). Schwartz showed a mild increase in compliance with education (60) while Neeley again failed to confirm her finding (53). Thus, no study has shown a strong influence of formal education on compliant behaviour and it appears unlikely that education will prove a valuable predictor of compliance.

One might anticipate that a psychological approach to the problem would be useful. Several studies have been done on psychiatric patients. One is not surprised that schizophrenics who are paranoid tend to take fewer pills than nonparanoid schizophrenics (41). Prior attitudes on questionnaire, relating to usefulness or side effects of tranquilizers did not appear to be related to compliance with recommended intake (62), although during the intake of pills, verbal resistance to the medication, hostility and aggression do appear to be related to non-compliance (62,63). Similarly, in a schizophrenic population, those with less favourable attitudes to medication, home, parents, and
authority tend to be noncompliant (64), at least while in a psychiatric hospital. Among non-psychiatric patients, Roth utilizing the MMPI on patients who do not take their antacids found that they tended to be hostile (31). Among women on the pill, those who forget to take the pill were found on the MMPI, Edwards Personal Preference Scale and a 16 Personality Factor Questionnaire, to be immature and impulsive and to avoid taking responsibility while being inclined to action rather than contemplation in solving conflicts and to differ from their husbands' personalities (65).

The use of psychological testing to predict compliance has produced some rather interesting results. Hostility, aggression and immaturity are associated with decreased compliance. However, one tends to have some concern about the validity of the tests used when applied in ill patients. Moreover, some of the questionnaires were derived specifically for the study's purposes and have not been validated in other circumstances. Thus, in general, one tends to be a little hesitant concerning the measurement of psychological variables and to be concerned about the reproducibility of the results observed.

Summary

In summary, many papers have dealt with the influence of characteristics of a patient on compliance. The extremes of age appear to be associated with a slightly lower compliance rate consistently with the effect being especially marked in young women. Social supervision, similarly, is associated with a higher rate of compliance. Sex, socioeconomic status, and formal education have little or no effect.
Further study may be needed concerning the effect of psychological variables and validated standardized techniques for measuring these would be desirable. It would appear that paranoia or hostility to therapy decrease compliance and immaturity and impulsiveness may have a similar effect. Nevertheless, of these predictors, none appear to have an over-riding effect and it is probably sufficient to study age as a predictor of compliance as this information is readily available and usually valid.

The Illness

The effects of the characteristics of the illness on compliance are complex. Obviously, this factor interacts with the characteristics of the patient, the therapist, the therapeutic regimen. Moreover, it would appear that the effects of the illness could not only encourage and remind the patient to take his medication but also could produce disabilities which might interfere with the patient's compliance.

For example, severely ill schizophrenics have been shown to be less likely to take medication than less ill schizophrenics (11). Similarly, those with severe anxiety who are believed by the therapist to have a poor prognosis and who have been treated elsewhere are less likely to take antianxiety medications than less ill patients (27). In a clinic population with a wide variety of diseases, Davis found that those with severe disability were less likely to comply with medical recommendations in a global sense (59). However, Davis noted that more severe illness tends to be associated with more complex
regimens. Moreover, the complexity of the regimen seems to interfere with the following of recommendations. Schwartz employed a public health nurse interviewer to assess a patient's ability to cope. (Unfortunately, her definition of "ability to cope" included the demonstration of sufficient understanding of the illness to follow doctor's instructions adequately). Ability to cope, thus defined, was the best predictor which she observed of compliance as measured by interview technique (60). Thus, significant disability or complexity of the regimen may be associated with more severe disease and lead to less compliance.

On the other hand, there are contradictory findings. For example, compliance has been found to be correlated with the degree of severity of a child's pharyngitis as perceived by the mother though not by the physician. Moreover, low compliance was observed in asymptomatic children who had a "red ear" noticed in physical examination (8). In a similar vein, of 26 schizophrenics who were asked why they had discontinued their medications, all claimed that they felt they did not need them (26). [Obviously, the perception of the mentally ill may not be accurate. Among schizophrenics, paranoids reject tablets more than any other group (41).] Thus, it would appear that the patient's perception of the severity of his illness may affect his compliance with a regimen aimed at controlling it.
Two studies are particularly relevant to the current one insofar as they deal with relatively simple regimens of self-medication in order to prevent deterioration in a patient's status. Both studies used interview or questionnaire techniques and dealt with reported compliance. They both suggest that some evidence of disease tends to increase compliance. Vincent, studying patients with glaucoma, found that of those blind in one eye, 59% complied with the therapeutic regimen whereas of those blind in neither eye, 41% complied, and of those blind in both eyes, 9% complied (66). Heinzelman studied 284 college students with a history of rheumatic fever. Nineteen per cent claimed to be on prophylaxis to prevent recurrences of rheumatic fever. Of those who claimed to have definite rheumatic heart disease, 68% were on prophylaxis, while of those without definite rheumatic heart disease, 13% were on prophylaxis. Similarly, of those who had two or more attacks of acute rheumatic fever, 46% were maintaining prophylaxis while of those with only one attack, 15% maintained prophylaxis. A history of hospitalization (an index of severity) was associated with a 31% maintenance of prophylaxis while a lack of such history was associated with a 10% maintenance of the prophylaxis. In addition, of those whose last attack was within five years, 45% were on prophylaxis, while of those whose attack occurred six years or longer previously, only 15% were on prophylaxis. Via questioning of the students, he was able to relate these findings more closely to the Kasl and Cobb model of health-related behaviour (67).
Thus, he found that the number of attacks related to prophylaxis only if the student believed that the attacks were "serious". The recency of the attacks was correlated to continuing prophylaxis only if the student believed he remained "susceptible" to the attacks. Similarly, the history of hospitalization related to continuing prophylaxis only if the student believed the attacks were "serious". Thus, the maintenance of prophylaxis was related to beliefs concerning the attacks, namely: 1. a belief concerning perceived susceptibility to a recurrent attack, 2. beliefs concerning the seriousness of the original attack, and 3. beliefs and knowledge concerning the various aspects of rheumatic fever (68). This last argument is essentially irrelevant to the current discussion.

Thus, the severity of illness may have some effect in order to either increase or decrease compliance. It would appear that the correlation is curvilinear so that a moderately severe illness will increase compliance while a severe illness with marked disability may well decrease compliance, with at least some aspects of a more complex therapeutic regimen. One would like further study in this area in order to utilize the more objective methods of measuring compliance and also to determine whether more objective indices of the severity of a disease would predict compliance.

In view of the complexities of this relationship, it is not surprising that no effect of the severity of the illness has been observed in
some studies. For example, in 56 patients with rheumatoid arthritis who were interviewed during a visit to an arthritis clinic concerning their compliance with a programme of home physiotherapy, no relationship was observed to the severity or duration of the disease. However, five patients were deleted from the study because they discontinued the therapy due to improvement (69). The experience of a cardiac work classification unit similarly did not reveal any correlation between compliance with recommendations and severity of illness (57). However, compliance with recommendations of such a unit may not be directly related to compliance with a regimen of medication and one might suspect that the restrictions suggested by such a unit would increase as the severity of the disease increased so that they might be more difficult to follow even as the patient’s motivation to follow them would increase. Roth studied hospitalized patients with peptic ulcers and found no relationship between compliance with a regimen of antacid intake and the symptoms on admission of pain, vomiting, nausea or melena although there was a tendency for patients to be more loyal in their antacid intake if they had melena with the probability of this being due to chance being 10% (55). However, one might anticipate that the spectrum of severity might be rather narrow among patients admitted to hospital for ulcers so that it might be difficult to demonstrate any effect in this situation.

In two studies concerning the chemotherapy of tuberculosis, no relationship of the activity of the disease was shown with compliance to a therapeutic regimen of INH in one study (42) although in the other study,
67.3% of those with active tuberculosis had positive urine tests for P.A.S. while 58.4% of those with inactive tuberculosis had similar positive tests (22). The definition of activity is unclear in both these studies and one would wonder whether the patient would be truly aware of whether his disease was active or inactive. Moreover, one would suspect that in these cases the duration of therapy might be directly correlated with increasing inactivity of the disease so that more than one variable might be affecting the results and the data might be better analyzed considering an interaction of these variables.

Three studies have shown no relationship to the duration of illness. Roth's study showed no relationship between compliance with a regimen of antacid intake and the length of time since the first episode of a peptic ulcer (31). Similarly, there is no relationship between compliance with recommendations from the cardiac work classification unit and the duration of cardiac symptoms (57). Neeley's study of compliance in the elderly with a medical regimen showed no relationship between such compliance and the duration of the present illness (53). Thus, compliance with a therapeutic regimen does not appear to be readily related to the duration of the illness for which the therapeutic regimen is prescribed, at least in chronic diseases.

However, the duration of the illness probably correlates to some extent with symptomatology, evidence of effectiveness or ineffectiveness of the therapeutic regimen and duration of therapy. Moreover, the
patients who are studied with a longer duration of illness are those who are continuing to seek medical care. Accordingly, the characteristics of the other factors which affect compliance may change as the duration of illness changes so that various interactions might be sought here as well.

Summary

In summary, the characteristics of the illness appear to interact with the patient and the therapeutic regimen in a complex fashion. In particular, the severity of the illness, as perceived by the patient, appears to increase compliance although significant disability or a complex regimen may interfere with compliance. No effect of duration or activity of the illness per se has been established in chronic illness. The most interesting results in this area have been based on interview data. It would be of interest to obtain more objective evidence concerning both the severity and other characteristics of the illness as well as more objective indices of compliance.

The Therapist

It appears highly likely that characteristics of the therapist and his interaction with the patient will affect the patient's compliance with any regimen that the therapist recommends.

Many studies of the doctor-patient relationship have been done in the field of pediatrics and the extent to which they are applicable to
adults is not entirely clear. Charney demonstrated increased compliance with a regimen of oral penicillin for acute illness if the regimen was prescribed by a family's doctor and if there had been a longer duration of the family doctor-patient relationship (8). The work of Francois suggests that the parents' satisfaction with the doctor-patient relationship in an Emergency Room and the extent to which a parent's expectations are met tend to increase compliance with the outlined regimen (14). Davis, in a careful study, found that re-vists between an authoritative patient and a passive, accepting physician decrease compliance. Similarly, tension in the relationship decreases compliance unless it is released. Moreover, failure of the physician to provide feedback to the patient results in noncompliance (70). On the other hand, Lipman demonstrated no relationship between the psychiatrist's attitude to, or liking of, his patient and the patient's compliance with the regimen he outlined (27). Thus, there appears to be an effect of the doctor-patient relationship on compliance and further study is undoubtedly indicated. Such studies require careful technique and are not immediately relevant to the current study. However, to the extent that the doctor-patient relationship may vary in different centres in this trial, compliance and results may vary among these centres in the trial. Thus, some variation may be introduced in compliance rates across centres and it may prove necessary to analyze this.
The extent of investigation may provide some index of the physician's approach to the patient and one might expect that an extensive investigation might impress the patient with the seriousness of his illness. This has not been extensively studied. Charney did not find any relationship between whether a child completed a course of penicillin for otitis media and whether a throat swab was taken by the physician (8).

One might expect that the therapist's attitude to the therapeutic regimen might affect the patient's compliance. It has been suggested that patients will comply better with a regimen of barbiturates if the therapist inquires for improvement and simply questions for side effects as opposed to probing for side effects and giving less hope for improvement. This conclusion was based upon observations on two psychiatrists, one of whom had 1 dropout from a double-blind clinical trial and the other of whom had 4 dropouts in the same trial. However, the psychiatrists also differed in their age, and the patients referred to either psychiatrist were probably selected differently (30). Irwin showed a slight increase in compliance of chronic schizophrenics if the staff believed that phenothiazines were necessary for them. The difference was not statistically significant (38). Whether a physician would convey his enthusiasm in a similar manner in a double-blind trial is less clear. In one study concerning tranquilizers, a similar degree of improvement was noted in the patients across eight
different physicians with different attitudes to tranquilizers (71). Accordingly, the physician's attitude to a therapeutic regimen may not have a strong effect on patient compliance, particularly if the physician is unaware of whether the patient receives active drug or placebo. One would wonder whether a physician's attitude to a trial in which he is a participant would affect his patient's compliance in fulfilling the requirements of that trial.

One study has shown an exceptionally high rate of compliance with a short course of penicillin in children. The patient population consisted of private middle class parents. Compliance was measured on the basis of pill counts and urine tests for penicillin. In this study, a printed instruction sheet was given to all patients (29). It has been suggested that this may be one method which produces a considerable increase in compliance. In the current study, a printed instruction sheet is given to all patients and the effect of this cannot be analyzed directly.

A second methodology of increasing compliance has been to instill fear in the patient. This has been studied in several experiments. It would appear that if a strong sense of fear is associated with a relatively weak sense of vulnerability or a relatively weak sense of fear is associated with a strong sense of vulnerability, compliance will increase (72). It would be of interest, though of no direct relevance, to study in the R.R.P.C.E. population the extent to which patients fear recurrence of their attacks or strokes and the extent
to which they feel they are vulnerable to such events.

Summary

In summary, it would appear that characteristics and approaches of the therapist may affect compliance. The study of these factors requires a direct approach which is not practical in the current study. However, different characteristics of the therapists may be factors which produce different results in different centres in any multi-centre trial. This is a recognized hazard of any such trial. It is possible to analyze the variation in results from different centres to determine if this is excessive.

The Therapeutic Regimen

Since the trial which serves as the basis for this paper deals only with a medication regimen, compliance with instructions concerning activity or diet will not be considered here.

In general, compliance with a medication regimen tends to decrease with the duration of time the patient has been on that regimen. (The duration of the regimen, of course, need not be identical with the time from diagnosis.) In a study concerning treatment of tuberculosis, complete discontinuation of medication was felt to occur at a rate of 1.3 to 2.5% per month with only 90% taking the medication. Reduced dosage tended to follow the same curve. The large number of patients
studied and the long duration of this study was possible due to the measurement of compliance simply as dispensed medication (25). However, Luntz and Austin demonstrated a similar fall-off in compliance with a medication regimen for tuberculosis after one year of therapy utilizing direct measurement of the drug in the urine (15). A most dramatic fall-off in the intake of penicillin by children over a ten day period was demonstrated by Bergman and Werner (17). This effect may have been partly due to disappearance of symptoms in the child. Two studies in rheumatoid arthritis showed a similar fall-off in compliance with a therapeutic regimen with time (3,28). Porter found that the strongest predictor of the failure of antenatal patients to take iron tablets was the duration of the therapy (24). On the other hand, in patients with peptic ulcer, compliance with the antacid regimen did not fall off with time (31). Similarly, in schizophrenic patients, there was a rapid fall-off in compliance in the first month but thereafter there was little further change (26). Thus, it would appear that the duration of therapy tends to decrease patients' compliance with the regimen. However, this may vary with the disease or regimen involved. Accordingly, one tends to suspect that time interacts with other variables including the patient's symptomatic state, his expectation concerning the results of therapy and evidence of improvement, and the patient's understanding of the appropriate duration of therapy. These factors may interact with either a natural tendency to become more careless with a routine as time passes or an opposite tendency for a long-standing routine to become ingrained on one's pattern of life. In any case, the duration of therapy appears
to be an important objective variable which cannot be ignored in the analysis of determinants of compliance.

The complexity of the medical regimen has been shown to have a consistently adverse effect on compliance. This has been documented in the treatment of tuberculosis (4), cardiac patients (73), and in children treated in the Emergency Room (14). Neely noted an increase in medication errors in the elderly as the number of different types of medications increased among those with a variety of conditions (53). Malaphy confirmed the phenomenon in a medical outpatient clinic (74).

While none of the methodologies in these studies is above criticism, the consistency of the results suggests that the complexity of the medical regimen, including the numbers of drugs that a patient is requested to take, has an adverse effect on compliance.

As Nugent studied glucocorticoid toxicity when steroids were administered as a single dose rather than divided doses, he noted the patients tended to be less compliant with doses throughout the day than with the first morning dose (28). Thus, in a complex medical regimen, the first morning dose is the least likely to be affected of a medication given more than once daily.

One would expect the patients would be less likely to be compliant with a medical regimen that produced side effects. This has been documented on several occasions. Some studies have shown this effect
indirectly by demonstrating that medications expected to be associated with increased side effects (e.g., Thoridazine, Imipramine, P.A.S.) are associated with decreased compliance (2,4,10,38). More directly, the presence of side effects has been demonstrated to be associated with decreased intake of tranquilizers (62), PAS (37), and anti-rheumatic medications (3). Thus, the presence of side effects consistently decreased the patient's compliance.

The efficacy of the medication might be predicted to increase compliance if the patient is aware of its efficacy. Perhaps because of the lack of evidence of the efficacy of many chronically taken medications, this matter has not been greatly studied. However, depressed patients were found to take less Chlorpromazine than Imipramine in a double-blind trial and one would predict that this behavior on the basis of the efficacy of these medications in depression (23).

Joyce's study concerning effectiveness and compliance is perhaps the clearest exposition of the problems in this field. He employed both pill counts and a urinary marker to determine compliance. The relevant study was a double-blind evaluation of two antiinflammatory agents and a placebo in rheumatoid arthritis. He was able to demonstrate that correcting for compliance using a regression technique increased the sensitivity of the trial since compliant patients showed fewer active joints and fewer toxic signs with fewer subjective side effects than less compliant patients (3). In spite of the quality of his paper,
one fears a circular argument may be present. Obviously, it is difficult for one to determine whether the decrease in the number of active joints was caused by the intake of an active medication or whether the intake of the medication was caused by the apparent improvement in joint symptoms. Certainly, one would expect that an efficacious medicine would be more likely to be taken if it produced some subjective improvement in the patient, and, if this improvement was perceived as being greater than the discomfort produced by any side effects.

Summary

In summary, consistent effects have been seen of the therapeutic regimen on compliance. The greater the duration of the therapeutic regimen, the greater its complexity, and the more side effects it produces, the less likely compliance appears to be. On the other hand, the greater the efficacy of the therapeutic regimen, the greater is the compliance with that regimen that is likely to be observed. The effects correlating negatively with compliance have been observed in many studies, although none of them taken alone might be considered outstanding. The effect of efficacy has been studied much less. Accordingly, since the R.R.P.C.E. Study provides an abundance of clinical data relevant to all these factors and excellent measures of compliance, it is desirable to further explore these relationships.
Conclusion

If we ignore the quality of the studies concerned and consider only those factors which have been demonstrated to affect compliance to some degree, we can apply these considerations to the R.R.P.C.E. Study.

Concerning the patient, as his age advances beyond 55, particularly if he is no longer married and is living alone, his compliance with the therapeutic regimen will decrease. If he is hostile and aggressive he is less likely to comply with the regimen. However, the only relevant factor measured in the R.R.P.C.E. Study is age. Nevertheless, further studies in this age group concerning the effect of age are important since the effect of age has been poorly and inconsistently documented in such patients.

With respect to illness, only severity has been extensively studied. The relationship to compliance is curvilinear so that as the severity of illness increases, compliance will first increase and then decrease. With respect to the R.R.P.C.E. Study, with extensive objective data available concerning the severity of a neurologic illness which may decrease the patient's ability to comply with the regimen, it will be of particular interest to obtain hard data concerning compliance.

With respect to characteristics of the therapist, it has been demonstrated that the therapist who produces satisfaction in his patients, and believes in the efficacy of therapy, is more likely to obtain increased compliance. Written instructions and the instillation of fear will also
increase compliance. Further documentation is necessary in this area but the R.R.P.C.E. Study will provide little data in this respect.

Finally, with respect to the therapeutic regimen, its duration, complexity, and its propensity to produce side-effects will all decrease compliance while its efficacy may increase compliance. The R.R.P.C.E. Study will provide an opportunity to study these factors in more detail and to observe their interaction.

As previously discussed, many of these factors deserve further study for past demonstration of their effect was often not based on firm data. Moreover, the definition of compliance varied in many of the studies and a more clinically meaningful definition of compliance would be useful and the factors affecting compliance thus defined would be of interest. Furthermore, further study is needed concerning the interaction of the various factors affecting compliance and the R.R.P.C.E. Study, with multiple factors being measured on the same patients, provides an outstanding opportunity to study such interaction. Finally, exploration of the effect on compliance of the following factors is possible in the R.R.P.C.E. Study and has not yet been adequately performed: duration of illness prior to institution of therapy; with respect to the prevention of attacks, the frequency of such attacks and their remoteness in time; comorbidity; impairment of mental status; impairment of speech; total neurologic impairment; and extent of investigation prior to prescription of a therapeutic regimen. Accordingly, the R.R.P.C.E. Study provides an opportunity to provide a valuable contribution to knowledge concerning factors affecting compliance.
LIMITATIONS OF THE DATA SET IN THE R.R.P.C.E. STUDY

The patient population in the R.R.P.C.E. Study has certain characteristics. All patients have had at least one transient ischemic attack and the population is composed of adults. These factors may limit the extent to which the results may be generalized.

The therapeutic regimen is limited to a medication regimen and accordingly compliance can be studied only with respect to a medication regimen.

Certain techniques have been employed to ensure compliance. One cannot predict the extent of the fear of the patients concerning recurrent transient ischemic attacks or strokes but suspects that this may be a motivating factor which will increase compliance. The study is extensive, employing multiple measures on the patients and frequent follow-up visits and one might suspect that this will increase the rate of compliance. A printed instruction sheet is provided to the patients and their family physicians and such instruction sheets appear to increase the rate of compliance. Accordingly, one might predict that compliance will be relatively good in this study.

A final current limitation is that the study is currently only beginning. Accordingly, the data set is limited to approximately 80 patients who have been in the study long enough to have been able to
complete six months of follow-up (regardless of whether they dropped out of the study prior to being in it for six months or not). Moreover, the data is not yet coded in its final form and all information concerning the patients is not yet available. A further inconvenience is imposed by the fact that the data remains in its raw form so that all analysis must be done by hand. Nevertheless, in relationship to this study, a preliminary review of the data set has been useful in revealing certain difficulties in relationship to various measures studied. These are readily correctable and will be considered in relationship to the consideration of the individual measurements concerned.

**MEASUREMENTS OF COMPLIANCE IN THE R.R.P.C.E. STUDY**

The methods of measurement of compliance in the R.R.P.C.E. Study are summarized in Table II.

**Dropouts**

Some patients are withdrawn from the study for lack of efficacy of the drug or the development of other disease. However, others are withdrawn due to unreliability in keeping appointments and/or taking of medication. This latter group of patients represents the most blatant type of noncompliance with a medical regimen. Accordingly, it is of interest to study the characteristics of such patients.
Unfortunately, when a patient drops out of the study, the opportunities to study the various measurements of compliance or the final outcome of his disease are limited. Nevertheless, it is of considerable importance to attempt to determine the final outcome in these cases. In addition, it is possible to compare the characteristics of the patients who drop out (as observed during the time in which they are in the study) with the characteristics of patients who comply and are observed during the same interval. This type of analysis may provide useful predictors of this form of noncompliance.

Reported Other Medication

During the initial clinical assessment, other medications which the patient has been taking are recorded. Subsequently, with each estimation of blood levels of acetylsalicylic acid or sulfinpyrazone a brief drug history is taken.

The reporting of such other medication during the trial may be an admission on the part of the patient that he is disobeying a part of the instruction sheet to avoid such medication. Accordingly, such reports may constitute a patient admission of a specific form of noncompliance. Moreover, one might expect if the patient is on a complex prescribed regimen for other diseases, that this may decrease his compliance in the R.R.P.C.E. Study. Thus, this data is important to consider from two points of view.
On the other hand, we must recognize that this data is recorded for other purposes. At the time of admission to the study, the purpose of the history is to detect drugs which may interact with platelets. In the subsequent drug histories, the purpose is to detect drugs which may affect the assay. Accordingly, this data may be incomplete in relationship to the intake of drugs which are irrelevant to the purposes for which the data is collected. Moreover, dosages of the various drugs may not be recorded.

Accordingly, it is most likely worthwhile to alert the investigators that this information is a valuable asset to the study in more ways than one. This may encourage them to record the data completely and, preferably, to also record the number of doses which the patient is taking. Furthermore, it will be necessary in the final coding of the data to retain this information so that it may be utilized to its full extent.

**Pill Counts**

Each patient is given 130 tablets and 130 capsules to take for each month he is in the study. Since this is an excessive number of pills for any month, it is possible to count the number of pills which the patient returns at each follow-up interval and calculate an index of compliance from this. This index of compliance will be referred to
hereafter simply as the "pill count" and the methodology of calculating it is illustrated in Appendix I.

This index covers the intake of medication over the entire interval prior to the follow-up visit. Moreover, it is applicable to any of the medication regimens. It is recognized in the literature as being a useful index of compliance with the medication regimen.

The pattern of deviation within the time interval is unknown. Thus, the calculation provides only a mean index of compliance over a fairly prolonged period of time. It is assumed that the patient misses doses in a random manner and that the doses missed in the period immediately preceding the follow-up visit are similar to the doses missed throughout the follow-up interval. Deviation from this assumption will lead to poor correlation between the pill counts and the following methods of measurement of compliance.

This difficulty is especially evident in the patient who runs out of medication prior to his visit. In this case, the pill count estimate will suggest that the patient took an excess of medication up to the time of the visit. However, in reality, he will have taken an excess of medication and then discontinued the medication at some time prior to his visit to the clinic. Accordingly, the estimates which are based on a single point in time at the visit to the clinic (in
particular, the blood levels of drugs and platelet function studies) will be measuring his intake during the preceding day or few days and will not be expected to correlate in any way with the pill count. Therefore, these patients should probably be excluded from the analysis which attempts to correlate the pill counts with these other measurements.

Pill counts pose two special coding problems. The patient who does not return but has excess medication requires identification. In a longitudinal study, the behaviour of these patients in previous and subsequent periods can be studied. Accordingly, it is possible to assess whether such patients, according to other criteria, are similar to those who do return their pills or whether they are indeed different. Unfortunately, in the current data available, in many instances, it is not possible to distinguish whether a lack of recorded pills returned constitutes a failure on the part of the patient to return his pills or failure on the part of the physician to record such data or request it. On the other hand, other investigators have recorded specifically that the patient did not return his pills and whether this indicated that the patient had no pills to return. It would be desirable to extend this practice so that the characteristics of patients who have medication left at home but do not return it can be identified.

A closely related problem relates to the recording of "0 pills returned". At the present, it is not possible to determine, in many
cases, whether this indicates that the patient has excessive medications at home and did not return them, ran out of medication at some time prior to his return to the clinic, or that the patient ran out of medication at the time he returned to the clinic. Accordingly, it would be advantageous to distinguish these three types of patients by recording whether the patient did have excessive pills at home or whether he ran out of pills, and if so, how many days prior to his return to the clinic he did run out of pills. This type of information would be valuable for reasons stated above.

Blood Levels of Salicylate and Sulfinpyrazone

Blood is drawn at each visit for the determination of blood levels of salicylate and sulfinpyrazone. Instructions for the drawing of these samples state that the patient should not have taken the drug that morning. Moreover, a brief drug history is taken with each sample in order to detect other drugs which may affect the determination.

This determination probably provides the most valid measurement of drug ingestion. However, an interpretation of the levels requires a brief review of the pharmacology of the two agents.

Acetylsalicylic acid is rapidly absorbed when taken orally and is distributed in a space of approximately 150 ml/kg of body weight. It is both metabolized and excreted unchanged in the urine. Urinary
excretion depends to a considerable degree on urinary pH. The half-life is relatively short being in the range of 2 to 4 hours with low doses, such as the ones used in this study. Because of the variable absorption, metabolism and excretion, Woodbury has stated that "although the main factor controlling plasma salicylate level is the dose administered, one cannot accurately predict the plasma level from the amount of drug given" (75).

Sulfapyrazone is similarly well absorbed from the gastrointestinal tract. After intravenous injection, its biologic half-life is approximately 3 hours (76).

It is unlikely that a drug taken earlier than 6 half-lives prior to the drug determination will affect the determination to any significant degree. Accordingly, the intake of both drugs is considered for about 18 hours previous to the taking of the sample. Thus, the plasma levels will depend largely on compliance with the therapeutic regimen following noon on the day prior to the visit to the clinic.

On the other hand, it would appear likely that if the patient ingested the drugs on the day of the clinic visit, he would have significantly higher levels than anyone who did not take the drug from the night before. If he did take the drug on the day of the clinic visit, he would presumably have taken it approximately one half-life prior to
the blood determination, whereas if he abstained from the drug on
that day, his blood level would have been determined 3 or 4 half-lives
following his last ingestion of the drug.

The plasma level will be affected by the volume of distribution of
the drug. This can be calculated on the basis of the patient's weight
and/or surface area. However, beyond this, multiple other factors
will affect the actual plasma level besides compliance with the
patient's regimen. These include the exact time of the last dose
ingested and the timing of the blood sample, the individual variation
in absorption, metabolism and excretion of the drug, and finally,
other drugs ingested. Only the body weight and height and the other
drugs being ingested at the same time will be available in inter-
preting the results. (It is noteworthy that both sulfinpyrazone and
acetylsalicylic acid are acidic drugs which will compete for plasma
binding so that the two drugs being directly studied may well affect
each other's levels as well as extraneous drugs. With the design of
this study, there is an excellent opportunity to study the effect of
ingestion of these two drugs on each other's blood levels.)

Accordingly, the blood levels represent compliance with drug intake
during the period immediately preceding the clinic visit. Nevertheless,
as discussed in the review of the literature, urinary samples taken
at one point in time tend to be fairly reliable predictors of overall
compliance. Accordingly, it will be of interest to compare the
plasma levels with other measures of compliance in this study.
It is essential that the instructions to the patient that he not take the drug on the day of the clinic visit be made clear to avoid spuriously high blood levels.

Since the actual drug levels are affected by so many parameters, it is essential that they be correlated with the other measures of compliance. If the correlation of the actual blood level with other measures of compliance is not good, it may be wise to reduce the level of data to nominal. In other words, the blood levels may require interpretation simply as indicating whether the drug is present or absent, i.e., whether it has been ingested recently or not.

Considering the limitations and expense of drug determinations, one might consider the possibility of using a qualitative test to detect the presence or absence of a drug. For example, it might be of interest to study whether the use of Phenistix will detect the presence of aspirin in the urine in this study.

**Serum Uric Acid**

Insofar as sulfinpyrazone is a potent uricosuric agent, one may predict that the fall in serum uric acid will be proportional to the patient's compliance with the therapeutic regimen concerning his intake of sulfinpyrazone. Accordingly, serum uric acids are measured initially
and at each follow-up visit.

The serum uric acid provides a simple, reproducible test which may reflect the intake of medication over a relatively prolonged period.

However, serum uric acid depends not only on the intake of sulfapyrazine but also on the patient's initial body stores of urate, his current rate of production and his current rate of excretion. These will be affected by multiple other factors so that, one might not observe a close correlation. Burns noted that the uricosuric effect and the change in serum urate were roughly dosage-dependent but that there was much individual variation and, indeed, the individual variation was as great as the variation due to dosage in the patients he studied (76). Moreover, he noted that the fall in serum urate was dramatic within four days. Longer term studies demonstrating the dose-response curve are necessary. Accordingly, it remains essential that the change in serum uric acid observed in this study be correlated with other indices of the amount of drug ingested.

Salicylates will completely abolish the uricosuric effect of sulfapyrazine in acid urine, and although the effect is slightly less marked in alkaline urine, a similar marked suppression of the uricosuric effect is seen (77). Thus, in the group which receives both sulfapyrazone and acetylsalicylic acid, it is possible that only a low correlation will be observed between serum urate and compliance
with the therapeutic regimen.

Acetylsalicylic acid in low dosage is recognized to be an anti-
uricosuric agent (78). This effect is dose-dependent with 1 gm/day
producing a mean serum uric acid increase of 6% /day while
2 gm/day produces an increase of 7% /day. However, in four cases on
the lower dosage, the range of increase of serum uric acid was 0 to
12% while in the seven cases on the higher dosage, the range of
increase was 0 to 22%. Thus, it would appear that the dosage of
aspirin does have an effect on the serum uric acid but that its
effect may be overridden by other unmeasured variables.

Nevertheless, it is reasonable to suppose that there will be some
correlation between the fall in serum urate and compliance with the
regimen of sulfipyrazone alone and the rise in serum urate and
compliance to the therapeutic regimen including aspirin alone. There
may be little or no effect in the group on combined therapy with
sulfipyrazone and aspirin. The design of this study allows one to
analyze these correlations in each therapeutic group and compare this
measure of compliance with other measures of compliance in order to
validate it. Moreover, this measurement of compliance may also be
validated against measurements of outcome. Insofar as the dose-response
relationship is unclear, this study provides an opportunity to assess
the form of that relationship by comparing the changes in serum uric
acid against other measures of drug ingestion. With large variation in the extent of changes in serum uric acid in different time periods, it may prove wise in the analysis to use a lower scale of measurement than the ratio scale, e.g. an ordinal or nominal scale. Thus, it may be simpler to state that the serum uric acid simply falls or rises rather than attempting to quantitate the extent of that fall or rise.

**Platelet Tests**

Several tests of platelet function are being performed at each visit. One may suspect that these may prove to be the best predictors of outcomes. Moreover, since these tests provide indices of the action of the drugs which are being given, they provide a measure of patient compliance.

Nevertheless, it is essential that these tests be validated against other measurements of compliance. It is unclear how good they are as predictors of drug ingestion and the dose-response curve and duration of the effect of these drugs on various platelet function tests is in some instances poorly documented. Thus, it is essential that this study avoid the pitfall which was demonstrated in many of the earlier studies concerning control of diabetes and outcomes in which blood sugar was demonstrated to be related to the outcome measurement but this was poorly related to any therapeutic regimen. Moreover, validation
against other methods of measurement of compliance is advisable since the platelet function tests may reflect compliance only during a relatively short interval prior to the performance of the test and compliance over a relatively longer period may be more directly relevant to the outcome measurements.

In addition, it may prove of interest to establish dose-response curves and the duration of the effect of drug ingestion on platelet function tests by performing studies in small volunteer groups. Because of large interpatient variation in these tests, the ideal group of volunteers would be the study sample.

Many of the quantitative tests demonstrate large variation. Moreover, it is proposed to study certain derivatives of the tests in order to determine if these will correlate against outcome measurements. Thus, many of these tests can be studied using a ratio scale of measurement. However, due to marked variation within the test and likely wide observer variation in obtaining derivatives from the tests, it may be wise also to analyze these data on a lower scale of measurement. For example, it may be wise to analyze the tests as demonstrating presence or absence of the desired effect rather than attempting to quantify the effect in some cases.

Collagen Aggregation

The aggregation of platelets on exposure to collagen has been demonstrated
to be inhibited by both sulfinpyrazone (79) and aspirin (80). It appears that the amount of suppression of aggregation is related to either drug's concentration in vitro and the dosage when sulfinpyrazone is given by intravenous infusion to maintain a constant blood level in rabbits (79). Thus, this test may provide a quantitative index of compliance with regimens containing sulfinpyrazone and/or aspirin.

However, the experimental data is based on acute experiments and the dose-response curve and duration of the effect of administration of the drugs to humans would benefit from further documentation. Such further documentation in this study will include correlation of this test with other measurements of compliance. In addition, a small study in volunteers to quantify these factors may prove of interest.

**Epinephrine Aggregation**

The second wave of aggregation of platelets on exposure to epinephrine is suppressed or abolished on exposure to aspirin. While there is individual variation in the dose needed to produce this effect, the dosage employed in this study exceeds that required. The duration of the effect has been shown to be dose-dependent, although ingestion of the drug for a period of 48 hours does not prolong the duration to any extent beyond that achieved by ingestion of a single dose (81). There is considerable individual variation in duration of the effect but it appears to persist for 3 to 7 days (81,82,83). Thus,
abolition of the second wave of aggregation of platelets on exposure to epinephrine is suggestive of recent ingestion of aspirin and constitutes an objective index of compliance.

However, O'Brien found that 4 out of 22 randomly selected people did not show the second wave of aggregation, even though they had not ingested aspirin (82).

Accordingly, this test may be best interpreted as follows. The presence of a secondary wave of aggregation on exposure to epinephrine indicates no recent exposure to aspirin and provides an index of non-compliance with the therapeutic regimen if that regimen included aspirin. On the other hand, absence of the secondary wave of aggregation may indicate only relatively low aspirin intake or be a normal variant. Thus, while derivatives of the epinephrine aggregation curve or delays in the secondary wave of aggregation may be analyzed on a ratio scale, it is preferable to analyze these curves as providing nominal data.

**Platelet Adhesiveness**

Platelet adhesiveness provides an index of compliance with a medical regimen including sulfinpyrazone. Weily (84) demonstrated that sulfinpyrazone in a dose of 400 mg significantly decreased platelet adhesiveness in patients with prosthetic mitral valves. However, with increase in the dosage of sulfinpyrazone to 800 mg/day, no further
decrease in adhesiveness was noted.

The duration of the effect of sulfinpyrazone on platelet adhesiveness is unclear. Moreover, from Weily's data, it is evident that failure of ingestion of 50% of the prescribed medication in this study would not be distinguished from 100% ingestion of that medication. Moreover, the measurement of adhesion of platelets to glass has been beset by procedural problems and demonstrates wide variation (85, 86, 87).

To better document the effect of each of the therapeutic regimens employed in this study on glass adhesiveness, it may prove useful to perform a volunteer study. Moreover, the data may be more clearly analyzed using ordinal or nominal scales of measurement utilizing ranges of suppression of platelet adhesiveness or the presence or absence of suppression of platelet adhesiveness. In any case, the multiple other measurements of drug ingestion which are available in this study may be correlated with this method of measurement in order to study its validity.

Template Bleeding Time

The template bleeding time is sensitive to aspirin intake. One gram of aspirin significantly prolongs the bleeding time, and the degree of prolongation appears to be related to the control bleeding time (in a relatively constant ratio, when the dosage of aspirin and time from the
dosage is held constant). Accordingly, this measurement provides an index of aspirin intake.

Unfortunately, the degree of prolongation shows relatively large variation in individual cases. The duration of the effect is unknown (83). The effect of sulfinpyrazone or the other regimens in this study on the template bleeding time is unclear.

Accordingly, the template bleeding time provides another index of compliance with the medical regimen. The dose-response curve, duration of effect, and validity of the measurements can be assessed by comparing this measurement of drug ingestion with the other measurements which are available in this study.

**Platelet Survival Studies**

Repeated platelet survival studies are planned in some patients in selected centres in this study.

Platelet survival time has been demonstrated to be prolonged with sulfinpyrazone in man (84,89) and with aspirin in experimental animals (80). However, aspirin did not decrease platelet turnover in platelets with prosthetic heart valves, although it did augment the effect on platelet survival of dipyridamole (90). Of particular
interest is that 800 mg of sulfinpyrazone per day significantly increased platelet survival above the survival observed for 400 mg/day in patients with prosthetic mitral valves (84). Accordingly, platelet survival data may provide a relatively sensitive index of compliance of the intake of sulfinpyrazone in those cases which are studied.

Unfortunately, platelet survival studies are complex.

This study will provide a further opportunity to document the effect of aspirin on platelet survival in man. Moreover, it will provide an opportunity to study this measurement as an index of medication intake (and thus compliance).

OUTCOME MEASUREMENTS IN THE R.R.P.C.E. STUDY

The outcome measurements employed in the R.R.P.C.E. Study are changes in the frequency of transient ischemic attacks and strokes or death. Since the data set is not in its final form, certain limitations are evident with respect to these measurements at the present.

Insofar as the decrease in frequency of transient ischemic attacks is a major outcome measurement, it is essential to ensure that the definition of transient ischemic attacks is employed in a consistent manner. This applies not only to the initial diagnostic criteria but also to the criteria related to the definition of a recurrent attack.
In particular, it is essential that neurotic symptoms and symptoms secondary to other organic disease, e.g. carotid sinus sensitivity, be excluded from the definition of transient ischemic attacks. The decision whether the patient has had a transient ischemic attack rests upon the attending neurologist and there appears to be some variability in the criteria the various neurologists use for the definition of an attack. Accordingly, it is advisable that the central committee review the records in order to ensure that the admission and exclusion criteria are fulfilled and that the recurrent transient ischemic attacks fulfill reproducible criteria for their definition.

The frequency of transient ischemic attacks will depend on multiple factors in addition to compliance with a therapeutic regimen. Perhaps, the most obvious of these is the initial rate of transient ischemic attacks. One would assume that subsequent attacks would occur in approximately the same frequency as the attacks which were observed in earlier periods. Accordingly, one would expect a linear relationship between the frequency of the attacks before treatment and during treatment. Nevertheless, this hypothesis will be tested by plotting the frequency of attacks in each treatment group against the initial attack rate and also by testing whether a linear regression model does fit the data.

Accordingly, in this study, if a linear model is consistent with the observed data, the definition of the frequency of attacks in subsequent
intervals in this paper will be the ratio of the frequency of attacks in subsequent intervals to the frequency of attacks in the pre-treatment interval. This will simplify the analysis and avoid using multiple linear regression to correct for the initial frequency of attacks in assessing other correlations. However, since transient ischemic attacks are notoriously variable in their frequency, one must recognize that this ratio may have a large variance which may make detection of effects more difficult.

Since the data is not yet in its final format, certain coding procedures are being utilized in this section of the study. In the current data set, the frequency of attacks is recorded for various periods before treatment, namely, a one month period, a six month period, and a one year period. It would appear most valid to use the mean frequency of attacks per month since the time of onset of the attacks as the index of the initial attack frequency. Accordingly, this has been calculated for each patient.

Certain difficulties are evident in the current charts. In one group of reporters, the number of attacks recorded as occurring in the first six months includes those attacks which occurred in the most recent month while the number of attacks which are recorded as occurring within the first year include those attacks which occurred in the last six months and the last one month periods. On the other hand, another
group of reporters record in each of these sections only those attacks which occurred in the most remote six months, the period from six months to one month and finally, the number of attacks which occurred in the last month. Accordingly, careful examination is necessary to extract the data to ensure that is comparable. Moreover, it would be preferable for the central coordinating system to clarify how these time periods are meant to be interpreted.

**METHODOLOGY OF ANALYSIS**

**General Strategy of Analysis**

The following sections deal with methodologies of analysis to detect the correlations among the methods of measurement of compliance, the correlations between the outcome measures and the various measurements of compliance, and the correlations between various characteristics of the patients, their diseases and regimens and compliance. The data will be analyzed by both parametric and non-parametric techniques and each of these methodologies has certain strengths and weaknesses and imposes certain conditions.

**The Parametric Approach to Analysis**

This approach is the most sensitive way of determining whether there is any relationship between the various measurements of compliance and can demonstrate the form of that relationship as well as its extent. Since packaged programmes are readily available, this analysis need not be laborious.
One disadvantage of this approach is that it entails fitting the data to be correlated to a mathematical model. For example, it may be assumed that the relationship between two variables is linear. Accordingly, before attempting to fit any model to any pair of data sets, it is necessary to plot a scattergram of the values of the two variables in order to determine which is the most appropriate model to attempt to fit.

The second disadvantage to this approach is the requirement that the distribution of values observed be bivariate normal. It is unlikely that this assumption will be fulfilled. Whether a failure to fulfil this assumption will have serious consequences is unclear.

The Non-Parametric Approach to Analysis

The non-parametric approach frees one from making assumptions concerning the distribution of the data. It will be necessary to employ this approach in cases where the data is measured on a nominal or ordinal scale of measurement. A further advantage is greater clarity of presentation. For example, classifying a patient as a good complier, fair complier or poor complier and stating to which extent the various methods agree on such a classification may prove more readily comprehensible than the presentation of a regression equation.

The major disadvantage of the non-parametric approach is its lesser efficiency. Accordingly, with this approach, one may not be able to
demonstrate a statistically significant correlation when such a correlation does in fact exist.

Insofar as many of the analyses done by non-parametric techniques will involve two-way tables, it will be necessary to choose correct division points. In the case of nominal data, this is no problem. However, in cases where the data has been measured on higher scales of measurement, one is free to impose arbitrary decision points for separating the data into classes. The methodology of such division is specific to the measurements being studied and will be considered in each of the subsequent sections.

METHODOLOGY OF ANALYZING AGREEMENT AMONG THE VARIOUS MEASURES OF COMPLIANCE

Since the various drugs are expected to have different effects on each of the measurements, each comparison will be done within a given therapeutic group. Moreover, since the duration of therapy decreases compliance, each of the methods of compliance being compared will be compared with respect to the measurements obtained at the same visit.

The Parametric Approach

The scales of measurement appropriate to the various methods of measurement of compliance have been indicated in Table II. The appropriate comparisons which will be made are indicated in Table III.
The first step in the analysis is to plot graphically the measurements against each other in order to assess the form of the relationship.

The next step in the analysis is to fit an appropriate model to the data. For example, a linear regression model may be fitted. Following this, the statistical significance of the association can be tested by the F test and the amount of explained variation calculated as $r^2$.

Due to the small numbers in each of the treatment groups at the present, this analysis is not currently feasible. However, Graph 1 demonstrates the initial phase of such an analysis in which the pill counts (rate of compliance) in the first interval was plotted against the uric acid (ratio of initial serum uric acid to serum uric acid at the first follow-up visit). Thus, the pill count is a direct index of compliance.

The uric acid ratio, as defined in this section, will be directly proportional to the fall in serum uric acid. This bizarre ratio was chosen because it is directly proportional to compliance, at least in the sulfinpyrazone group.

Aspirin is expected to increase the serum uric acid. Accordingly, one would expect this ratio to be inversely related to compliance. One would predict the values to extend from the upper left part of the graph to the lower right.
Sulfinpyrazone is expected to decrease the serum uric acid. Accordingly, one would expect the ratio of uric acid employed to be directly correlated with sulfinpyrazone intake. Here one would expect that the ratios would extend from the lower left to the upper right part of the graph.

In the other two instances, that of combined therapy with sulfinpyrazone and aspirin or aspirin alone, one would predict little or no correlation.

The numbers are sufficiently small that any interpretation is fraught with hazard and will not be attempted. Accordingly, it does not appear worthwhile to attempt to determine whether these data suggest a linear correlation or not. Nevertheless, this demonstrates the feasibility of the approach.

The Non-Parametric Approach

The first step in the non-parametric approach is the selection of appropriate division points for the data. The data relevant to the six measurements of compliance in the immediately preceding section has no self-evident cutting points. Accordingly, it appears appropriate to obtain a visual display of the data, partitioned into relatively equidistant groups according to the measurement obtained. An example of such partitioning is seen in Graph 2 which represents the pill counts observed in the first three intervals. A glance at this data reveals a marked clustering of patients close to 0%.

A mathematically more sophisticated approach to the same problem is well exemplified with this data. In this case, one would use the model that serum uric acid observed at the first follow-up visit is linearly related to the initial serum uric acid and the pill count. This model was rejected because it does not readily adapt itself to graphic representation so that if a non-linear relationship existed, this might be overlooked.
which represents perfect compliance. Conversely, there is a marked paucity of patients in the groups representing noncompliance rates of 25% or greater. Accordingly, it appears inappropriate to partition the data according to quartiles or percentiles. Due to the large number of very compliant patients and small number of very noncompliant patients, if one were to attempt to divide the patients into groups containing relatively equal numbers, one would of necessity be dividing relatively compliant patients into several groups while adding moderately noncompliant patients to a group containing severely noncompliant patients. Accordingly, it is proposed to divide the data on the basis of relatively equidistant intervals between the measured values rather than attempting to obtain equal number of patients in each interval. One can then impose a division point which is meaningful insofar as it indicates a significant degree of noncompliance and yet ensure that the division point is not so severe that no noncompliers will be detected. For example, from this series of histograms, 26% or great deviation from full compliance was selected as the division point. This step must be repeated for each of the continuous variables in order to obtain meaningful partitions.

Following this step, it is necessary to examine correlations between the variables. The variables to be compared in this manner are indicated in Table IV. An example of the outcome of such a comparison
is demonstrated in Table V. Here, the percentage of sulfinpyrazone tablets that were ingested is compared with the ratio of serum uric acid on the initial visit to the first follow-up visit in the few patients in which this data is available.

The appropriate statistical test for the significance of such associations will be the chi-square test when sufficient numbers are available. Of equal interest are indices of agreement and prediction (see example). The best test of the division point is whether using it allows one to make good predictions in subsequent periods.

Moreover, it is important to follow patients in whom there are discrepancies seen in such a table. If the measurements remain discrepant in subsequent periods, this suggests a biologic variant peculiar to the patient. However, if it is different patients in whom the measurements disagree in subsequent periods, this suggests errors in the measurements.

THE METHODOLOGY OF ANALYSIS TO OBTAIN A CLINICALLY MEANINGFUL DEFINITION OF COMPLIANCE

Advantages

The value of an index, which will correlate with the dosage of drug ingested and with the efficacy of that drug, to the clinician has been previously mentioned. While accepting that other factors than the medication regimen may determine the final outcome, the clinician is highly desirous of obtaining such a predictor of sufficient therapy.

Accordingly, it is desirable to correlate the various measurements
of compliance in this study not only with each other but also with outcome measurements. Moreover, such an approach provides information concerning other issues. First, it allows one to study whether compliance with a placebo regimen (e.g., as measured by a pill count) correlates with a favourable outcome. Second, in the final analysis of the study, the efficiency of the statistical analysis may be increased by considering compliance as a covariate and using the analysis of covariance to minimize the effect of compliance or non-compliance on the outcome measurement (3). Third, a demonstration of a correlation between compliance and the attainment of a desired therapeutic result within any of the active treatment groups adds strength to the argument that the medical regimen caused the decrease in number of transient ischemic attacks or the prevention of a stroke. Conversely, if compliance to a known extent (e.g., ingestion of 50% of the medication) is associated with as good an outcome as 100% compliance this will suggest that the dosage of medication employed in this study was greater than is actually required.

Effect of Duration of Therapy

The analysis correlating compliance with a therapeutic regimen with a reduction in frequency of transient ischemic attacks or prevention of strokes is more complex than looking for simple correlations.
between different measurements of compliance taken at the same point in time. Compliance with a therapeutic regimen in one interval conceivably could affect the outcome measures in a subsequent interval. If the drugs prevent adherence of platelets to the vessel wall and to early atherosclerotic plaques, they may prevent the progression of atherosclerosis and have a long-term benefit. Accordingly, they may prevent stroke at a much later period and decrease transient ischemic attacks for a longer period of time than the period during which they are ingested. Accordingly, it is not sufficient to analyze the data only within each time interval. The events in later time intervals should be analyzed in comparison with a composite index of the total drug ingestion throughout the time the patient is in the study. In the parametric approach employing data measured on a ratio scale, the final measurement employed would be the mean of the values obtained in each interval weighted for the duration of that interval. In the non-parametric approach, this composite index would be the time during which the patient was felt to be compliant divided by the total time the patient was in the study.

The Parametric Approach to Analysis

The parametric approach in this section is similar to that in the preceding section. In this case, the dependent variable becomes the change in attack rate, as previously defined. The independent variables are those listed in Table III.
Again, the first step is to obtain a visual display of the data in order to assess whether a linear model is appropriate and then the statistical testing of whether the linear (or any other model) decreases the variation in the observed frequency of attacks to a statistically significant extent employing the F test.

This analysis would be done for each of the follow-up assessments within each treatment group. In addition, the frequency of attacks at a later follow-up period (e.g., six months or one year) would be assessed against the composite index of compliance defined above.

Finally, to determine whether several of the measurements of compliance would be a better predictor than the individual indices, it would be of interest to perform a step-wise linear regression utilizing the above variables.

The Non-Parametric Approach to Analysis

This approach involves three stages: 1. the use of the Kruskal-Wallis One-Way Analysis of Variance, 2. the use of two-way tables, and 3. the use of stratification.

1. The Kruskal-Wallis One-Way Analysis of Variance

An initial consideration is whether the various tests and measures of
compliance have any effect on the frequency of transient ischemic attacks. This question is of biologic interest.

The Kruskal–Wallis one-way analysis of variance will be used to test the null hypothesis that the frequency of transient ischemic attacks (and incidence of strokes) is not decreased by compliance.

This test does not make any assumption concerning the distribution of the variables. It appears unwise to assume that the frequency of attacks or the independent variables in the various treatment groups are normally distributed. Moreover, this test has a power-efficiency of 95.5% as compared to the F test which would be used in the parametric approach. Accordingly, it is a most valid and efficient method of testing whether the various tests of platelet function or compliance predict the outcome.

An example of the methodology employed in this analysis is found in Appendix 2.

2. The Use of Two-Way Tables

Of more interest to the clinician is whether the patient complies to a sufficient degree to achieve the outcome desired. He wishes to observe a single boundary which will define sufficient compliance and insufficient compliance to obtain the end desired.
To employ two-way tables requires imposing division points. The partitioning of independent variables will be according to the boundaries derived in the previous section. Of the dependent variables, the occurrence of stroke will be defined as either present or absent. It is necessary to define the decrease in frequency in transient ischemic attacks in a clinically significant manner. For example, a decrease in the frequency of transient ischemic attacks by 10% would be meaningless clinically and could not be employed. Accordingly, the decrease in frequency of transient ischemic attacks will be divided as less than 50%, greater than 50%, and complete abolition (the latter category to be employed if sufficient number of cases demonstrate complete abolition of attacks).

These division points allow one to classify the patients as compliant or noncompliant and as improved or not improved. (If the three-way division concerning frequency of attacks is available, one can define the patients as not significantly improved, significantly improved, and attacks abolished.) The appropriate statistics to test the significance of this situation is a chi-square. However, of equal interest would be indices of sensitivity and specificity concerning how well compliance, thus defined, predicts improvement or lack of improvement. An example of such a table is found in Table VI.

Stratification

A final step in the analysis is to combine the measurements of
compliance and noncompliance and correlate the combined measurement against outcomes. For example, one would initially select the two and then the three best predictors of outcomes. One would then classify the patients as compliant on the various combinations of these parameters and determine the frequency with which each of the outcomes, as defined above, is observed in each stratum. Again, the appropriate statistical test is a chi-square test to determine the statistical significance of the prediction. However, again, greater interest might be expressed in indices of sensitivity and specificity.

From this last part of the analysis, one would obtain the most valid measurement of compliance for predicting outcome measurements. This may be a single measurement or a combination of measurements. This measure would then be used as the dependent variable in the next part of the analysis.

PREDICTION OF COMPLIANCE

Definition of Compliance

The operational definition of compliance will be derived from the previous sections. Accordingly, it is unclear at this point how compliance will be defined.
Nevertheless, it is desirable to have an operational definition of compliance employing an index (e.g. pill counts) that is applicable to all treatment groups. This will allow comparison across the treatment groups to determine if the type of treatment, per se, has any effect on compliance and will also allow one to study the placebo group. In this latter group, it will be of interest to determine whether compliance correlates with decrease in attack rate (apparent effectiveness). In addition, such an index of compliance that is applicable to all groups, if the groups were otherwise comparable would expand the size of the sample which can be studied so as to increase the sensitivity of the investigation.

Accordingly, it is proposed to use pill counts as a secondary definition of compliance (if they do not constitute the definition derived above) to test the following hypotheses. The level of pill count which will constitute compliance will be derived operationally as the percentage of adherence to the pill count regimen which is associated with effectiveness in the categories in which the drugs are effective.

Four other aspects of noncompliance are of interest. These are patients who are withdrawn for noncompliance with the therapeutic regimen, patients who admit to the intake of other medications, and patients who take excessive medication. In a second part of the analysis, these groups will be characterized according to the factors which are listed in the hypotheses. The fourth issue is whether noncompliance in one period are noncompliance in other periods. If patients are consistent in this respect, this suggests that compliance is a stable characteristic of an individual. If patients are inconsistent, this suggests that individuals respond to their current circumstances with respect to compliance. Accordingly, one must follow individual patients throughout the study duration to study this problem.
Statement of Hypotheses

1. Sex alone does not predict compliance.
2. Age alone does not predict compliance.
3. Stratification by age and sex does not predict compliance.
4. Apparent effectiveness (decrease in attack rate) does not correlate with compliance in the same treatment period.
5. Effectiveness (decreased attack rate) does not predict compliance in the subsequent follow-up period, with placebo or ineffective treatment.
6. An increased frequency of attacks prior to treatment does not predict increased compliance in the first follow-up visit.
7. A greater frequency of attacks in the period prior to treatment does not predict compliance in the third follow-up period.
8. Recent onset of attacks does not predict compliance in the first follow-up period.
9. Shortness of the interval from last attack to the initiation of therapy does not predict compliance in the first follow-up period.
10. Visibility of the illness (persisting symptoms) does not predict compliance in any follow-up period.
11. Increased co-morbidity does not predict decreased compliance.
12. The number of types of other medications does not predict decreased compliance.
13. Impaired mental status does not predict decreased compliance.
14. Impaired speech does not predict decreased compliance.
15. Total neurologic impairment does not predict decreased compliance.
16. Performance of angiography does not predict increased compliance.
17. Performance of lumbar puncture does not predict increased compliance.
18. An increased number of side effects does not predict decreased compliance.
19. The duration of therapy does not predict decreased compliance.

Definitions

Effectiveness is defined as the ratio of the attack rate in any interval to the initial attack rate. The initial attack rate is as defined above: the mean frequency of attacks per month since the onset of attacks prior to therapy.

The number of persisting symptoms will be the sum total of the symptoms recorded on the summary sheet. In addition, the following syndrome clusters will be analyzed:
1. Headache;
2. Drowsiness, convulsions, syncope, or vertigo;
3. Hearing loss, hoarseness, dysphasia, dysphagia, or diplopia;
4. Visual symptoms;
5. Sensory changes;
6. Motor changes.

The presence of any one symptom in the cluster will constitute reason for inclusion in the cluster. Each of these symptom clusters will be analyzed individually against compliance rate. Secondly, the number of such symptom clusters will be analyzed as a predictor of compliance.
A co-morbid disease will be stated to be present if it is recorded as present in Section 4.1 or claudication is recorded as being present in Section 5.1. The presence of an abnormal chest x-ray (Section 4.5) will not be sufficient for defining a second disease as being present.

The definition of impaired mental status will depend upon annotation in Section 3.6 of impairment of consciousness or mentation and intellectual function. Similarly, impaired speech will be defined as an annotation in the same area.

The exact definitions of the above symptoms or signs are found in the Reference Manual of the R.R.P.C.E. Study.

Methodology of Analysis

First, the data listed in the hypotheses will be handled as nominal data. The first step in the analysis is to perform two-way tables comparing compliance in each of the therapeutic and diagnostic groups to determine if the compliance rates in the various groups are the same so that the entire sample can be used for analysis of the various hypotheses. The two-way tables will be tested via chi-square testing.

The next stage will be to derive appropriate division points for the independent variables which are continuous. Accordingly, an ordered listing of the data should be obtained and observed to see if there are
any natural division points. If there are no obvious division points occurring within each data set of independent variables, these should then be re-listed in conjunction with the compliance rates. Again, any natural division would be sought and if no such natural division point is seen, it will be apparent that the independent variable does not affect compliance rate and it would probably be appropriate to divide it at the midpoint in order to demonstrate its lack of ability to predict.

Utilizing the data in this way, one obtains a series of two-way tables. These can be tested for statistical significance via chi-square testing and indices of sensitivity and specificity and predictive ability derived.

The independent variables contained in hypotheses 2, 4 through 12, and 18 to 19 constitute continuous variables which are on a ratio scale. However, it is unlikely that the distribution of the values observed in these variables is normal. Accordingly, these will be analyzed also utilizing the Kruskal-Wallis one-way analysis of variance, to increase efficiency.

The Effect of Combined Factors on Compliance

One of the strengths of the R.R.P.C.E. Study is that multiple measurements are available on the same individuals. This provides an opportunity
to study the effects of interaction of such variables. Moreover, there is a logical problem in considering the various hypotheses listed above individually. If any of the independent variables correlate, one will observe either a potentiation or a masking of the effect of each variable. This may lead to spurious results. For example, let us assume that being younger than 55 will lead to non-compliance and being male will have no effect. Let us further assume that all males in the study are under the age of 55. In this case, during the analysis, one would find that both being under 55 and being male produced noncompliance. This, of course, would be a spurious result. Accordingly, it is necessary to observe the effect of the various factors on compliance not only individually but also in a combined manner in order to obtain accurate results.

Methodology of Analyzing for Combined Effects

At this stage in the analysis, one will have a series of two-way tables in which significant prediction of compliance is seen. One begins with the two-way table which predicts compliance the best. One then selects the cells in this table and lets each cell constitute the sample for the next stage in the analysis. Then, within each sample, one constructs a two-way table employing the next predictor of compliance. One can continue this methodology of nesting one two-way table inside the cells of another until the numbers become too small to be meaningful. One would predict that this cut-off point would come when the expected number of patients in more than one cell was less than 5.
For example, one might observe that age less than 55, increased frequency of attacks prior to treatment, and greater effectiveness could be analyzed against the combined opposite variables in a two-way table to predict compliance. On the basis of such a combined table, one could then test significance via a chi-square test and again derive indices of sensitivity, specificity, and predictive value.

Thus, this methodology of nesting one table within another in some cases will increase the power of prediction of compliance. In other cases, there will be no increase in the prediction of compliance but the values obtained for the second predictor will correlate with those seen for the first. In this case, one may assume that both predictors are measurements of the same variable and select only the first as the predictor of compliance. In this way, nesting of the tables allows one to observe directly how the various predicting variables interact in predicting compliance.
SUMMARY

The measurement of compliance is essential in clinical trials to assess the efficacy and side effects of treatment. Multiple methods of measuring compliance and several predictors of it have been reviewed. However, in previous studies, noncompliance has been defined using arbitrary "cutting points" determined by the method of measurement. Such "cutting points" should be validated against an external measurement.

In the Study of Recent Recurrent Presumed Cerebral Emboli, multiple measurements affected by the drugs being studied have been obtained on multiple occasions in the same subjects. This thesis has explored ways in which one can assess the extent to which these measurements agree as indices of the intake of those drugs. Furthermore, it demonstrates how such measurements can be validated against an external measurement, the outcome desired, in order to choose valid "cutting points" to define compliance and non-compliance. Having obtained such a validated definition of compliance, it is suggested that further studies be performed. Thus, the thesis outlines methods to predict compliance and non-compliance.
and to study whether compliance is a constant characteristic of certain subjects or varies through time, being affected by time or various events (e.g., extent of visible disease or side effects) in the course of therapy.
<table>
<thead>
<tr>
<th>TYPE OF MEASUREMENT</th>
<th>ADVANTAGES</th>
<th>DISADVANTAGES</th>
<th>EXAMPLES OF USE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interview of patient</td>
<td>can ask patient's perception of cause, can determine pattern of missed medication</td>
<td>errors of interviewing, bias to over-reporting of compliance</td>
<td>12, 12, 11, 13, 14, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 23, 24, 25, 26, 27, 28, 29, 30</td>
</tr>
<tr>
<td>Interview of physician or other health professional</td>
<td>very easy</td>
<td>severely inaccurate</td>
<td>2, 4, 7, 8, 9, 10, 11, 12</td>
</tr>
<tr>
<td>Dispensing of medication</td>
<td>easy</td>
<td>may obtain elsewhere, may obtain but not ingest it, only a global estimate</td>
<td>24, 25, 26</td>
</tr>
<tr>
<td>Measurement of residual medication</td>
<td>greater accuracy</td>
<td>less simple</td>
<td>3, 13, 13, 14, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30</td>
</tr>
<tr>
<td>Measurement of drug in blood or excreta</td>
<td>very accurate</td>
<td>complex, a sample of one point in time, if patient supplies to &quot;pass the test&quot;</td>
<td>2, 4, 8, 10, 12, 15, 16, 17, 18, 19, 20, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41</td>
</tr>
<tr>
<td>Measurement of a marker in drug or excreta</td>
<td>accurate</td>
<td>simple, a sample of one point in time, if patient supplies to &quot;pass the test&quot;</td>
<td>3, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41</td>
</tr>
<tr>
<td>Determination of outcome</td>
<td>valid risk of compliance</td>
<td>compliance frequently neither necessary nor sufficient to medication</td>
<td>13</td>
</tr>
<tr>
<td>TYPE OF MEASUREMENT</td>
<td>ADVANTAGES</td>
<td>DISADVANTAGES</td>
<td>EXAMPLES OF USE</td>
</tr>
<tr>
<td>---------------------</td>
<td>------------</td>
<td>---------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>Determination of outcome</td>
<td>- clinically useful</td>
<td>- outcome may occur too late</td>
<td>1,48,49,50,51,52</td>
</tr>
<tr>
<td>Determinant of predictor of outcome</td>
<td>- necessity to validate predictor</td>
<td>- may be complex</td>
<td>- factors other than compliance may affect predictor or outcome</td>
</tr>
<tr>
<td>VARIABLE</td>
<td>ADDITIONAL INFORMATION</td>
<td>EXPECTATIONS</td>
<td>OUTCOME TO PEER COMPARISON</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>------------------------</td>
<td>--------------</td>
<td>---------------------------</td>
</tr>
<tr>
<td>Record of Drug Use</td>
<td>- accurate, the most frequent form of measuring intake</td>
<td>- loss of other data due to compliance or intake</td>
<td>- follow to determine efficacy of the medication</td>
</tr>
<tr>
<td>Patient report of other medication</td>
<td>- a specific form of measurement applicable to any of the medication regimes</td>
<td>- data collected for other purposes and may be incomplete</td>
<td>- emphasis on need for complete reporting</td>
</tr>
<tr>
<td>Pill counts</td>
<td>- covers intake over entire interval applicable to any of the medication regimes</td>
<td>- data incomplete due to: 1) patient failure to return pills 2) lack of analysis of study personnel 3) recording of the pills returned includes pills forgotten by patient 4) patient ran out of pills 5) patient had exactly &quot;correct&quot; number of pills 6) need to assume non-compliance occurs at an equal frequency throughout time</td>
<td>- code 1), 6), and 11) differently at initial recording</td>
</tr>
</tbody>
</table>

**Scale of Measurement**
- Nominal: A scale that measures classification or ranking.
- Ratio: A scale that measures equal intervals and a meaningful zero point.
<table>
<thead>
<tr>
<th>Variable</th>
<th>Measurement</th>
<th>Precautions</th>
<th>Value Interpretation</th>
<th>State of Measurement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood levels of drug</td>
<td>valid measure of drug injection</td>
<td>- check levels of drug over time to estimate drug intake at one point in time</td>
<td>- ensure intake of drug on day of test</td>
<td>- ratio</td>
</tr>
<tr>
<td>Serum uric acid</td>
<td>simple</td>
<td>- a biochemical side-effect</td>
<td>- validate against other measures</td>
<td>- nominal</td>
</tr>
<tr>
<td></td>
<td>reproducible</td>
<td>- may reflect compliance over relatively long time period</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- analysis of variance and correlation separately</td>
<td></td>
</tr>
<tr>
<td>Platelet tests</td>
<td>may be best predictors of response</td>
<td>- try to pair &quot;predictors&quot; of drug intake</td>
<td>- analyze against other measures of drug injection as well as observed</td>
<td>- ordinal or nominal</td>
</tr>
</tbody>
</table>

Serum uric acid: If variation too great, analyze as "present" or "absent". Consider Freulinx test for this.
<table>
<thead>
<tr>
<th>Factor</th>
<th>Effect</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Young adulthood</td>
<td>decrease</td>
<td>2, 15, 27, 10, 42</td>
</tr>
<tr>
<td>(especially in females)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age above 55</td>
<td>decrease</td>
<td>15, 60</td>
</tr>
<tr>
<td>Ability to cope</td>
<td>increase</td>
<td>60</td>
</tr>
<tr>
<td>Marriage</td>
<td>increase</td>
<td>22, 60</td>
</tr>
<tr>
<td>Social supervision</td>
<td>increase</td>
<td>25, 21, 26, 38, 60</td>
</tr>
<tr>
<td>Hostility and aggression</td>
<td>decrease</td>
<td>31, 62, 65, 64</td>
</tr>
<tr>
<td>Immaturity and impulsiveness</td>
<td>decrease</td>
<td>65</td>
</tr>
<tr>
<td>Illness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild severity</td>
<td>increase</td>
<td>8, 28, 64, 63</td>
</tr>
<tr>
<td>Marked severity</td>
<td>decrease</td>
<td>11, 27, 59, 66</td>
</tr>
<tr>
<td>Therapeutic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Induction of satisfaction</td>
<td>increase</td>
<td>3, 11, 70</td>
</tr>
<tr>
<td>Belief in efficacy of drug</td>
<td>increase</td>
<td>30, 58</td>
</tr>
<tr>
<td>Written instruction</td>
<td>increase</td>
<td>29</td>
</tr>
<tr>
<td>Instillation of fear</td>
<td>increase</td>
<td>72</td>
</tr>
<tr>
<td>Therapeutic Horroch</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration</td>
<td>decrease</td>
<td>3, 18, 27, 21, 23</td>
</tr>
<tr>
<td>Complexity</td>
<td>decrease</td>
<td>4, 11, 53, 73, 71</td>
</tr>
<tr>
<td>Side effects</td>
<td>decrease</td>
<td>5, 4, 19, 59, 39, 62</td>
</tr>
<tr>
<td>Efficacy</td>
<td>increase</td>
<td>23</td>
</tr>
</tbody>
</table>
APPENDIX I

Sample calculation of Pill Count

1. \( Z \) = Number of tablets (or capsules) dispensed
2. \( R \) = Number of tablets (or capsules) returned
3. \( X \) = Number of tablets (or capsules) consumed = \( Z - R \)
4. \( D \) = Number of days from previous visit to follow-up exam
5. \( E = D \times 4 \) = predicted number of tablets (or capsules) ingested

\[
PC = \text{Pill Count} = \frac{X}{E} \times 100 \% = \frac{Z - R}{4D} \times 100 \%
\]

e.g. for F30, first follow-up visit:

\( Z = 130 \text{ tabs} \)
\( R = 31 \text{ tabs} \)
\( X = 99 \text{ tabs} \)
\( D = 27 \text{ days} \)
\( E = 27 \times 4 = 108 \text{ tabs} \)

\[
PC = \frac{99}{108} \times 100 \% = 91.7 \%
\]
**Table III**

Comparisons to be plotted and tested by parametric techniques.

<table>
<thead>
<tr>
<th>Pill Count</th>
<th>Blood Levels</th>
<th>Uric Acid</th>
<th>Glass Adhesiveness</th>
<th>Template Bleeding Time</th>
<th>Platelet Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Blood Levels</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Uric Acid</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Glass Adhesiveness</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Template Bleeding Time</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Platelet Survival</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

**Pill Count** = % of pills ingested of amount predicted to be ingested on basis of number of days in interval x 4

**Blood Levels** = serum total salicylate and serum anturan

**Uric Acid** = initial serum uric acid/serum uric acid at follow-up

**Glass Adhesiveness** = % platelets adherent initially/ % adherent at follow-up

**Template Bleeding Time** = template bleeding time at follow-up/ initial template bleeding time

**Platelet Survival** = platelet survival at follow-up/ initial platelet survival
Graph II:
Relationship of Fall In Serum Uric Acid to Pill Count

Sulfinpyrazone

Sulfinpyrazone - Aspirin

Aspirin

Placebo

% Compliance (expressed as "Pill Count")

5 4 3 2 1 0

0 1 2 3 4 5

Full in Uric Acid (expressed as uncorrected Urine excretion)
GRAPH II - Pill Counts - % missed Third Follow-up Visit
<table>
<thead>
<tr>
<th></th>
<th>Pill Count</th>
<th>Blood Levels</th>
<th>Uric Acid</th>
<th>Glass Adhesiveness</th>
<th>Template Bleeding Time</th>
<th>Platelet Survival</th>
<th>Epinephrine Aggregation</th>
<th>Collagen Aggregation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pill Count</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Blood Levels</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Uric Acid</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glass Adhesiveness</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Template Bleeding Time</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelet Survival</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epinephrine Aggregation</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Collagen Aggregation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Definitions of first five variables are as above

Epinephrine aggregation - abolition of second wave of aggregation (yes or no)

Collagen aggregation - impaired collagen aggregation (yes or no)
Table 1

Comparison of Pill Count and Change in Serum Uric Acid as Indices of Complianc e in the Patients Receiving Sulfinpyrazone Alone

<table>
<thead>
<tr>
<th>Compliant per Pill Count</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>No</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>

Compliant per Pill Count: Pill Count of 75% or greater
Compliant per Change in Uric Acid: Initial uric acid level of 5mg/dL followed by >3.8mg/dL

Sensitivity of change in serum urate as predictor of compliance per pill count:
\[
\frac{6}{6} = 1.0
\]

Specificity of change in serum urate as predictor of compliance per pill count:
\[
\frac{2}{2} = 1.0
\]

Predictive value of change in serum urate for compliance per pill count:
\[
\frac{6}{6} = 1.0
\]

Predictive value of less change in serum urate for noncompliance per pill count:
\[
\frac{2}{2} = 1.0
\]

Index of Grade Agreement
\[
A = \frac{c + 0 + 2}{c + 0 + 2} = 1.0
\]

Cohen's adjusted index of agreement
\[
A_2 = \frac{1}{n} \left( \frac{a}{arb} + \frac{c}{cde} + \frac{d}{dfe} \right)
\]
\[
A_2 = \frac{1}{n} \left( \frac{6}{6} + \frac{2}{2} + \frac{2}{2} \right)
\]
\[
A_2 = 1.0
\]

Statistical significance not calculated due to small numbers.
TABLE VI

Sample of Two-Way Table

Effect of compliance to the extent of ingestion of 75% of prescribed sulfinpyrazone on attack rate at first follow-up visit

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complied</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Did not Comply</td>
<td>4</td>
<td>0</td>
</tr>
</tbody>
</table>

\( \geq 50\% \) decrease in attack rate

Sensitivity = \( \frac{7}{11} = 0.636 \)

Specificity = \( \frac{0}{2} = 0 \)

Predictive value of compliance for improvement \( \frac{7}{9} = 0.778 \)

Predictive value of noncompliance for no improvement \( \frac{0}{4} = 0 \)
APPENDIX II

Sample Calculation of Application of Kruskal-Wallis One-Way Analysis of Variance.

Null Hypothesis: A compliance rate of 75% as assessed by pill counts does not predict a decreased attack rate ratio at the first follow-up visit in patients receiving sulfapyrazine alone.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Tablets Consumed</th>
<th>Attack Rate</th>
<th>Compliance</th>
<th>Survivorship</th>
</tr>
</thead>
<tbody>
<tr>
<td>P31</td>
<td>96.3</td>
<td>0</td>
<td>2.5</td>
<td>2.5</td>
</tr>
<tr>
<td>P15</td>
<td>70.5</td>
<td>0</td>
<td>2.5</td>
<td>2.5</td>
</tr>
<tr>
<td>F11</td>
<td>95.4</td>
<td>0</td>
<td>2.5</td>
<td>2.5</td>
</tr>
<tr>
<td>F26</td>
<td>100.2</td>
<td>0</td>
<td>2.5</td>
<td></td>
</tr>
<tr>
<td>G9</td>
<td>98.3</td>
<td>0.0166</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>A1</td>
<td>100.3</td>
<td>0.0540</td>
<td>6.5</td>
<td>6.5</td>
</tr>
<tr>
<td>F22</td>
<td>100.5</td>
<td>0.0484</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>F19</td>
<td>98.2</td>
<td>0.3214</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>F10</td>
<td>98.4</td>
<td>0.5225</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>F16</td>
<td>100.9</td>
<td>0.7859</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>F10</td>
<td>86.3</td>
<td>1.3011</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>G10</td>
<td>96.3</td>
<td>2.0224</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>9.444</td>
<td>13</td>
<td></td>
</tr>
</tbody>
</table>

$T = 306$  $K = 11$  $n = 12$

$H = \frac{12}{12} \sum_{k=1}^{K} \frac{R_k^2}{n_k} - 3(K+1)$

$= \frac{12}{12} \left( \frac{306^2}{11} + \frac{5^2}{12} - 3(12+1) \right)$

$= \frac{2727.9219 + 7.5 - 3(12+1)}{13^2 - 13}$

$= \frac{2727.9219 + 7.5 - 36}{169 - 13}$

$= \frac{2727.9219 + 4.5}{156}$

$= 17.4219$

$= 3.0427$

$\text{d.f.} = k-1 = 2-1 = 1$

Therefore $p > .50$
REFERENCES


