COMPLIANCE OF MEDICAL OUTPATIENTS WITH PRESCRIBED MEDICATION

COMPLIANCE OF MEDICAL OUTPATIENTS WITH PRESCRIBED MEDICATION: A PROTOCOL FOR A CONTROLLED TRIAL OF CLINICAL INTERVENTION

By

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ABSTRACT

Lack of compliance with therapeutic regimens is an important cause of inadequate or incomplete medical care.

For the purposes of furthering knowledge about problems of compliance, this thesis first surveys issues of compliance as reported in the current scientific literature and then proceeds with the development of specific strategies to improve compliance and finally with the development of a research design for testing these strategies in a controlled clinical fashion among a cohort of medical patients newly initiated into therapy.

The compliance-intervention strategies include, first, special techniques in patient education, utilizing potent behavior-oriented teaching materials, second, a flexible, opportunistic approach to fitting medical appointments and medication-taking into a patient's existing rituals and daily routine, a process here termed "tailoring", and, third, a behavior modification paradigm which reinforces prescribed behavior.

Hypertension has been chosen as a disease appropriate for the testing of the strategies because of its high prevalence and its known harmful effects, because of the existence of efficacious treatments for it, and because of the

small proportion of its victims who are receiving adequate treatment, whether for lack of detection of the condition or lack of compliance with its therapy.

A steel mill (Dominion Foundries and Steel Company) in Hamilton, Ontario, has been selected as an ideal study site for several reasons. First, the Company is owned by its employees and this has led to an exceptionally stable employee group. Second, it has an active and cooperative employee health service. Thirdly, the health service staff has become concerned about the problem of untreated hypertension through its periodic health assessment program and the high prevalence of hypertension among employees lost from active duty through vascular disease.

At the time of this writing the project has been funded through the Medical Research Council and is just getting underway.

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1. INTRODUCTION

A person who seeks medical care from a health professional will generally find himself caught up in a temporal sequence of events beginning with the collection of historical data, proceding to a physical and laboratory examination, and then, if a problem is perceived, to a diagnosis and a prescription for therapy.

At this point, the sequence becomes somewhat more complicated. If the application of the therapeutic prescription requires some skill, for example a surgical procedure, then the patient will be asked to declare his intent or acquiescence in writing by signing a consent form. The health professional will then perform the procedure and the process is ended. However, if the consummation of therapy requires no special skills, for example, the taking of medicine in the form of pills, then the patient will usually be expected to administer the treatment himself, according to the health professional's instructions, and no consent, formal or informal, is sought. Save in some special situations where lack of patient cooperation is feared, for example in the outpatient treatment of tuberculosis or the psychoses, the cooperation of the patient is usually assumed.

As reported in the review which follows, ample evidence exists to reject this assumption as unwarranted.

Firstly problems in accurate self-medication are protean, extending into all fields of health and disease care rather than just those few areas presently given attention. Secondly, health professionals are able to predict the co-operation of individual patients with only chance accuracy.

The degree to which the patients' activities correspond to appointment schedules and the therapy prescribed in self-administration situations may be termed compliance and, conversely, their divergence termed noncompliance. Divergence comprises under- and over-compliance as well as taking the wrong medication. Issues of compliance and non-compliance are the subject of this thesis.

Lack of compliance of patients with therapeutic regimens can severely limit the effectiveness* of otherwise efficacious* treatments and thus undermine medical care. Furthermore, noncompliance can vitiate attempts to evaluate old or new treatments, in both individual therapy and proper clinical trials, giving rise to pessimistic or misleading conclusions.

It is contended that noncompliance is a problem of sufficient magnitude and importance to warrant far more attention on the part of health professionals and researchers

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* Here effectiveness refers to the extent to which a treatment acts among those to whom it is offered whereas efficacy refers to the extent to which a therapy does more good than harm to those who take it.

alike. Furthermore, it is contended that practical and relatively inexpensive solutions appear of sufficient merit, in preliminary testing in various clinical situations, to warrant formal evaluation in a prospective-clinical trial.

In the ensuing text, issues of compliance and non-compliance are outlined through a review of the current scientific literature. Next, based partially on findings reported in the review, three intervention strategies are developed in detail. Finally, a research design is presented for the testing of the strategies in a randomized clinical trial.

2. A REVIEW OF THE LITERATURE ON COMPLIANCE

2.1 Introduction

The current scientific literature on compliance with therapeutic regimens is rather sparse. Index Medicus does not have a subject heading for compliance so that would-be reviewers are obliged to peruse article titles for words such as "compliance", "adherence", "cooperation", "dropouts", "defaulters" and the like. Once a relevant article is obtained one can then follow up any references given which appear appropriate and can search through Science Citation Index for future citations of the article itself. At best such a process is doomed to be unsystematic enough to be unreproducible.

The review presented here comprises primary sources only. Approximately half of the references were obtained through the painstaking work of Ms. Jane R. Cloak (working as a research assistant under Dr. D.L. Sackett) who selected them from titles contained in Index Medicus from 1971 and 1972 and in Current Contents for June through December, 1972. The rest were obtained by follow-up references cited in the collected articles and from the private file of Dr. A.R. Feinstein who has contributed to research in this area and who has been collecting articles on the subject for several years.

No attempt has been made in this review to assess the methodologic merit of the cited articles, although such a process is presently being undertaken in preparation for future research and a symposium on compliance tentatively scheduled for the Spring of 1974. Suffice it to say that the majority of studies are of a descriptive nature, many are retrospective and few could be termed rigorous in any meaningful sense of the word.

The review proceeds in the following fashion. First, the magnitude of the problem of noncompliance is surveyed. The review is largely restricted here to reports of compliance rates among ambulatory patients with chronic medical conditions, in keeping with the focus of the research design which follows the review. Next, factors which have been investigated for their possible effects on compliance are categorized. Finally, strategies which have been utilized to increase compliance are presented.

2.2 Magnitude

Lack of compliance with therapeutic regimens cuts across diagnostic boundaries and, as will be demonstrated in the section dealing with the determinants of compliance, the type and, indeed, seriousness of the disease is not a major determinant of compliance. However, most investigators are of discreet medical disciplines and for the sake of convenience the magnitude of the problem is described within the therapeutic milieu in which it is reported in the

literature. This method of description, then, does not imply any association of the disease type and the observed compliance rates.

A last word of introduction is in order. One of the difficulties in assessing compliance rates is that different authors apply different standards and definitions of compliance. Thus rates of noncompliance ranging from 15-93% as reported by Davis [23] may not be from comparable samples nor, alas, according to standardized criteria. In order to add some clarity to the following descriptions, summary tables have been included for each section. As crude guidelines, first, about two-thirds of patients under active medical treatment may be classified as compliant when compliance is defined as adhering to at least two-thirds of the prescribed therapy and second, the variance within individual samples and among samples is very large.

The compliance rates among general medical outpatients are summarized in Table 1. Davis [23] in a prospective study of new patients to a general medical outpatient department, followed over three visits, found that 37% of the 154 complied with less than half of the medical advice given and that 5% complied with none at all. Jenkins [57] measured compliance with medication among 30 patients pre-selected from his private practice for their faithful attendance at appointments. He found that 22 (73%) kept their regular appointments and of these 22, 4 (18%) were

completely faithful to their medication prescription, 12 (54%) took less than 60% of their pills, 4 (18%) took half and 2 (9%) took none. The average compliance rate was 50%. Porter [81], again in a private practice setting, found that 69% (33/48) of his patients on short-term antibiotics erred by less than one day's prescribed medication during the trial period.

In two studies of chronic medical outpatients, Tagliacozzo and Ima [97,98] reported, in the first study, that 61% (97/159) were still attending clinic at the fourth scheduled visit and, in the second, 49% (96/195) stopped attending between the first and fourth months following this first visit. Among chronic ambulatory patients over the age of 60, Schwartz and his co-workers [89] found that 47% (126/269) omitted all or part of their treatment whereas 10% (26/269) made errors in dosage. Porter [81] found that 34.5% (20/58) of his private patients on long-term medications took less than 80% of their prescribed medication. In 82 chronic medical patients followed six months after discharge from hospital, Donabedian and Rosenfeld [26] found that 37% were not compliant with medical supervision recommendations, 22% failed to heed diet restrictions and 13% were no longer taking any of their prescribed medication. However in a similar study, Brook and his associates [14] found that only 12% (33/268) admitted that they had stopped taking their medication completely, six months after medical discharge from public hospitals.

TABLE 1: COMPLIANCE AMONG GENERAL MEDICAL OUTPATIENTS

REFERENCE	SETTING	N	TYPE OF COMPLIANCE	METHOD OF MEASUREMENT	RESULTS
23	General medical outpatient clinic	137	proportion of doctor's advice followed	patient interview compared with doctor's orders	37% complied with less than half of advice given
57	private general practice	30	proportion of prescribed medication taken for a variety of conditions	pill count of returned medication compared with doctor's orders	27% failed to return pills; 54% of those who returned pills took less than 60%
81	private general practice	48	proportion of short-term antibiotics taken	patient's statement compared with doctor's orders	69% erred by less than 1 day's prescribed medication
97	chronic medical outpatient clinic	159	attendance at scheduled appointments	clinic records	61% still attending at 4th scheduled visit
98	chronic medical outpatient clinic	195	attendance at scheduled appointments	clinic records	49% stopped attending between 1st and 4th month
89	chronic ambulatory patients over 60 years	269	errors in medication (too much, too little, wrong pill)	patient interview compared with doctor's orders	47% omitted all or part of medication 10% made "serious" errors

TABLE 1: COMPLIANCE AMONG GENERAL MEDICAL OUTPATIENTS (continued)

REFERENCE	SETTING	N	TYPE OF COMPLIANCE	METHOD OF MEASUREMENT	RESULTS
81	private general practice	58	proportion of long-term medication taken	patient's statement compared with doctor's orders	34.5% took less than 80% of prescribed medication
26	chronic medical patients six mon. after hospital discharge	82	medical supervision; diet restrictions; prescribed medication	patient interviews in home compared with chart orders	37% not compliant with medical supervision recommendations; 22% not heeding diet; 13% not taking any prescribed medication
14	chronic medical patients six mos. after hospital discharge	268	medical supervision; medication taking	chart review patient interview compared with chart orders	29.5% failed to keep appointments 12% stopped taking prescribed medication

Three research groups report substantially different compliance rates for patients with cardiac complaints (see Table 2). Davis and Eichhorn [20], studying shifts in compliance over time in 82 farmers with cardiac conditions, discovered that 36% reported continued compliance with medical advice about work, diet and personal habits, 13% who initially complied admitted discontinuing treatment, 34% who were initially noncompliant began complying, and 17% admitted never complying. These investigators also looked at the effect of complexity of regimen on compliance [22]: among patients for whom recommendations included all three aspects (work, diet, and personal habits) 10.6% of 239 patients complied with all three aspects, and 26% failed to comply with any recommendation. By contrast, Johannsen and his co-workers [58] in a retrospective analysis of data from a cardiac work classification unit found that self-reported compliance with medical recommendations at six month follow-up was 92.7% (38/41), with psycho-social recommendations was 66.7% (28/42) and with vocational recommendations was 76.4% (97/127). Of 127 patients, 91 (71.6%) did not reject any recommendations and six (4.7%) rejected all recommendations. Intermediate compliance rates were found among patients taking digoxin for congestive heart failure. Weintraub and his associates [105] found that 67% (75/112) stated that they never failed to take their medication. When six of the 13 "compliant" patients with low

TABLE 2: COMPLIANCE AMONG CARDIAC OUTPATIENTS

REFERENCE	SETTING	N	TYPE OF COMPLIANCE	METHOD OF MEASUREMENT	RESULTS
20	farm cardiac outpatients over four years	82	following medical advice about work, diet, personal habits	patients statements at home interview only	36% continued to comply 13% stopped complying 34% started complying after initial noncompliance 17% never complied
22	farm cardiac outpatients over four years	82	following medical advice about work, diet, personal habits	patient's statements at home interview only	if advice given about all three aspects: 10% complied with all 3 26% failed to comply with any
58	outpatients six months after discharge from a cardiac work classification unit	41 42 127 127	medical advice psychosocial advice vocational advice	patient interview compared with doctor's orders	92.7% followed medical advice 66.7% followed psycho-social advice 76.4% followed vocational advice 71.6% followed all advice 4.7% rejected all advice
105	outpatients with congestive heart failure	112	proportion of medication taken	patient interview only	67% denied missing any pills

serum digoxin levels were questioned further, three confessed that their compliance was not as complete as they had previously stated.

Caron and Roth [17], utilizing direct observation of peptic ulcer patients (see Table 3) on various diet regimens in hospital, found that a strict diet was adhered to on 67% of 1084 patient days and a liberal diet on 75% of 989 patient days. In peptic ulcer outpatients taking antacid and atropine, Roth and his co-workers [87,88] reported that 40% (64/160) dropped out of treatment entirely. Of the 96 who continued treatment, the mean antacid intake was 54% of that prescribed; only 70% asked for refills of as much atropine as had been prescribed and only 38% had atropine present in their urine at clinic visits.

Several studies have dealt with noncompliance among hypertensive patients (Table 4). Caldwell and co-workers [15], in reviewing clinic records, discovered that of 76 patients starting therapy at the clinic during an arbitrary time period, only 38 (50%) were under care 11 months later and 5 years later a more 10 (17%) were under treatment. Finnerty and his associates [31] reported an average drop-out rate of 42% over several years at a "well organized, efficient" hypertension clinic. The low therapy continuation rates and high prevalence rates of untreated hypertension are amplified by the community surveys of Wilber and Barrow.

TABLE 3: COMPLIANCE AMONG PEPTIC ULCER PATIENTS

REFERENCE	SETTING	N	TYPE OF COMPLIANCE	METHOD OF MEASUREMENT	RESULTS
17	veterans; peptic ulcer inpatients	206	proportion of adherence to strict and liberal ulcer diet	direct observation of patient at cafeteria	67% adhered to strict diet 75% adhered to liberal diet
87 88	peptic ulcer outpatients	160	proportion of antacid, atropine taken	amount of antacid consumed on home bottle collection; proportion of prescribed atropine requested at clinic visits; atropine in urine at clinic visit	40% dropped out entirely of 96 who remained: 54% of antacid was consumed 70% of atropine was requested 38% had atropine in urine

TABLE 4: COMPLIANCE AMONG HYPERTENSIVE OUTPATIENTS

REFERENCE	SETTING	N	TYPE OF COMPLIANCE	METHOD OF MEASUREMENT	RESULTS
15	hypertensive outpatients	76	clinic attendance	chart review	50% still attending at 11 mos. 17% still attending at 5 yrs.
31	hypertensive outpatients	--	clinic attendance	chart review	42% drop out rate over several years
109	community survey for hypertension	6012	seeking care when so advised; attaining b.p. control	survey - interview - b.p. measurement	for each 100 screened: 25 found hypertensive 16 sought care 8 continued care over several months 4 attained b.p. control
107	community survey for hypertension	630	proportion under therapy and under "good" control of those who know they are hypertensive	survey - interview - b.p. measurement	58% of hypertensives knew of it 30% of these were under therapy 56% of these were under "good" control

TABLE 4: COMPLIANCE AMONG HYPERTENSIVE OUTPATIENTS (continued)

REFERENCE	SETTING	N	TYPE OF COMPLIANCE	METHOD OF MEASUREMENT	RESULTS
107	private practice - hypertensive patients	542	continued therapy through physician	chart survey of private physician's files	56% of patients begun on therapy were "lost track of" within 3 mos.
100	hypertensive outpatients pre-screened for compliance		proportion of prescribed medication taken	pill count at scheduled visits compared with prescribed amounts	44% took less than 90% of prescribed amount
101 102	hypertensive outpatients, clinical trial	280	attendance at appointments; proportion of prescribed medication taken	doctor's impression; clinic records of attendance; pill count; riboflavin added to pills and checked in urine	25% of patients excluded for "gross non-compliance" in doctor's opinion further 25% excluded because of failure to keep appointments, take 90 - 105% of medications in pretrial

In one survey [109], for each 100 persons screened, 25 were found hypertensive, 16 of these 25 actually sought care when advised to do so, eight continued on therapy over several months and only four achieved adequate control of their blood pressure. In the second survey [107], 58% of those found hypertensive were aware of their hypertension but only 30% of those who were aware of it were receiving treatment and of those on treatment, only 50% were under "good" control. A chart survey of files of physicians in private practice in the community was performed in conjunction with the community screening and it was discovered that 56% of patients begun on therapy were "lost track of" within three months. Compliance with antihypertensive therapy is incomplete even when patients are carefully screened. In the United States Public Health Service cooperative hypertension study [100], patients who deviated even slightly from medication and appointment schedules during a two to three month pre-trial "faintness of heart" period were excluded from the study. Even with this precaution, 44% of patients took less than 90% of their medication during the initial months of the trial. Using similar methods, the Veterans Administration Cooperative Studies Group on antihypertensive agents [101, 102] excluded 50% of patients, otherwise eligible for the study, because of "gross noncompliance" initially and because of deviations from appointment and medication schedules in pre-trial studies.

In the earlier literature on compliance among medical outpatients the major focus of attention was on tuberculous patients leaving sanitoria on various prophylatic agents such as isoniazid (INH) and para-amino salicylic acid (PAS) (see Table 5). Moulding and his co-workers [75] excluded "grossly noncompliant" patients from their study of a medication monitor and actively encouraged the rest of their patients to comply. The compliance rates among their 112 subjects were as follows: 60.7% removed more than 90% of their prescribed medication from the monitor, 22.1% removed 70-90% and 13.1% removed less than 70%. Other studies which also employed strenuous efforts to promote compliance had less encouraging results. Maddock [68], using urine tests at regular clinic visits, found that 64% of 50 patients on INH were compliant and 49% of 33 patients on PAS were compliant, where compliance was defined as having less than or equal to 20% of urine tests negative for the drug prescribed. Pragoff [83] studied the compliance of tuberculous outpatients one year after discharge from a state institution with comprehensive follow-up services. He was able to locate 66 of 77 patients discharged within an arbitrary time period one year earlier and found that 71.2% of the 66 had "satisfactory" compliance with drug prescriptions, 42.4% with diet prescriptions and 42.4% with activity recommendations. Pitman and co-workers [82] studied compliance among tuberculous outpatients taking PAS and found

TABLE 5: COMPLIANCE AMONG TUBERCULOUS OUTPATIENTS

REFERENCE	SETTING	N	TYPE OF COMPLIANCE	METHOD OF MEASUREMENT	RESULTS
75	tuberculous outpatients prejudged as not "grossly unreliable"	112	proportion of prescribed medication removed from medication monitor	medication monitor with prepackaged daily medication	60.7% removed more than 90% of packages from monitor; 22.1% removed 70-90%; 13.1% removed less than 70%
68	tuberculous outpatients	50	proportion of INH taken or proportion of INH and PAS taken	Belles-Littleman test for urinary INH; Phenistix for urinary PAS at scheduled clinic visits; pharmacy record of amount dispensed compared with amount prescribed	64% of patients on INH alone had at least 80% of urine tests positive; 49% of patients on INH and PAS had at least 80% of urine tests positive
83	tuberculous outpatients one year after hospital discharge	77	medication prescriptions, diet advice, activity advice	patient interview compared with chart record	11 could not be located; of the remaining 66: 71.2% complied with drugs 42.4% complied with diet 42.4% complied with activity

TABLE 5: COMPLIANCE AMONG TUBERCULOUS OUTPATIENTS (continued)

REFERENCE	SETTING	N	TYPE OF COMPLIANCE	METHOD OF MEASUREMENT	RESULTS
82	tuberculous outpatients on PAS	61	taking prescribed PAS	patient interview; urinary PAS test	59% of urine tests were positive; interviews in accord
25	tuberculous outpatients	151	taking of PAS	test for urinary PAS	50% had positive tests
84	tuberculous outpatients	25	taking of INH and PAS	patient interviews; urinary tests for INH, PAS; doctor's estimate	72% had positive urine tests at clinic visits 3 months post-hospital discharge
9	tuberculous outpatients	26	taking of INH	urine tests at unannounced home visits	96% had at least half of urine tests positive
55	tuberculous outpatients following hospital discharge	264	taking of INH, PAS	proportion of (free) medicines obtained at clinic pharmacy compared to amount prescribed	10% did not return for follow-up 33% took less than 50% of pills at 6 mos. 43% took less than 50% of pills at 1 yr. 73.5% took less than 50% of pills at 2 yrs.

that 59% (36/61) of urine samples were positive for salicylates. Dixon and co-workers [25] found that 50% (76/151) of urine samples were positive for salicylates among patients on PAS. Three months following hospital discharge, patients taking INH and PAS in Preston's study [84] were found to have positive urine tests in 72% (18/25) of scheduled clinic visits. Berry and his associates [9] found more encouraging rates of compliance: he estimated from urine samples collected at unannounced home visits that 96% of his 26 randomly selected patients took their INH at least half the time. However, despite the fact that home visits were unannounced one wonders if a "policing" effect was not present in Berry's study as patients were each visited a total of eight times during a one month period. Ireland [55] followed 264 tuberculous patients prospectively from the time of hospital discharge. Ten percent never returned for follow-up; by six months, 33% were taking less than 50% of prescribed medication; by 12 months 43% were taking less than 50% of medication and; by 24 months, 73.5% were taking less than 50% of medication.

Among diabetic outpatients (see Table 6), Stone [94] found that 62% of 160 patients were under poor control, a fact which he attributed to lack of compliance primarily with diet prescriptions.

Compliance among arthritic patients has evoked the interest of several investigators (see Table 7). Oakes and

his co-workers [78] assessed the use of hand splints to be worn nightly by 66 arthritic patients who volunteered to use the splints. Female patients used the splints 78% of the time whereas male patients managed only 41% use. Nugent [77] studied the use of prednisone among patients with active rheumatoid arthritis who were simultaneously taking as much acetylsalicylic acid "as they could tolerate", INH, one tablet per day, and prednisone, one tablet four times per day. He found that 21% (8/38) dropped out of the initial part of the study and a further 20% (6/30) dropped out of the crossover phase (only six of the 14 dropouts were due to uncooperativeness). Of those who remained in the study, 25% took less than 75% of the prescribed dose of prednisone for more than 50% of the observation periods. In a controlled trial of placebo, phenylbutazone and C20410 among patients with rheumatoid arthritis also taking acetylsalicylic acid with or without codeine, corticosteriods, or physical therapy, Joyce [59] found that 51% of 78 patients had less than a five day discrepancy at pill counting at the end of each 28 day phase of the trial.

Vincent [104], studying the use of eyedrops by out-patients with glaucoma (see Table 8) found that 42% (26/62) claimed that they omitted taking the drops less than once per month for each time the drops were prescribed per day.

TABLE 6: COMPLIANCE AMONG DIABETIC OUTPATIENTS

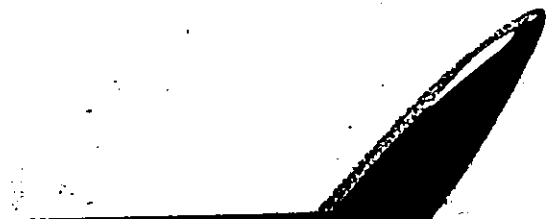
REFERENCE	SETTING	N	TYPE OF COMPLIANCE	METHOD OF MEASUREMENT	RESULTS
94	diabetic outpatients	160	adherence to medication, diet	patient interview compared with doctor's orders	62% "poorly controlled" due mainly to diet deviance

TABLE 7: COMPLIANCE AMONG ARTHRITIC OUTPATIENTS

REFERENCE	SETTING	N	TYPE OF COMPLIANCE	METHOD OF MEASUREMENT	RESULTS
78	outpatients with rheumatoid arthritis	66	use of hand splint at night	patient interview	females used splint 78% of time males used splint 41% of time
77	outpatients with active rheumatoid arthritis	38	taking of prednisone (clinical trial)	pill count at scheduled visits compared with doctor's orders	6 dropouts - due to uncooperativeness of the rest: 25% took less than 75% of their pills
59	outpatients with rheumatoid arthritis	78	taking of prescribed medication (clinical trial)	pill count at scheduled visits compared with doctor's orders	51% had less than a 5 day discrepancy at the end of each 28 days

TABLE 8: COMPLIANCE AMONG GLAUCOMATOUS OUTPATIENTS

REFERENCE	SETTING	N	TYPE OF COMPLIANCE	METHOD OF MEASUREMENT	RESULTS
104	outpatients with glaucoma	62	use of eye drops	patient interview compared with doctor's orders	42% claimed to miss less than once per month for each time per day



In conclusion, these data clearly lack congruity in definition and measurement and, even where comparable, in magnitude. However, it appears safe to infer that lack of compliance is a substantial problem whenever treatments are self-administered.

2.3 Determinants of Compliance and Noncompliance

In an attempt to understand and deal with problems of noncompliance numerous studies have been undertaken. Unfortunately, review analysis of the resultant data is once again confounded by the often inadequate methodology, inconsistent definitions, contradictory findings and additionally by the evident complexity of the problem itself. Nevertheless, several factors emerge as relatively constant correlates of compliance or of noncompliance and some of these are unexpected to say the least.

2.3.1 Sociodemographic Factors (see Table 9)

Numerous authors have reported extensive investigations into the relationship between various sociodemographic factors and compliance rates. Surprisingly, few of them have found significant correlations.

Age is positively correlated with compliance in only one report: older women of childbearing age are more faithful in taking their birth control pills [91]. Age has been found negatively correlated with compliance in three clinical settings: preventive dental care [99]; very elderly chronically ill patients [89] and; adolescents on rheumatic fever

TABLE 9: SOCIODEMOGRAPHIC FACTORS CORRELATED WITH COMPLIANCE

	CORRELATION BY REFERENCE		
FACTOR	POSITIVE	NEGATIVE	NIL
age	91	42,89,99	3,7,18,20,22,26,46,47, 53,67,68,75,81,83,105
education	89,91,99		3,7,18,20,22,28,34,42, 46,50,53,68,75,104
sex - female vs male	83,99,104	25,42	3,18,26,46,47,53,67,68, 75,81,89
social class			28,34,42,53,81
family size	91	42	3,18,50,75
race - white vs black	28,91,99		53,67,75,83
"demographic variables"			23,75,81
income	99		26,28,31,46,68,75
social isolation		89	81
intelligence			31,47
religion: catholics vs protestants	104		
marital status:	correlations found: 83, 89,91,104 (see text)		7,68,81
family stability	28,67		42
parity	81,91		
occupation	25,50,76,83		26
mother working (pediatric patients)		3	
telephone in home	106		
urban vs rural	99		

prophylaxis [42]. Most investigators report no effect of age among adults [20,22,26,46,53,68,75,81,83,104,105] or children [3,7,18,34,67] and one study [67] directly contradicts the results cited above for patients on rheumatic fever prophylaxis.

Education was found correlated with dental prophylactic behavior [99] and the taking of oral contraceptives [91] and was found negatively correlated with medication errors among elderly patients [89]. Most authors, however, found no correlation between education and compliance [3,7,18,20, 22,28,34,42,46,50,53,68,75,104].

Similarly, most authors found no correlation between sex and compliance [3,18,26,46,47,53,67,68,75,81,89]. Dissenting reports were split, with three authors finding compliance greater among women [83,99,104] and two authors finding the opposite [25,42]. In the dissenting studies, the findings were isolated to one segment of the age structure (middle aged women [104] or adolescent males [42] being found more compliant), or were clearly conflicting (Pragoff [83] and Dixon [25] found opposite results among populations of tuberculous outpatients).

No author found social class to be a determinant [28,34,42,53,81].

Family size was found positively correlated with the faithful taking of birth control pills [91] and negatively correlated with compliance with prophylactic

penicillin among post-rheumatic fever patients [42]. Other authors, however, found no such relationship among adults [75] or pediatric patients [3,48,50].

Three studies reported greater compliance among whites than blacks [28,91,99] but four studies reported no such racial difference [53,67,75,83].

Income was correlated with compliance only for dental prophylactic behavior [99]; otherwise it was not correlated with compliance [26,28,31,46,68,75].

Social isolation was negatively correlated with compliance in two studies [81,89], although the relationship was not statistically significant in Porter's study ($p = .1$) [81].

Two authors found no correlation between intelligence and adherence [31,47].

One author reported higher compliance among Catholics compared to Protestants [104].

The findings with respect to marital status are somewhat confusing and conflicting. Among glaucoma patients, widows were found more compliant than married women, though the opposite was true for males [104]. Married women are more compliant with oral contraceptive use than single women [91]. Among patients over 60, married and single patients made fewer errors in self-medication than those who were separated, widowed or divorced (that is, those who had changed marital status) [89]. Another study had somewhat

conflicting results in that compliance was significantly better among patients who were married or widowed compared to those who were single, divorced or separated [83]. Three authors report no correlation with marital status [7,68,81].

Family stability was positively correlated with compliance in two studies [28,67] but was found to have no effect in a third [42].

Occupational level was found correlated with compliance in four studies [25,50,76,83] with those employed being more compliant than those not working and with those in skilled, clerical or professional positions being more compliant than those in unskilled positions. One investigator found no such correlations among chronically ill patients [26].

Working mothers were found correlated with poor compliance among pediatric patients [3].

Parity was found correlated with compliance with birth control medication in one study [91] and with prenatal iron pill taking in another [81].

Urbanites were found to undertake more prophylactic dental behavior than rural people [99].

In summary, with some conflicting results noted which may or may not emanate from special circumstances, it would appear that sociodemographic factors bear little or no relationship to compliance or noncompliance.

2.3.2 Disease Features (see Table 10)

As with sociodemographic factors, few investigations have demonstrated correlations of features of the disease, such as previous bouts, specific diagnosis, or even seriousness, with compliance and where correlations have been reported conflicting findings often exist.

The duration of the disease was not found correlated with compliance to therapy among farm people with cardiac conditions [20].

Only one author reported an association of previous bouts of the same disease with improved compliance [7] whereas four investigators reported that previous bouts did not affect compliance [18,20,67,96]. It is of interest here that one study found a significant correlation between recency of last attack of, and history of previous hospitalization for, rheumatic fever with compliance but only if the patient felt the attack was serious and that he was susceptible to a recurrence [50]. This relationship is discussed further in section 2.3.3 Patient Characteristics.

In studies which did not control for patients' perceptions, one study found previous hospitalization correlated with penicillin prophylaxis compliance among post-rheumatic fever patients [42] but in a second study it was found negatively correlated with compliance with psychotropic drugs among neurotic outpatients [65]. Several other studies, however, failed to demonstrate any correlation

TABLE 10: DISEASE FEATURES CORRELATED WITH COMPLIANCE

	CORRELATION BY REFERENCE		
FEATURE OF DISEASE	POSITIVE	NEGATIVE	NIL
duration			20
previous bouts	7		18,20,67,96
previous treatment	65		
previous hospitalization	42	65	47,67,68,83
positive family history			42
seriousness	26,42	13,65	18,67,83
diagnosis			18,47
symptoms		59	18

between previous hospitalization and compliance with therapeutic regimens [47,67,68,83].

Again, when objective seriousness of the disease is the feature examined, the association with compliance is discordant. Among chronically ill outpatients, those with the most severe disabilities were found most compliant but this finding could not be separated from the fact that these people invariably received more care and supervision [26]. Among post-rheumatic fever patients, one study found significantly higher compliance among those with cardiac damage [42] but a second study on patients with the same disease did not find any correlation [67]. A negative correlation was found in a group of pregnant women: those with initially low hemoglobins took oral iron less faithfully than those with normal hemoglobins [13]. Similarly, neurotic patients judged independently to have a poorer prognosis were found to default more frequently [65]. Two other studies failed to demonstrate any correlations: the extent of disease bore no relationship to adherence with antituberculous prophylaxis in one [83] and the severity of acute pharyngitis and/or otitis media was not associated with compliance in the other [18].

With respect to diagnosis, no correlation was found with compliance among psychiatric patients [47]. Unfortunately the study did not cite the evidence on which this claim is based.

Even the presence of symptoms has not been found positively correlated with adherence. The reported duration of symptoms among pediatric patients with acute streptococcal infections was not correlated with compliance with oral penicillin therapy in one investigation [18] and the presence of symptoms among patients with rheumatoid arthritis was actually negatively correlated with compliance with test medications including placebo in one controlled trial [59].

Thus any intuitively attractive hypotheses regarding relationships between disease features and patient compliance find little support in current studies.

2.3.3 Patient Characteristics (see Table 11)

In contrast to the negative or equivocal findings with respect to sociodemographic factors and features of the disease, the patient's personal perceptions of the disease, the doctor, and the treatment and his previous behavior with regard to compliance would appear to be important determinants of his adherence to prescribed medical regimens. The most concisely formulated verbalization of the relationship between a patient's perceptions and his health seeking activities is the "health belief model" of Hochbaum, Rosenstock and Kegeles. As reported by Haefner [46] the health belief model is an explanation of health behavior undertaken by a person with no symptoms. It has the following key elements: health behavior is related to

TABLE 11: PATIENT CHARACTERISTICS CORRELATED WITH COMPLIANCE

	CORRELATION BY REFERENCE		
PATIENT CHARACTERISTIC	POSITIVE	NEGATIVE	NIL
perception of			
-disease as serious	18,34,46,50,97,99	99	85
-personal susceptibility	7,28,46,50,99		85
-efficacy of therapy	7,46,50,59		42,85,99
-therapy as painful		85,99	
-doctor as friendly	34,62		65
satisfaction with doctor	7,23,62,75		
expectations met by doctor	34,62		
general attitudes towards health professionals and source of care	28		3,20,22,42,52
intention to take treatment			81,85
high work orientation		110	20
futuristic orientation	96	42	
influence of			
-family	49,78		22
-friends			20
resisting of treatment			
-children			3
-adults		26,94	
concurrent illness in family		67	18
compliance with other parts of regimen	22,88,104		17
"feeling well"		15,105	
feeling of "too much" medication		105	
knowledge of disease	28,97,99		8,42,96,104,105

1) the extent to which people feel they are susceptible to a disease; 2) how serious people think that the occurrence of the disease would be; 3) how beneficial people believe certain actions would be in reducing their susceptibility to or the severity of the condition in light of any barriers to taking the actions.

Several authors report the correlation of compliance with the patient's perception of seriousness of the disease [18,34,46,50,97,99], with the patient's perception of his susceptibility to the disease [7,28,46,50,99] and with the patient's perception of the efficacy of treatment [7,46,50,59]. One study found no correlation of any of these three things with compliance among college students urged to obtain a tetanus booster but the author felt that this was due to dislike for and inconvenience of obtaining the "shot" [85] and his findings are thus not inconsistent with the model. Two other studies did produce inconsistent results. In a study of dental prophylactic behavior, it was found that seeking prophylaxis was correlated with a feeling of low susceptibility to dental disease (here, again, perceived pain of treatment was found a deterrent of compliance), and it was found that the patient's feeling that dental prophylaxis is effective was not correlated with compliance [99]. Similarly, in a study of patients on rheumatic fever prophylaxis, perception of the efficacy of penicillin was not correlated with compliance [42].

An equally important perception on the part of the patient, it would appear, is that of satisfaction with the individual doctor: four studies reported a positive correlation [7,23,62,75]. However, attitudes in general towards health professionals and source of care were found to be correlated with compliance by only one investigator [28] with no correlation being found by five others [3,20,22,42,52]. At any rate, when the patient's expectations were met by the doctor, compliance was positively affected [34,62].

Oddly enough, intention to take treatment was not correlated with compliance in two studies [81,85] and general concern for health was similarly unassociated with compliance in two studies [20,31] though it was in a third [7].

A high work orientation was found negatively correlated with compliance among a heterogeneous population of post-myocardial infarct patients [110] but it was found uncorrelated with compliance among farm people with cardiac conditions [20]. A futuristic orientation towards life was correlated positively with compliance with the use of a safety glove among sugar cane cutters [96] but a fatalistic attitude among parents was correlated with compliance with rheumatic fever prophylaxis among children [42].

Family influence was found to be positively correlated with compliance in two studies [49,78] but patients in a third study did not admit to influence by family [22] or, in a fourth study, by friends [20].

Resisting treatment was not found to affect compliance among pediatric patients [3] but among adults it was given as a reason for noncompliance in two studies [26,94].

Concurrent illness among other family members was concluded to adversely affect compliance among pediatric patients on rheumatic fever prophylaxis in one study [67] but was not correlated with compliance in another study of pediatric patients on short-term antibiotics [18].

Patients who complied with one part of a regimen were found to comply with other parts in two investigations [22,88] but not in a third [17]; compliance with medication for a comorbid condition was found correlated with compliance with eye drop prescriptions among glaucomatous outpatients [104].

The most frequent reason given by patients for stopping medication in two studies was "feeling well" [15,105]. Another reason given was fear or dislike of taking "too much" medication [105].

A somewhat astonishing finding, especially in view of vigorous current efforts in the field of health education is that knowledge of disease has more often than not been found to bear no relationship to health behavior and compliance. One investigator found knowledge of disease to be a predictor of compliance but it was less potent a predictor than the patient's perception that the illness was serious and it

ceased to be a predictor under conditions of high experience with illness and under conditions of a high number of physician contacts for the current illness [97]. In a study of preventive dental health behavior, patients with high knowledge of dental health were more compliant [99] and in a study of patients on rheumatic fever prophylaxis, knowledge that penicillin controlled streptococcal infections was significantly correlated with compliance [28]. However, several studies, including one of rheumatic fever prophylaxis [42], found no relationship between knowledge and compliance [8,96,104,105].

To summarize then, the patient's perception that the disease is serious and that he is susceptible to it are strong correlates of compliance and his perception that the treatment is efficacious is a weaker correlate whereas perception that the treatment is painful is negatively correlated with compliance. Furthermore patient satisfaction with the therapist appears to be an important determinant of compliant behavior but knowledge of the illness does not.

2.3.4 Features of the Therapeutic Source (see Table 12)

Several studies of various features of the doctor-patient relationship and the therapeutic setting have done little to clarify the relationship of these aspects to compliance: the results of the studies have been inconsistent or conflicting. Two features stand out, however: first, the level of supervision is a strong correlate of compliance

TABLE 12: FEATURES OF THE THERAPEUTIC SOURCE CORRELATED WITH COMPLIANCE

	CORRELATION BY REFERENCE		
FEATURE OF THE THERAPEUTIC SOURCE	POSITIVE	NEGATIVE	NIL
level of supervision	32,33,39, 47,56		
therapist's prediction re compliance			16,18,25,26,75
the particular physician	17		18
private vs public physician	109		105
friendly approach of physician	34,62		65
active vs passive acceptance of patient	23,53		
doctor's attitude towards patient			65
"doctor-patient relationship"	31		20,22
use of persuasion to attend clinic		91	
regular vs surrogate physician	7,18		3
doctor's attitude re efficacy of therapy			56
amount of waiting time at clinic		31	
time between screening and referral appointment		32	
method of referral after screening	108,109 (see text)		

[32,33,39,47,56]; second, health professionals are unable to estimate the compliance of those under their direct care with better than chance accuracy [16,18,25,26,75].

Isolated or conflicting findings include the following. The particular physician was found to influence compliance in one study [17] but not in a second [18]. Private physicians had a higher drop-out rate for hypertensives but blood pressure control was better among those who remained than among public patients [109]; however, a second study found no correlation of compliance with private practice or public care among cardiac outpatients [105]. Parents of pediatric patients who perceived the approach of the pediatrician as friendly were found to have more compliant children [34,62] however "liking" versus "disliking" the physician was not associated with compliance among adult neurotic outpatients [65].

Active rather than passive acceptance of the patient and his statements by the doctor was correlated with compliance in two studies [23,53]. However, the doctor's attitude towards the patient was not associated with compliance [65] nor was his attitude towards the efficacy of treatment [56]. On a less specific level, the doctor-patient relationship was not related to compliance in studies of farmers with cardiac conditions [20,22] but drop-outs from a hypertension clinic gave as their main reasons for leaving the poor doctor-patient relationship and long waiting periods [31].

The use of persuasion to induce "needy" women to attend a family planning unit was associated with poor compliance when the persuaded group were compared to volunteers [91].

After blood pressure screening in the community, it was found that the longer the time between screening and the follow-up appointment, the smaller was the proportion of screeners who kept the appointment [32]. In another hypertension survey, the method of referral to a central hypertension clinic was also found to be important: the most effective referral method was a letter sent to the home; less effective was a phone call and less effective still was a message given verbally by a survey crew blood pressure technician [109].

2.3.5 Features of the Therapeutic Regimen (see Table 13)

Reports relating various aspects of the therapeutic regimen to compliance contribute only modestly to the understanding of the determinants of compliance and several are in conflict.

Four investigators report a decrease in compliance over time for both acute and chronic diseases [18,29,55,81] whereas three failed to observe this phenomenon [9,25,81]. Two explantions of many which may apply here are first, people stop taking their medications when they feel well [15,105]; second, careful analysis of compliance behavior reveals five patterns: 1. always compliant, 2. some-

TABLE 13: FEATURES OF THE THERAPEUTIC REGIMEN

	CORRELATION BY REFERENCE		
FEATURE OF THE THERAPEUTIC REGIMEN	POSITIVE	NEGATIVE	NIL
duration	20	18,20,29, 55,81	9,20,25, 81
cost of medication		15,26,105 109	68,76
type of medication	47,55,56,81		18,25,65, 72
type of behavior required	22,26,58 - (see text)		
complexity of regimen	22,88,98,104	17,20,34,89, 105	18
side effects		15,81,105	
use of safety dispenser		63	

times compliant, 3. never compliant, 4. compliant at start only, 5. noncompliant at start but later compliant [20]. Thus studies of compliance at one point in time will yield variable results depending on the proportion of each pattern observed and the interaction of each pattern with time and treatment. Furthermore, among individual patients duration may have opposite effects as is demonstrated in one study spanning four years [20].

Cost of treatment was found negatively correlated with compliance in four studies [15,26,105,109] but had no effect in two others [68,76].

Type of medication was stated to affect compliance in some studies but not others. Phenothiazines were significantly more associated with noncompliance compared to dibenzazapines [47]; chlorpromazine was more frequently taken than thioridazine [56]; imipramine was less well taken than placebo [81] and; PAS was less well taken than INH which was less frequently taken than streptomycin [55]. Among patients on PAS, however, different preparations of PAS had no apparent effect [25]. Conflicting findings include the facts that among psychiatric patients taking placebo, chlorpromazine, meprobamate, or phenobarbitol, there was no difference in compliance rate [72] and, similarly, in neurotic outpatients on meprobmate or placebo no compliance differential was observed [65]. Finally,

among pediatric patients, pill or liquid form of medications made no difference [18].

Two studies suggest that the type of behavior required of the patient is a determinant: among chronic medical outpatients, diets were found more frequently neglected than medication [26]; among farm cardiac outpatients, work recommendations were heeded more than diet recommendations and even more than personal habit recommendations [22] and; follow-up examinations of a cardiac work classification unit revealed that medical recommendations were more heeded than vocational or psychosocial recommendations [58].

Conflicting reports also exist with respect to the effect of complexity of therapeutic regimen on compliance rate. One study on peptic ulcer outpatients found a correlation between antacid intake and atropine intake but not between clinic attendance and atropine consumption [88]. In a descriptive study of glaucoma outpatients, those who took daily medications other than eyedrops were found also to take eyedrops faithfully [104]. Similarly cardiac outpatients who complied with work recommendations were found to comply more frequently with diet and personal habit recommendations [22]. Finally, patients for whom heavy medication and diet prescriptions were in effect attended clinic more faithfully than those for whom there were no such recommendations [98].

These findings suggest that the probability of compliance with a new therapeutic regimen is increased if a patient has previously shown compliance with therapy even if that therapy continues along with the new one. Compliance in the past is thus predictive of compliance with new or added regimens. Viewed from another perspective however, it appears easier for a patient to manage one therapy than two or more as the following studies demonstrate. Yet, whether this is due to increased complexity or sheer quantity or both remains to be seen.

Compliance with an ulcer diet was not correlated with antacid consumption in an inpatient study [17]. Among acute pediatric outpatients, compliance was less if three or more medications were prescribed or if both medications and medical procedures were prescribed [34]. Among chronically ill, elderly medical outpatients, errors increased as the number of medications increased from zero to three but decreased for those on four to nine medications [89]. Among cardiac outpatients compliance dropped off severely for patients for whom three regimens were prescribed as opposed to one or two [20]. Among outpatients on digoxin, concomitant use of a diuretic was associated with a significant decrease in the proportion of patients who stated they were compliant [105]. Only one investigator, studying pediatric outpatients on short term penicillin, found no effect of concurrent medications on compliance [18].

Three studies gave side effects as a reason for noncompliance among a relatively small proportion of patients [15,81,105].

In one study, the use of a safety container was associated with a significant decrease in compliance compared to the use of a regular container [63].

In summary, duration of therapy appears to be negatively correlated with compliance in general but adequate analysis is confounded by changes in compliance in both directions in individual patients. The cost of treatment appears to be a deterrent. Certain medication types appear to affect compliance. Pill taking, work change, diet change and personal habit change are successively more difficult for patients to handle. Complexity of regimen is negatively correlated with compliance but analysis is hampered by the finding that compliance with one regimen is positively correlated with compliance with additional regimens. Side effects and safety containers decrease compliance.

2.4 Strategies for Improving Compliance

Reports of attempts to improve compliance with medical regimens are scarce in the current medical literature and properly controlled clinical trials are distinctly rare. Nevertheless, a certain amount of useful information can be gleaned from the available data and applied directly or heuristically.

2.4.1 Patient Education

The prime strategy for improving compliance in current use is patient education. It takes a variety of shapes and forms and has been applied to a variety of clinical and health problems. Haefner [46], in a controlled trial, subjected volunteers to three films on cancer, tuberculosis, and heart disease, urging a periodic health check and roentgenogram. Compared to a control group who saw no films, a significantly greater proportion of the study group obtained both the check-up and roentgenogram while asymptomatic during the eight months following the study. The study group was found to rate their susceptibility to the diseases and the efficacy of treatment higher after they had seen the films (see 2.3.3). Glogow [40] randomized patients screened for glaucoma into one of five information groups including no information (appointment for follow-up given), minimal information, in-depth information, problem solving (minimal information plus helping with arrangements for follow-up appointment), with a fifth "overflow" group being sent to the receptionist for an appointment. There were no differences among the four information groups in attendance at the follow-up visit though compliance was significantly less for the group merely given an appointment by the busy receptionist.

Evans [29] used various types of messages, including 1. high fear, 2. low fear, 3. positive appeal,

4. recommendations only and 5. elaborated recommendations, to induce junior high school children to brush their teeth effectively. He found a significant increase in reported compliance among those receiving the "high fear" and "recommendations only" messages but objective measures revealed a significant difference in actual behavior among those given the "elaborated recommendations" and "positive appeal" messages. There was a substantial drop-off in compliance and attitudes over six weeks and there was no correlation between retention of information and either reported or actual behavior in any health message group.

Barnes [6] attempted to induce 80 recalcitrant school children in "urgent" need of dental care to go for treatment by sending randomly one of four messages to their homes. Message formats included 1. high fear, 2. low fear; 3. combined high-low fear, 4. control. Unfortunately 30% of his study group could not be located at follow-up six months later. Of those who could be located, there was no significant effect when all the persuasive groups together were compared with the control groups, nor when the three test messages were compared to each other though the trend in the three test groups was towards increased compliance.

Holder [52] tested the effect of message source on compliance among new mothers. He found that although patients felt it was more appropriate for nurses to give

the information (on baby and maternal care and family planning) their compliance was improved if the message was delivered by a mother with no medical training. Unfortunately, there was no comparison group to assess natural compliance rates in the absence of special education.

Radelfinger [85] used high fear, low fear and factual taped messages about tetanus in an attempt to induce college students to obtain a free tetanus booster shot. His compliance rates were so low that he was unable to draw inferences about differences between compliers and noncompliers.

Large scale multimedia educational campaigns to promote healthful behavior in whole communities have met with limited or no success. Suchman [96] observed a trend towards use of a safety glove by sugar cane cutters associated with high exposure to media (television, radio, newspapers) which had carried health education messages about the safety glove during a community safety campaign, however the result was not statistically significant. Robbins [86] found no discernable decrease in delay in seeking care reported by patients found to have cancer comparing results before and after a public anti-cancer campaign in New York urging check-ups.

Numerous other authors report the use of educational efforts to induce compliance in situations where compliance

is assumed to be especially poor such as in tuberculosis prophylaxis [9,25,55,82,83,84] and diabetes mellitus [94]. Unfortunately these studies are uncontrolled and other services such as home follow-ups are included so that the results are difficult or impossible to interpret.

2.4.2 Behavior Modification

Both classical and operant conditioning have had limited testing in medical outpatient settings, their major use to date being in psychiatric inpatient settings. Azrin and Powell [4] compared compliance rates with half-hourly pill schedules among volunteers using a regular pill container, a pill container with a three second buzzer attached to a timer and a pill container with a similar buzzer which rang until the subject shut it off. Compliance was significantly improved in the latter group. Meyer and Henderson [71] report the use of behavior modification techniques to promote diet planning, weight reduction, smoking reduction, and exercise increase among middle-aged volunteers considered at risk for coronary disease. The comparison groups were 1. doctor-consultation 2. doctor-consultation plus individual health counselling and 3. doctor-consultation plus behavior modification; the results favored the behavior modification group. Methodologic considerations make the results little more than heuristic, however, because the subjects were volunteers to begin with, the behavior modification group spent much more time with

their "therapists" than did the other groups, the enthusiasm of the therapists may have biased the results and the behavior modification programme was expensive.

2.4.3 Level of Supervision

The level of supervision seems an important variable in the determination of compliance. Irwin [56] found a progressive drop in compliance among psychiatric patients when he compared closed ward, open ward, and day patients. Finnerty and his associates [32] have demonstrated significant improvement in compliance in their Hypertension Detection and Follow-up Program (HDFP) trial when their patients are compared with those randomly assigned to a general medical outpatient clinic. The HDFP approach may be characterized as a flexible extension of supervision of care where warranted. Unfortunately, it is difficult to assess what part supervision plays and what part is due to improving the convenience, efficiency and continuity of the clinic in the latter study.

2.4.4 Tailoring

A multi-faceted approach to improving compliance which is at least in part an extension of supervision may be termed "tailoring". In this, medications are fitted to the patient's daily routine or rituals, appointments are fitted to daily schedules and the "tailor" acts both as a patient advocate and a supervisor. Several authors report the use of such tactics, frequently with consider-

able success. Anderson and his co-workers [2] report the return for "necessary" pediatric care of 95% of 79 previously recalcitrant families, with continued attendance of 70% over the following six months without further prompting. In a controlled prospective trial, two public health nurses achieved a trebling of compliance with such measures among acute care pediatric outpatients [33]. Although the study was uncontrolled for compliance levels, Gavron and his associates [39] describe the maintenance of a population of children on rheumatic fever prophylaxis with over 80% success over several years. Tactics utilized included: 1. establishing a good relationship between the clinic staff and children and their families namely through continuity of care provided by nurses rather than physicians; 2. maximizing efficiency of the clinic; 3. utilization of a "tolper" service (tracing of lost persons); 4. utilizing nurses as instructors and patient advocates; 5. allowing for home visits when necessary; 6. holding clinics at times which seemed most convenient for the most number of patients. Most of these procedures could be classified as fitting the service to the patient or tailoring. Finnerty's approach mentioned above is likely another example although his description of the process is not complete enough to permit any confident classification.

2.4.5 Modality of Referral

Reports of experience in community screening for hypertension have outlined useful procedures to improve compliance with follow-up appointments after the finding of elevated blood pressure. As stated previously, Wilber and Barrow [109] found that letter referrals resulted in greater compliance than telephone referrals or on-the-spot referrals by blood pressure technicians hired from the community. Finnerty and co-workers [32] discovered that 80% of those found hypertensive on screening failed to show up at a follow-up appointment when the appointment was scheduled one to two weeks ahead, but personal contact with people who failed to appear reduced the drop-outs to 29% of the total and, perhaps most important, scheduling the appointments within 24 to 48 hours was associated with a mere five percent drop-out rate.

2.4.6 Modality of Therapy

Alternate modes of therapy may be important with respect to compliance. Siegel and co-workers [91] found significantly higher continuation of contraception at a one year follow-up among women utilizing intra-uterine devices compared to those taking oral contraceptives. Unfortunately, the subjects were permitted to choose the method they used so that the study groups may lack comparability. In Bonner's study [13], women were randomly assigned to free

or self-payment prenatal iron therapy; a slight but statistically insignificant improvement in compliance was noted in the former group. In Feinstein's study [30] of rheumatic fever prophylaxis, the use of intra-muscular benzathine penicillin virtually eliminated compliance problems compared to oral penicillin groups. Similar improvements in compliance were reported by Ireland [55] with the use of intra-muscular streptomycin compared to the use of oral INH and/or PAS for tuberculosis prophylaxis. Within the oral medications, compliance seems to be better with certain preparations than others. As mentioned previously (section 2.3.5) compliance is poorer on thioridazine compared to chlorpromazine [56]. Additionally, if the complexity of a therapeutic regimen is negatively correlated with compliance, the use of combination preparations such as those of hydrochlorothiazide and reserpine or alpha-methyldopa for hypertension may significantly improve compliance though this remains to be tested.

2.4.7 Conclusions

Patient education seems to have short-term or negligible effects on compliance. By contrast, "tailoring", a flexible approach to fitting the treatment to the patient, appears to be a potent tool to improve compliance in outpatient settings. As might be expected, the level

of supervision is a direct correlate of compliance rate. Behavior modification programmes have not been adequately tested in medical outpatient settings but initial results appear encouraging. The medication modality may affect compliance, a finding that is useful mainly where alternative modalities exist. The effect of the combination medications on compliance remain to be tested. As for medication modality, the modality of referral as well as the time between referral and the follow-up appointment appear to be important determinants of compliance.

Patient education, tailoring and behavior modification will be discussed in greater depth in section 3 which follows.

3. RESEARCH DESIGN PART I

3.1 The Development of Compliance-Improvement Strategies

3.1.1 Introduction

The results of the investigations cited in the previous sections suggest that lack of compliance with therapeutic regimen is a problem of considerable magnitude. Further, several features of the patient and the therapeutic setting are strongly correlated with compliance, though the evidence is insufficient to establish causal links. Finally, relatively few studies have tested strategies for improving compliance and none of those cited has observed in a controlled fashion the effect of compliance intervention procedures among outpatients over an extended period of time. However, the available data suggest a number of promising approaches to improving compliance which merit extended prospective testing.

The remainder of this thesis is devoted to the development of a protocol for a randomized clinical trial of a series of treatment strategies which may increase compliance with drug therapy for benign essential hypertension.

Hypertension is an ideal disease condition for study for a number of reasons including these: 1. it is perhaps the most prevalent chronic medical condition existing in the

community; 2. in an untreated state even small blood pressure elevations are associated with awesome morbidity and mortality (100,101,102,103); 3. efficacious treatments exist for all levels of hypertension as has been dramatically demonstrated for both malignant (27,48,74,80,92) and benign essential (35,36,37, 100,101,102) hypertension; 4. because of the high prevalence of hypertension, its dearth of symptoms in its early stages and the recency with which efficacy of therapy has been demonstrated, substantial numbers of untreated hypertensives can be found within any population and followed prospectively as a cohort brought under treatment at the same time (Feinstein's "inception cohort") (38,64,66).

Described below are three separate tactics designed to improve compliance with antihypertensive therapy among newly treated hypertensives at a steel plant in Hamilton, Ontario. The reasons for the choice of the site and the fashion in which the individual strategies will be tested is outlined in the protocol which follows the descriptions. This two stage process, development of the specific tactics to improve compliance then development of a strategy for testing them, has been necessitated by the lack of clinical precedents in the study of compliance intervention.

3.2 Specific Proposals for the Improvement of Compliance among Hypertensive Outpatients

3.2.1 Introduction

Perhaps the most frequently tested strategy for improving compliance has been "patient education" in one form

or another. Few of the techniques used have been described clearly enough to permit the reader to assess the merit of their educational methodology. This is unfortunate because, for the most part, these studies have failed to demonstrate any lasting improvement in compliance and one would hope that the disappointing findings to date are the result of poorly designed or utilized educational methods rather than the inability of the human animal to respond adaptively to new knowledge about his health. It is on the former premise that potent behavior-oriented learning tools were developed for the proposed study.

A second strategy of compliance-intervention to be included in the study is that of behavior modification. To the author's knowledge this has not been formally described among free-living adult medical outpatients. Its use among humans is relatively new but it is presently being utilized with extensive success as a therapeutic tool in institutional settings and as a teaching tool in educational settings. Whether it can be utilized to modify the behavior of free-living populations is problematic; the rewards necessary to reinforce desired behavior can become exorbitantly expensive when a person has free access to inexpensive commodities which serve as rewards for institutionalized patients. Yet the development of this tool for just such situations would be an important addition to therapeutic armaments.

The final strategy to be tested is a technique here termed "tailoring". It is presently a nondescript process which fits treatment into the patient's existing daily routine and which attempts to make treatment, doctor visits, and other health-seeking behaviors as tolerable and convenient as possible. As reported previously (section 2.4.4), tailoring in one form or another has been applied with what would appear to be great success in a variety of clinical situations but it lacks careful characterization and has not been formally tested among chronic medical outpatients.

3.2.2 Patient Education

The philosophy underlying patient education is appealing: teach a patient about his disease and its treatment and he will be enabled to act appropriately and responsibly. If volition and intellect were one and the same this would no doubt be a useful concept. But one need only ask a smoker or alcoholic to recite the evils of his addiction to demonstrate the breadth of the split between knowledge and willpower or at least between knowledge and behavior.

Translation of knowledge into behavior is not always of the same magnitude of difficulty as in the extinction of the "bad habits". It is seldom difficult, for example, to teach a patient with angina pectoris to use nitroglycerine tablets. Unfortunately, however, health educators are frequently confronted with the problems of inducing healthful but unpleasant new behaviors such as regular dental visits or

regular pill-taking to asymptomatic patients. When the results of patient education for such purposes have been measured the findings have been far from encouraging when the end-point assessed has been actual behavior and the duration of effect has been taken into account (see section 2.4.1).

Educational psychologists have recently directed a great deal of interest and research towards the discordance between knowledge and behavior. One result is the currently popular teaching activity of expressing all educational objectives in terms of precise acts of behavior (for example, "write", "list", "select") rather than presumed and non-measurable cerebral states (for example, "know", "understand", "appreciate") [69]. It is clear that such activities are appropriate to the task of patient education when the goal is an overt behavior, namely compliance with prescribed therapy, rather than just knowledge of the medical problem.

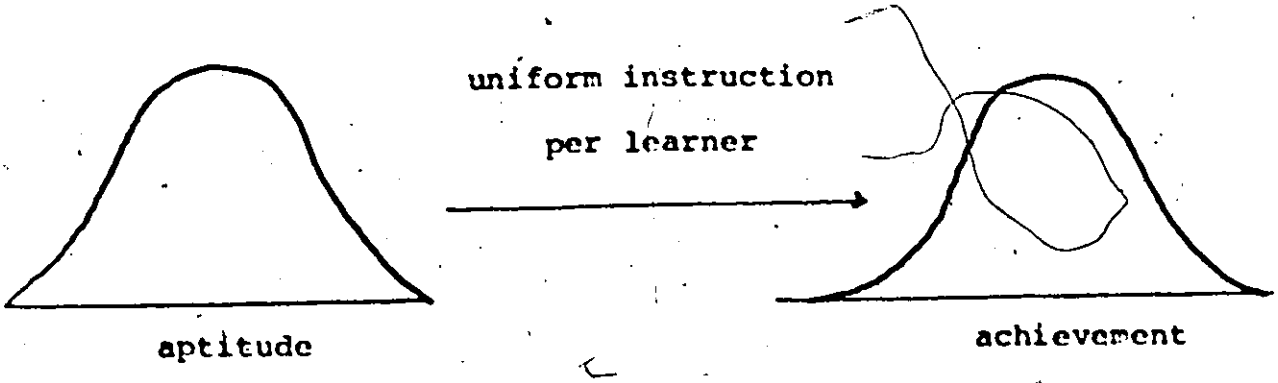
Two educational techniques which appear particularly suited to the achievement of behavioral goals are programmed learning, originated by B. F. Skinner [24], and a methodology termed "mastery learning", developed by B. S. Bloom [12].

The first, programmed learning, is claimed to be more efficient and effective than optimal classroom teaching because it gives frequent feedback and rewards correct answers to questions immediately. Prolonged application of

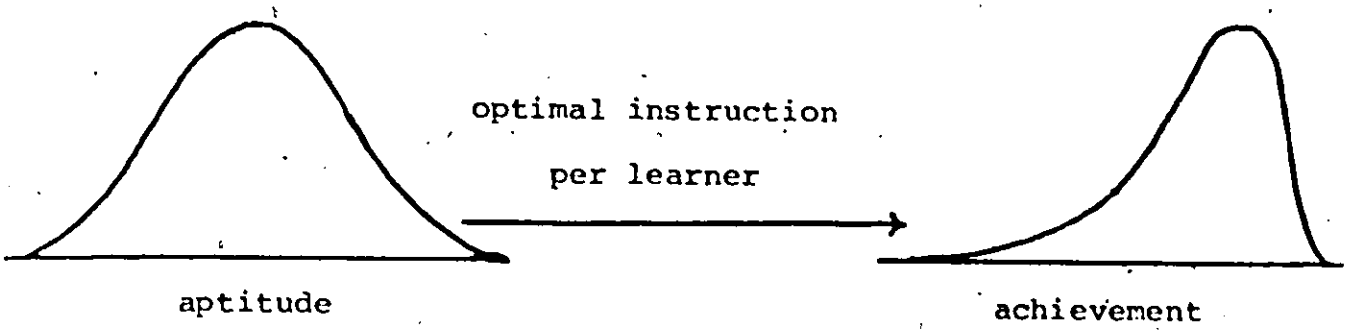
programmed materials has led to some disenchantment with their acceptability and success, but for short term learning tasks of a descriptive nature they are both inexpensive and effective.

The second technique, mastery learning, is a relatively recent development. It is based on two central premises. First, aptitude is defined as the amount of time required by a learner to attain mastery of a subject, the underlying assumption being that, given enough time, virtually every student can master instructional materials at any level of complexity. (It is worth noting here that most grading systems in present use reflect the expectation that only about 20% of students will achieve mastery, that is, attain "A's".)

Bloom's second premise begins with the assumption that, if aptitude is normally distributed and instruction is held constant as in the usual classroom situation, then achievement will be normally distributed:



If optimal learning techniques were utilized, however, Bloom theorized that it would be possible to move most learners into the high achievement (mastery) area:



The theory seems pedestrian until one considers that by "most learners" Bloom was referring to 95% of students, excluding only those with special learning disablities, and by "optimal instruction" Bloom was referring to strategies which can be applied within the classroom with the usual time and personnel constraints.

The strategies proposed by Bloom include:

1. defining objectives in concrete behavioral terms so that students know exactly what is expected of them;
2. using "formative" evaluation techniques which serve to provide frequent feedback to both students and teachers;
3. identifying, in advance, alternative learning methods and materials to be used if learning bogs down; and

4. providing small group teaching and individual tutoring only in circumstances where the first three tactics have failed.

In one classroom trial, applying the above methods, the proportion of students achieving "A"-level scores on the same examination which had been used in previous years to test students receiving conventional instruction increased from 20% to 80% in the first and 90% in the second year.

The techniques described above are said to be best suited to:

1. subjects which require minimal prior learning (or previous learning which most students already possess),
2. subjects which are best learned sequentially, and
3. subjects which tend to be "closed" (that is, requiring convergent rather than divergent thinking).

If mastery learning concepts are applied to the education of patients, it appears that one can predict a substantial increase in the knowledge of patients about their diseases. If a certain behavior is the objective of patient education then mastery learning, since it defines its objectives behaviorly, avoids the displacement of objectives from "behavior" to "knowledge". A major reservation persists, however; it is one thing to exhibit the behaviors "listing", "writing", "reciting", and it is quite another to "consume" four pills per day for life. The operational goals of

mastery learning to date have been confined to the mechanical act of regurgitating knowledge in some discernable form rather than to the performance of the dictates of that knowledge. Thus it remains to be demonstrated, in a project such as that proposed here, whether more than simple "printout" behavior can be effected by any learning technique when the goal sought is compliance with a medical regimen. On the other hand, patient education as a method of improving compliance cannot be dismissed until it has been shown in a methodologically sound investigation that the most powerful learning methods now available and feasible have failed.

For the proposed study, a programmed-learning package has been developed which includes a slide-tape presentation, a take-home booklet, and a back-up tutor (an educational assitant with no special training). An attempt will be made to have all patients achieve mastery learning levels in the following fashion:

A pre-test will assess the patient's initial level of knowledge ("entry behavior" [24]) and will give the patient an indication of what to expect from the slide-tape presentation.

The slide-tape presentation provides information about:

1) the definition of hypertension,
2) the frequency with which hypertension occurs,

3) a statement of the potential long-term effects if it is untreated,

4) a general review of therapy and its efficacy, which leads directly to and reinforces specific medication instructions from the clinician,

5) a frank discussion about the problems of maintaining compliance,

6) hints which the patient can utilize to make his pill-taking fit into his daily routine, and

7) a brief summary of the salient points.

The slide-tape show stops periodically for the patient to answer questions relating to the text. A post-test will be taken following the presentation and will be marked immediately by the educational assistant in order to diagnose areas of lack of understanding. "Criterion" performance levels will be determined in tests of the "educational package" prior to the initiation of the trial. The assistant can then direct the patient's attention to the appropriate part of the companion booklet and/or the slide-tape show. If supplemental quizzes reveal a remaining knowledge deficit, the patient will be referred for special tutoring by the clinic nurse who will provide alternate or simpler explanations leading to the same information contained in the slide-tape show. The educational materials will be translated into Italian and Croatian in order to accomodate the major linguistic groups at DOFASCO.

Post-tests will be administered periodically at two, four, and six weeks and monthly thereafter to these patients, to reinforce learning and to detect those who require reteaching. Achievement levels on various components of the material will be compared with compliance and blood pressure outcomes during the trial.

3.2.3 Behavior Modification

Both classical and operant conditioning techniques are being increasingly employed to modify human behavior. In "classical" conditioning, a neutral stimulus, for example a light, is presented an instant before a stimulus of some value to the subject, such as food ("unconditioned stimulus"). When the response normally evoked only by the unconditioned stimulus is triggered by the formerly neutral stimulus presented alone, the response is termed a "conditioned response" and the neutral stimulus, a "conditioned stimulus". This process may also be termed "signal learning" since the conditioned stimulus acts as a "signal" for the desired behavior. In operant conditioning, the response is rewarded or "reinforced" only once it has occurred. A positive reinforcer is anything which increases the frequency of the desired response (the author wishes to disavow responsibility for the circularity of the definition of "reinforcer"!). In procedural terms, the differences between these two conditioning techniques include the fact that, in classical conditioning the reinforcer (unconditioned stimulus) occurs

on every trial; in operant conditioning, the reinforcer occurs only when the correct response occurs and, even then, need be given only intermittently. Furthermore, in classical conditioning, the presentation of the reinforcer is followed by the response whereas in operant conditioning the response is followed by the presentation of the reinforcer. Empirically, it has been found that responses reinforced by operant conditioning are stronger, more frequent, and of greater duration than those of classical conditioning [24].

The instances where behaviorist techniques have been successfully applied to human subjects (psychiatric in-patients, the mentally retarded, institutionalized delinquents, and, more recently, school children) have one common feature: the behaviorist can control the subject's environment sufficiently that rewards or reinforcers for the desired behavior can be created from objects or activities which are taken for granted among free-living populations. Thus, rights and easily obtained commodities in the free world become privileges and inaccessible commodities in the conditioning environment, to be paid for with the currency of exhibiting the behavior required by the behaviorist.

Not only are inexpensive, legal, and appropriate rewards difficult to find among free-living populations, but it is also difficult to arrange a situation in which the person to be conditioned is not obliged to administer the rewards himself. No formal strategy has been developed, as

far as the author is aware, to induce outpatients, through operant conditioning, to take their medications in the exact dosage and schedule prescribed, although a group at Stanford University have used behavioral modification techniques to induce weight loss, decrease cigarette consumption and increase exercise with initially encouraging success [71].

For the proposed trial the following operant conditioning paradigm has been devised. One-third of the patients found to be noncompliant at the sixth month compliance check will be assigned, by random process, to the behavior modification group. These patients will be requested to purchase an inexpensive blood pressure cuff and stethoscope and will be issued a chart on which they will plot daily pill consumption and blood pressure. They will be instructed in the taking of blood pressure measurements and will be asked to follow the following procedure: at the time the morning medication is to be taken, the number of pills taken on the previous day will be recorded on the chart, then the morning medication will be taken, and then the blood pressure will be taken and recorded on the chart. Initially, the patient will visit a designated DOFASCO clinic nurse weekly. The nurse will measure his blood pressure and record it on his chart. If his compliance rate is high and his blood pressure is reduced she will praise his efforts and will refund a small portion (perhaps $1.00) of the cost of the cuff and stethoscope. Poor compliance will be admonished if blood pressure

remains elevated and the patient will be encouraged to do better; similarly, he will not receive a refund. If blood pressure is down the compliance rate will not affect the amount of reinforcement given even if compliance is poor; rather, the dose of medication will be titrated according to blood pressure response and the patient will be requested to record his pressure twice a day to insure that the reduction is sustained. Patients whose blood pressure response is insufficient despite adequate compliance will be referred to their physicians for further management. If a patient's blood pressure remains at a reduced level and his compliance remains good, the frequency of checks by the nurse will be reduced, eventually to the point where the patient is on his own save for checks when he visits his physician. In this way it is hoped his behavior will become progressively self-sustaining.

In this paradigm, the value of blood pressure as a reinforcer is uncertain. It may constitute mere "bio-feedback", the reinforcing value of which is in some doubt [11]. However, attempts will be made to give normal blood pressure a positive, (or more positive) value by associating it with reduction in risk factors, with praise and with a monetary reward at the time of the clinic checks.

It might be anticipated that some patients will resist the initial purchase of the cuff and stethoscope despite the possibility of "earning" their investment back.

If such patients fail to respond to noncoercive persuasion, rather than lose them to the study they will be "loaned" the cuff and stethoscope and be permitted to "earn" it in installments by displaying satisfactory compliance and blood pressure responses.

It is not known at this time if the monetary reinforcer is required for the success of the conditioning process. It is felt by a consultant in behavior modification, Dr. D. Streiner* that it may be necessary. Thus it has been decided to retain it in the paradigm with the intention of testing different components of the total strategy in the future if the complete "package" proves successful in this investigation. In any event, the behavior modification process will be less expensive to implement than tailoring, the other compliance-intervention strategy, because of the considerably lower use of costly personnel resources.

3.2.4 Tailoring

Whereas the theories of behavior modification and patient education have been extensively delineated, their use in outpatient settings as described here has not been studied and their future succes is thus uncertain. Quite the opposite is the case for the method known as "tailoring".

* Dr. Streiner, a clinical psychologist and statistician, is an Associate Professor of Psychiatry at McMaster. He is currently engaged in research in operant conditioning of blood pressure among patients with labile hypertension.

"Tailoring" is a tactic which has received fairly extensive utilization in one form or another by practising health professionals, frequently with apparent success, but little attention has been afforded it as a central issue in clinical therapy and its philosophy, strategies and impact remain largely undescribed (see section 2.4.4). Perhaps its most frequent application in academic settings has been in clinical research where the investigator has a vested interest in maintaining the study population and insuring their co-operation with therapy [31]. Accounts of the process under these circumstances are often limited to a few comments about making clinic visits tolerable, doling out transportation vouchers, and expressing gratitude to the clinic's public health nurse, "without whose devoted work the project would not have been possible". The omission of more detailed reports of this strategy is unfortunate; it may be argued that, for many if not most treatments, compliance may be as much at issue as is the efficacy of the treatment itself.

In view of the dearth of information, it is with some reluctance that the term "tailoring" is applied to the processes which are to be included in this clinical manoeuvre. Nevertheless, "tailoring" seems to describe best the main thrust of the tactic, and for purposes of this study it would appear to have the following attributes:

1. <u>Fitting medications to daily routine.</u> Here the "tailor" obtains from the patient a description of his daily

routine or "rituals". The taking of medications is then attached to any constant features. For example, a man who shaves every single day of the week will be advised to keep a supply of his pills next to his razor, taking his dose as he picks up his razor.

2. Fitting appointments to activity schedule. Doctor's appointments often clash with a patient's work or recreation. Simply finding the most mutually convenient times for doctor-patient interactions should reduce barriers to compliance with appointments.

3. Acting as a "patient-advocate". Many logistical problems such as transportation, babysitting, waiting interminably at the clinic and budgeting for medications can be managed relatively easily. Additionally, patients who have doubts about therapy or about what is expected of them may have difficulty verbalizing this to the physician, or may feel that their problems are too unimportant to discuss with the physician. The tailor can facilitate the answering of the patient's questions and can alert the clinic staff to any additional problems or doubts the patient is having with therapy.

4. Acting in a "reinforcement" capacity. Sufficiently close contact is maintained between the patient and tailor for the tailor to be aware of any change for

the worse in the patient's compliance pattern. When such changes are detected the tailor can seek out any underlying problems, become more actively encouraging, and alert and recruit the help of the clinic staff if necessary. (It is this exploration for, and solution of, problems causing poor compliance which distinguishes tailoring from operant-conditioning.)

The above is not intended to be exhaustive, but attempts to characterize the tailoring approach as flexible, individualized and opportunistic. The general principles imply that compliance depends at least in part on the degree to which therapy capitalizes upon rituals and avoids disruption of the patient's life style and daily routine. It appears from the studies cited that the tailor can be a person without formal medical or other health professional education.

In the proposed trial, one-third of noncompliant patients detected at the sixth month check will be randomly assigned to the tailoring group. The tailor will see these patients individually and make an assessment of the patient's daily rituals, life style, financial situation, stated reasons for noncompliance and the like, according to a fixed format which is presently being developed. The only prior information supplied to the tailor will be the patient's next clinic appointment and his medication schedule. Thereafter, it will be the task of the tailor to help the patient comply, within these guidelines.

a. no coercive, threatening, or authoritarian tactics are to be used

b. the tailor must not give out medical information, but may facilitate the exchange of such information by arranging doctor-or-nurse-patient interactions.

c. the tailor will refrain from personal, political or religious interactions with the patient.

For the purpose of describing, classifying and analyzing these tailoring interactions, the tailor will record all problems discussed and solutions offered according to a fixed format.

4. RESEARCH DESIGN PART II

4.1 A Protocol for Testing Compliance-Improving Strategies

4.1.1 The Research Objectives

Within the population of untreated hypertensive male employees of the Dominion Foundries and Steel Company (DOFASCO) of Hamilton, Ontario, it is proposed to investigate these questions:

1. What are the relative effects upon compliance with antihypertensive therapy when this therapy is provided from different clinical sources:
   a. physicians in the employee health service at DOFASCO ("industrial care") and
   b. these employees' family physicians in the community ("community care")?
2. In both of these clinical settings, what is the effect of special educational programmes upon compliance with drug regimens?
3. Among those patients exhibiting reduced compliance after an initial therapeutic induction phase of six months, can individual compliance be improved by either of two additional clinical strategies, here termed:
   a. "tailoring" and
   b. "behavior modification"?

Thus the objective of the research project is to test a series of clinical strategies which are designed to increase compliance with drug therapy for hypertension, thereby improving the effectiveness of treatment for this disease.

To this end, clinical end-points will include measures of compliance and blood pressure reduction. In addition, absenteeism and social and emotional function will be assessed among the study subjects.

4.2 The Study Site

DOFASCO (Dominion Foundries and Steel Company) is a unique industrial setting for relevant clinical research:

a. Due to a profit-sharing plan, introduced in the depression, in which an employee may receive in excess of $130,000.00 at retirement, employee turn-over is exceptionally low. The resulting study population possesses the stability necessary for follow-up studies.

b. Hiring policies at DOFASCO are extremely liberal with respect to health status. For example, all job applicants with diastolic blood pressures less than 115 mm Hg are eligible for employment, and individuals whose blood pressures subsequently exceed this level remain DOFASCO employees, their specific job in the mill being modified only in the case of an incapacitating cardiovascular event or the appearance of drug-induced postural hypotensive symptoms.

c. DOFASCO has a remarkably active employee health service which provides assessment and care for job-related trauma and industrial hazards. In addition, and consistent with the close relationship that exists between "management" and "labour" in this non-unionized company, a system has been established whereby each employee is eligible for a comprehensive periodic health examination (P.H.E.) every 18 months, including a physical examination, blood pressure determination and E.C.G. Participation rates in this P.H.E. programme exceed 95% of eligible employees.

d. Pilot investigations have revealed a growing, but generally low, level of initiation of antihypertensive therapy by community physicians among hypertensives employed at DOFASCO. In 1970, as a result of the P.H.E. programme, 100 letters of referral to community family physicians were made for hypertension; a subsequent follow-up revealed that only four patients were seen by their family physicians. In 1971, 100 similar letters resulted in 20 physician-patient interactions. As a result of these pilot studies, it is estimated that less than 10% of the known hypertensives at DOFASCO are under treatment at the present time.

e. It is believed that anti-hypertensive management can be carried out at the DOFASCO site, by DOFASCO clinicians:

(1) both labour and management encourage the development of programmes designed to reduce the morbidity and mortality of workers;

(2) the clinic has health records dating back up to 20 years on DOFASCO employees;

(3) the clinic staff see many employees more frequently than the employees' personal physicians do; and

(4) the clinic is convenient in its location and in that it can be utilized on company time.

Preliminary discussions between DOFASCO physicians and individual community physicians have indicated the acceptability of the concept of "industrial care" to the private sector. It should be emphasized that it is not the intention of the DOFASCO physicians to compete with or to duplicate existing health services. The employee health service physicians simply wish to assess their ability to initiate and maintain appropriate antihypertensive therapy in those hypertensives, who are not presently receiving this care from other sources.

Mention must be made of the possibility that the programmatic treatment of hypertension as would be the case at DOFASCO may constitute a method of improving compliance. The report of Finnerty and his coworkers [32] indicating the initial success in improving complaince with antihypertensive therapy of their Hypertension Detection and Follow-Up (HDFP) center suggest that the disease-specific approach may, indeed, increase adherence to treatment. However, most reports on compliance from "specialty" clinics (see section 2.2.) including previous experience in Finnerty's hypertension clinic

[31] do not lend support to this view. Rather, the superior HDFP results in Washington, D.C., may be interpreted as due to a combination of several measures utilized there including special convenience for the patient, extended supervision and some aspects of "tailoring".

With respect to treatment at DOFASCO, it would be difficult to replicate a more convenient setting for the patient. Appointments are arranged by the clinic staff on Company time and patients are bussed back and forth from their work location on a clinic bus.

While it can be expected that this will virtually eliminate complete dropouts from therapy, just what the effect will be on compliance with prescribed medication remains to be seen.

In any event, the uniqueness of the therapeutic milieu at DOFASCO would greatly reduce the generalizability of compliance observations there. Consequently, as is further outlined below, patients will be randomized to treatment at DOFASCO ("industrial care") or treatment through regular sources of primary care in the Hamilton community ("community care").

With respect to current medical services in Hamilton, the city is fortunate to have an adequate complement of primary care physicians, a substantial proportion of whom are actively involved in both community affairs and their own continuing education and this has facilitated the development of a new

medical school, the principle focus of which is primary care. The results of the study within this group of patients receiving their care from local , general and family practitioners can be expected to be representative of those which might be obtained from any community with adequate to good primary medical care services.

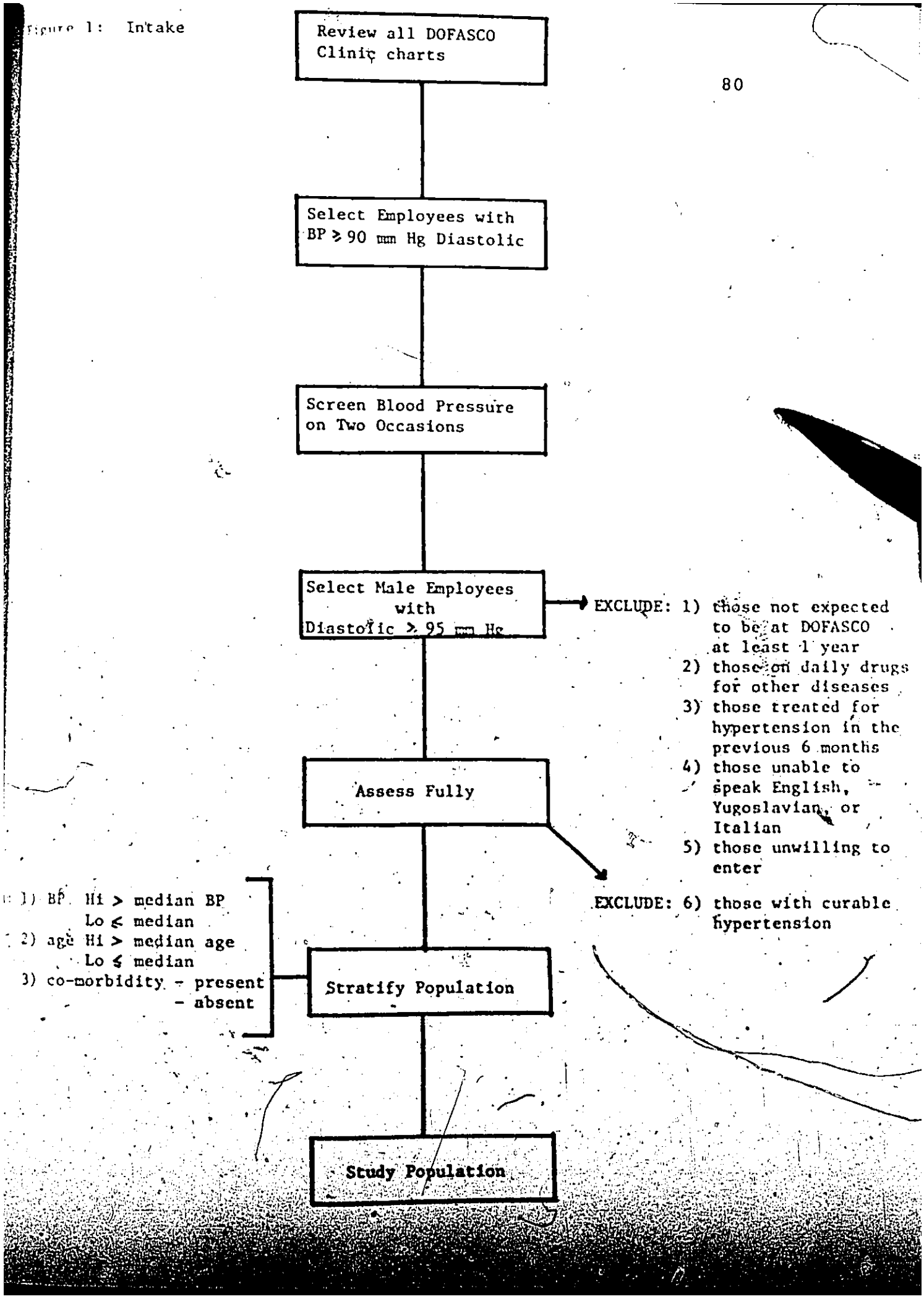
4.3 Methods of Procedure

The method of procedure for this study is described in four parts. The first part, "Intake", deals with the the initial six months of the trial in which 1) community care is compared with care at the employee health service ("industrial care") and 2) special educational techniques are assessed within segments of each group for their effects upon compliance rates. The third part, "Phase I Evaluation and Phase II Intake", describes the methodology of the first assessment of target variables and the process by which Phase II group is defined. Fourthly, in "Phase II", the procedures of two additional clinical strategies for improving compliance, and their use within the Phase II study population, are described. At the end of this section, a statement describes the estimation of the relevant sample sizes.

4.3.1 Intake

Intake procedures are outlined in Figure 1. All DOFASCO employees have a thorough historical review, physical examination and laboratory study prior to employment and over

Figure 1: Intake



95% undergo re-examination periodically therafter at approximately 18 month intervals. A clinic nurse, Mr. Patrick Farrelly, has taken a special interest in cardiovascular fitness and blood pressure and over the last four years virtually every employee has had one or more careful blood pressure determinations depending on the duration of his employment. Thus by reviewing the clinic charts, all employees with elevated blood pressures can be detected.

Employees discovered in the chart review with diastolic blood pressures at or above 90 mm Hg will be further assessed, and those meeting the following qualifications will become the study population:

1. male. The study population has been restricted to males because a) the proportion of female employees at DOFASCO is very low (less than 10%), b) hypertension appears to be a much more benign condition in women than men, and c) the efficacy of antihypertensive therapy has not been demonstrated for women as yet.

2. Dofasco employees with no expected termination of employment for the year following the initiation of the study. Exclusion of employees expecting job termination, whether for reasons of retirement, temporary position, or personal plans, will facilitate maintenance of the study population. It should be reaffirmed that maintenance is not expected to be a difficult problem at DOFASCO; the staff turnover rate is less

than 1% per annum, due largely to the profit-sharing plan described earlier.

3. No treatment for hypertension for at least six months prior to intake into the study. Men who are receiving treatment for hypertension are excluded from the study because a) the continuity of their care may be disrupted by placing them in the trial and b) they will have established a compliance pattern which diminishes their comparability with others who have not [7,97,104]. On the other hand, it is frequently the case that hypertensive patients not currently under active therapy have been treated some time in the past, and to exclude these people would compromise both the size of the study population and the clinical relevance of the study results. It is possible that the reason for cessation of therapy among previously treated hypertensives was low compliance, suggesting that these men will have lower than average compliance rates in the study. Therefore, subjects will be stratified by previous therapy prior to randomization, and the subsequent data analysis will be performed separately for them, being pooled with that of other subjects only if similar patterns emerge.

4. No conditions aside from hypertension requiring long-term daily medications. Those employees with other chronic conditions requiring continuing medication are excluded from the trial because it has been frequently demonstrated that

compliance decreases with the increasing complexity of a medical regimen.

5. Diastolic blood pressure remaining at or above 95 mm Hg. Blood pressure evaluations will be made on at least 2 separate occasions by a trained blood pressure technician, using the recently modified Garrow "random-zero" device [111], with the patient sitting, at rest, at least five minutes in a quiet room.

6. Able to speak and read English, Italian, or Croatian. The languages cited constitute the three most frequent languages spoken at the mill. It is felt that the additional effort necessary to accomodate other language groups for the interviews and compliance-intervention strategies in a study of this size would be excessive, in view of the small additional numbers likely to be included by such efforts.

7. No surgically remediable form of hypertension. The reasons for this are self-evident. The assessment for remediable forms of hypertension will take place during the comprehensive intake evaluations described below. The protocol for this assessment is identical to that used in the HDFP of The National Institues of Health; this protocol was developed by a group which included Dr. Harriet Dustan of the Cleveland Clinic, Dr. John Laragh of Columbia University, and other acknowledged authorities in the evaluation and management of hypertension.

A potential candidate for the study population as selected from the chart review (see figure 1) will undergo two brief screening sessions at the DOFASCO mill where his status with respect to the first six admission criteria will be established by observation (1), direct questioning (2, 3, 4), blood pressure recording (5), and questionnaire testing for literacy (6). Following these screening sessions, all those found hypertensive (diastolic measurements at both screenings at or above 95 mm Hg) will be so informed. Those who fail to meet any of the remaining five criteria will be offered the choice of assessment and treatment at the employee health service or referral to the physician of their choice; in any event, they will be excluded from the trial but the numbers of employees so excluded will be recorded. Those who meet the first six admission criteria will be informed of the full nature of the trial, any attendant risks which might be involved, and what would be expected of them if they chose to participate. The individuals involved in the investigation would enjoy freedom from assault and the ability to withdraw from study at any time. All personal information from the trial would be kept strictly confidential. The potential gains from new knowledge and from antihypertensive therapy arising from the trial have been carefully weighed and it has been concluded that they vastly outweigh the risks to the participants. Those who do not wish to participate will be offered the same alternatives as those who do not meet the entry criteria.

Those consenting employees who are eligible for the study population will undergo a comprehensive evaluation including an interview questionnaire assessing health attitudes and knowledge of hypertension; medical history; physical examination; chest X-ray; IVP where indicated (by history of renal trauma or disease, abnormal urinalysis, BUN, or creatinine); EKG; and appropriate laboratory investigations including Hemoglobin, white blood cell count and differential, platelet count, erythrocyte sedimentation rate, urinalysis and urine culture, BUN, serum creatinine, serum uric acid, serum electrolytes, SGOT, alkaline phosphatase, and where indicated by physical examination, 24 hour urine for catecholamines, plasma cortisol levels, and one and two hour post glucose load blood sugar. Those found to have remediable forms of hypertension will be referred for appropriate care. Once again, this clinical evaluation will follow the protocol developed for the HDFP trial of the National Heart and Lung Institute.

Personal physicians of members of the study population as constituted above will be identified at this point. These physicians will be fully informed of the nature of the trial and will be invited to participate and to permit their patient to participate. The stated role of the community physicians will be to treat those patients referred to them through the trial in whatever way they see fit. They will be fully informed of the periodic independent checks (see below) of blood pressure

control and compliance and likewise informed that their patients may receive special patient education or may be entered into the compliance-intervention study should their compliance rate fall below a certain level (namely, taking at or less than 75% of their prescribed medication). A complete summary of the initial assessment will be sent with each patient referred, and the physician will be asked to record any side effects encountered by the patient during the course of the trial, including signs, symptoms, and laboratory abnormalities.

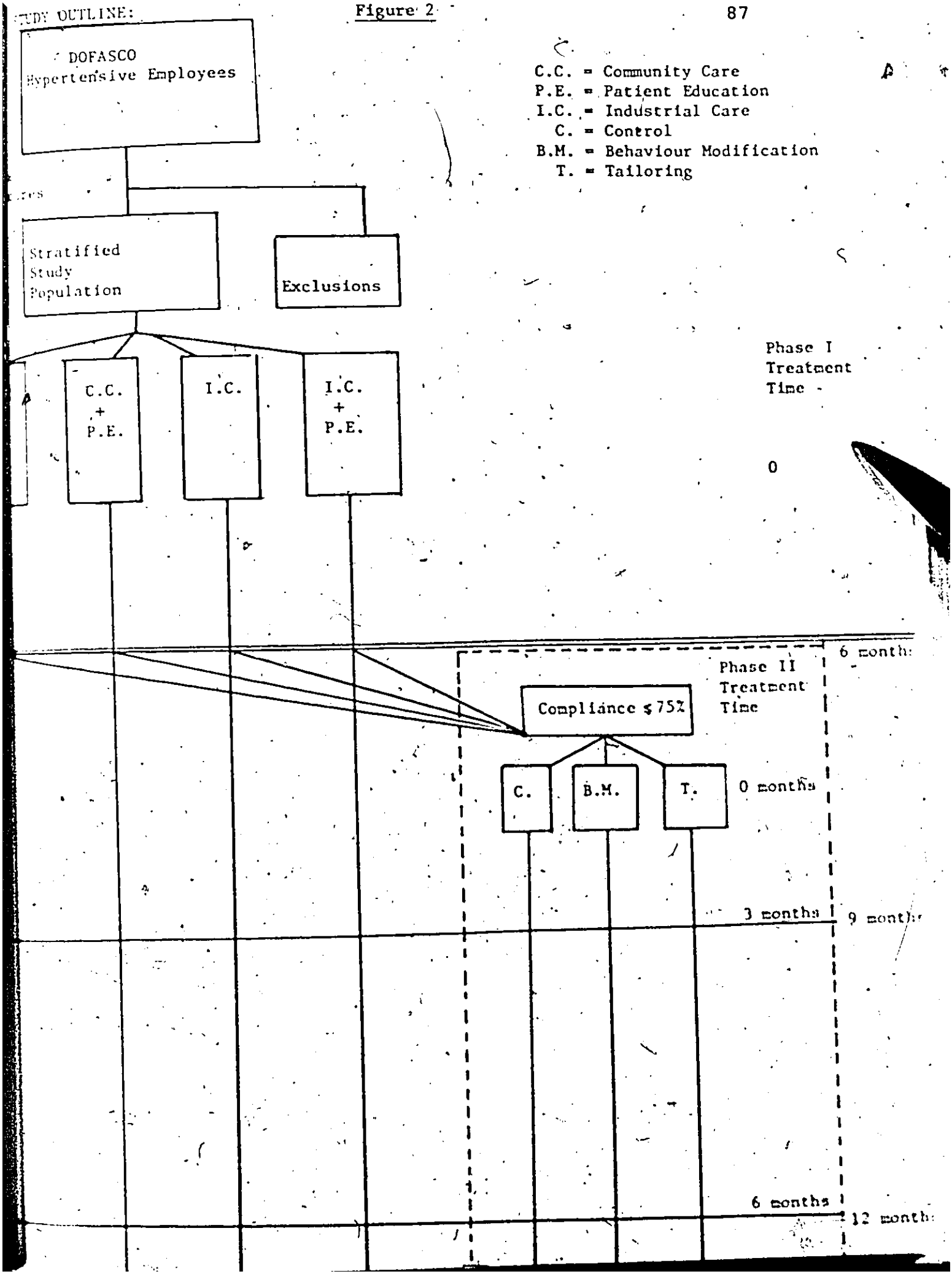
With the study population and the community physicians defined, and full information provided to both groups, consent will be sought from both the study subjects and their community physicians. For those from whom consent is obtained (subsequently referred to as the "study population"), the intake is complete and the study proper can commence. Potential subjects who refuse to participate (or whose community physicians refuse to participate) will be excluded from the study, but maintained in a follow-up group.

4.3.2 Phase I.

Phase I is outlined in Figure 2. On the basis of data collected during the intake procedures, the study population will be stratified according to the following attributes:

STUDY OUTLINE:

Figure 2



1. Diastolic blood pressure.

The population will be divided into "high" and "low" hypertension groups according to the relationship of individual diastolic pressures to the median diastolic blood pressure for the total group (determined as the average diastolic reading from the two screening sessions).

2. Age.

The group will be divided into "high" and "low" age groups by virtue of the relationship of their age (as of their last birthday) to the median age of the group.

3. Comorbidity.

The group will be divided into those with and those without comorbidity, defined here as the documented presence of diabetes mellitus, gout, ischemic heart disease (including a clear cut history of angina pectoris and/or myocardial infarct), thyroid disease and peptic ulcer. Explicit clinical criteria are being developed for these conditions.

4. Prior antihypertensive drug therapy, as outlined earlier.

The possible interaction of these independent variables with the primary target variables is sufficient to warrant the above stratification. Initial blood pressure elevation is related to the amount of medication required, and thus probably to both compliance and the occurrence of side effects; age is related to morbidity, and possibly to responsiveness to therapy, but not directly to compliance in these age ranges; comorbidity

is related to contraindications for certain forms of therapy, complexity of drug schedules, and confounding of symptoms with side-effect assessments.

The study population will be allocated to the phase I treatment groups by random process within the strata, thus insuring: 1. even distribution of members of a given stratum among the treatment groups and 2. treatment groups of equal size.

The four treatment groups in Phase I are 1. community treatment; 2. community treatment plus special patient education; 3. industrial treatment; and 4. industrial treatment plus special patient education. For those patients assigned to community care, the study staff will arrange the first appointment for the patient and will send along a summary of the findings of the initial assessment. Thereafter, medical therapy will be entirely at the discretion of the community physician; however, depending upon the randomization, the patient may receive, in addition, special patient education during the first six months of the trial, or tailoring or behavior modification during the last six months. In any event, the physician will be informed if his patient is to be subject to these procedures, and his prescribed therapy would serve as the compliance goal to be achieved by the procedures.

"Industrial treatment" involves antihypertensive therapy administered through the employee health service at DOFASCO:

Treatment at DOFASCO will generally follow the "stepped care" protocol which is presently in use in the National Heart and Lung Institute's hypertension intervention trials. In stepped care, as described in Appendix 2, therapy begins with a long-acting thiazide diuretic. If response is inadequate, other antihypertensive medications such as reserpine, alpha methyldopa and quanethidine are added to, or replace, the previous medication in a fixed order until a satisfactory blood pressure response is attained or intolerable side effects are incurred. Intolerable side effects would include any symptom, sign or abnormal laboratory test which the physician feels warrants the cessation or reduction of the medication. This would include orthostatic hypotension causing syncope despite caution in assuming erect posture, rashes believed due to drug allergy, blood dyscrasia believed induced by medication, lupus-like syndrome for hydralazine, depression or peptic ulceration for reserpine, evidence of liver damage (jaundice, increased SGOT) for alpha methyldopa, or impotence if this is felt by the patient to be an intolerable side effect. A copy of the modified stepped care protocol and a description of potential side effects and procedures to be followed if they occur is included in

"Special patient education" (see Section 3.2.2), consists of a programmed self-instruction package in a slide-tape and booklet format, utilizing behaviorly defined

objectives and "mastery learning" methods which purport to maximize the probability that the student will master the material being taught. Patients will be taught about hypertension, the efficacy of treatment, the problems of compliance, and methods of facilitating their own pill taking.

The package is in the pre-testing stage at present. It is anticipated that the formal instruction period would take 30 minutes. An educational assistant will be hired part-time to assist patients with the material and to evaluate their progress. Periodic checks at one week, two weeks, four weeks, and then monthly will be made to evaluate retention of material and reinforce learning. If a patient slips below a criterion level (to be established in pre-testing) he will go through the programme again.

Patient education is placed in the first part of the study because it is the most frequently advocated and utilized method of improving compliance, because it is the least expensive of the intervention techniques, and because there is reason to believe it is the least effective of the three clinical strategies. With respect to the latter point, if patient education fails to improve compliance, larger groups will be available for testing the two remaining strategies in the second part of the study, Phase II. This may or may not be an important consideration, depending on the "natural" compliance rate among patients before any compliance intervention has been attempted.

Patient education will be assessed in both community and industrial settings because it is felt that the determinants of compliance may vary within each setting. For example, if patients treated at DOFASCO miss fewer appointments because of the convenience of the clinic, more frequent changes in therapy may be incurred and more side effects may ensue, resulting in decreased compliance. A second reason for allocation into the four groups as specified in Phase I is that this balances the factorial design, facilitating statistical analysis of the results.

Stepped care will be used routinely only in the industrial care group because it is considered neither feasible nor desirable to impose this protocol on the community physicians: at the very least it would tend to alter the present nature of community care and thus reduce the general applicability of the information gained from this side of the trial.

With respect to comparisons between groups, community care will be used as a standard against which to measure industrial care. The comparison will not be strictly against existing and usual forms of treatment, since the community physicians will be aware of the nature of their participation in the trial. This knowledge is ethically imperative if the permission of the physician is to be obtained for his patient to be entered into the compliance-intervention aspects of the trial. In any event, this situation has the

advantage of being methodologically "conservative", because it reduces rather than augments the chances of demonstrating a difference between community and industrial care.

The effect of patient education will be assessed by contrast to the appropriate control group in both the industrial and community care settings which will receive no special education beyond that given routinely by the physician.

4.3.3 Phase I Evaluation and Phase II Intake

Once Phase I has been initiated, it will continue uninterrupted for a period of five months. It is intended that this will permit sufficient time for most patients to reach and settle into a steady state with respect to blood pressure control and medication type, dosage, and schedule. Study subjects will undergo Phase I Evaluation when they meet the following criteria:

1. on antihypertensive medication for at least five months
2. on a constant type, dosage, and schedule of medication for at least one month and/or for two consecutive clinic visits, whichever is the greater in time
3. in any event, within six months from the first visit of a patient to his physician (whether in the industrial or community setting).

The reason for the first criterion has been stated above. The second criterion has been added to increase the likelihood

that patients have attained a steady state at the time of evaluation. Since all physicians will be aware of the time constraints of the trial, it will be assumed that they consider their patients in a steady state if they make no change in medication at two consecutive visits in the time period leading up to the fifth month of treatment. Regardless of the first two criteria, all patients will be assessed by the sixth month from their initial therapeutic contact as it is felt this is a reasonable amount of time for most patients to reach control.

The Phase I Evaluation will be performed by an independent team comprising a research assistant and a registered nurse with special training in blood pressure assessment. The team members will not be involved in patient management and will not know the treatment or education groups to which individual patients belong.

Each subject will be classified according to three primary target variables: 1) blood pressure, 2) compliance rate with medication, and 3) side effects. It is clear that the short term aim of any antihypertensive medical regimen is blood pressure reduction. In addition to this target, the present study concerns itself with the extent to which lack of adherence to prescribed medications is associated with lack of blood pressure control and the extent to which various strategies designed to improve compliance can affect both compliance rate and blood pressure reduction. Side

effects are emphasized as a primary target variable because it is felt that the benefits of full treatment and increased compliance may be offset partially by more frequent side effects than are found under usual treatment conditions.

Additional parameters to be considered include short-term changes in function such as:

1. absenteeism - initial studies at DOFASCO indicate that absenteeism increases when a man is labelled as hypertensive and is further increased when therapy is added. While it can be anticipated that short-term absenteeism will be offset by a reduction in long-term absenteeism and employee loss due to hypertension-related morbid and mortal events such as stroke and congestive heart failure, DOFASCO would like additional documentation of this phenomenon.
2. changes in psycho-social function (see below). This aspect of the study will be developed and arranged by Ms. Jana Mossey, a doctoral fellow in Epidemiology at the University of North Carolina.

Compliance rates will be assessed through a combination of procedures including:

1. questioning the patient directly in a non-threatening manner.
2. pill count. The patient will be requested to bring his pill containers to the second blood pressure assessment.

3. comparison of amount of medication prescribed and the amount purchased. For the duration of the trial, patients will be requested to purchase their medications at the DOFASCO clinic pharmacy. Additionally, duplicate copies of all prescriptions will be sent in by the community and DOFASCO physicians to the study staff. This would permit calculation of any discrepancies between prescribed and purchased medication. Furthermore, since the medication will be purchased by patients at standard prices, it will be assumed that medication purchased is likely medication consumed at least for the first and subsequent prescription refills.

4. urinary excretion of riboflavin. Since all medications will be purchased at the same pharmacy (at the DOFASCO clinic) it may be possible to "label" the medications with riboflavin. This is a harmless substance which fluoresces in the urine for up to 12 hours after its ingestion. The first blood pressure check of the Phase I Evaluation will not be announced until the day of evaluation. Urine samples will be collected at the visit.

It should be noted that none of the compliance measures gives an exact rate (10,41,43,44,51,54). A patient's accuracy cannot be relied upon, if only because memory is fallible. Purchase of medication does not necessarily result in consumption. The presence of riboflavin in the urine does

not indicate the number of pills a patient is taking per day, nor the proportion of days on which he is taking his medication as directed. Pill counts at an isolated point in time, especially when that time is known in advance by the patient, can also be unreliable. The application of these measures together, however, may be expected to give a fairly accurate picture, particularly if there is accord among the various measures and the patient's/blood pressure is taken into account. For the purposes of the study a patient will be considered compliant if, 1) he has purchased more than 75% of the prescribed medication; 2) he states he has consumed, on the average, more than 75% of the prescribed medication; 3) he has riboflavin in his urine on the unannounced check; and 4) his pill count shows that more than 75% of the medication is missing since the prescription was last filled. If a discrepancy occurs in these four measures, the following will obtain:

1) if a patient has not purchased more than 75% of his medication at the DOFASCO clinic pharmacy and it can be ascertained that he did not purchase it elsewhere, then he will be judged non-compliant regardless of what compliance rate the other measures indicate;

2) if a patient admits to consuming 75% or less of his medication then he will be judged non-compliant;

3) if riboflavin is absent in the urine, the patient will be considered compliant only if the other measures all

indicate compliance; and

4) a patient will be judged non-compliant if his pill count reveals less than or equal to 75% of his prescribed medication missing since the last refill date. Every effort will be made to be as discrete as possible about assessing an individual's compliance rate, though no deception is intended.

Side effects will be assessed by questioning patients directly about symptoms including vertigo, gastrointestinal upset, rashes, fevers, depression, or orthostatic lightheadedness and syncope, fatigue, double or blurred vision and so on, as outlined in the symptom questionnaire from the HDFP trials. Additionally, physicians will be polled concerning side effects they have observed in their patients, and blood tests will be done including hemoglobin, white blood cell count and differential, platelet count, erythrocyte sedimentation rate, serum uric acid, and random blood glucose level.

Finally, the interview questionnaire which was originally administered to assess health attitudes, self-perception, marital adjustment and knowledge about hypertension will be readministered. Any patients found non-compliant will also be asked directly, in a matter-of-fact, non-threatening manner, why they did not comply.

At the completion of the Phase I Evaluation, a group of patients will be defined with these features:

1. blood pressure above "control" level (above 90 mm Hg diastolic, average of two readings)

and 2. compliance rate unacceptable (≤ 75% of prescribed medication consumed)

and 3. free from intolerable side effects.

This group will be entered into the Phase II trial. The remainder will be dealt with as follows:

1. those with: a) adequate blood pressure control (< 90 mm Hg Diastolic) and b) without intolerable side effects will persist with their original source and course of therapy, regardless of compliance rate, and would be re-checked at nine and 12 months

2. those with a) inadequate blood pressure control but b) judged compliant, with or without intolerable side effects, will be referred back to their physician (whether at plant or community) with a summary of their findings.

3. those with intolerable side effects will be referred back to their physicians with an appropriate summary of their findings regardless of their blood pressure or compliance rate.

Patients entering Phase II will continue to receive antihypertensive therapy from their original source as well. Physicians of patients entering this trial will be sent a summary of the Phase I Evaluation findings and a note that their patient(s) will be entering the compliance-intervention study.

4.3.4 Phase II

In this phase, the relative effectiveness of two additional techniques designed to improve compliance will be assessed. Patients fulfilling the above entry criteria will be stratified according to:

1. compliance rate. Patients will be divided into "poor" and "moderate" compliance groups using median compliance rates, as determined by the Phase I Evaluation, as a divider.
2. source of therapy, industrial or community.

They will then be allocated randomly within the strata to one of three groups:

1. tailoring
2. behavior modification
3. control - no additional intervention

Tailoring and the behavior modification paradigm have been described in Section 3.

In Phase II, results will be assessed by contrast with two comparison groups. Firstly, patients will enter the phase with a known and unacceptable compliance rate, thus acting as their own controls. Secondly, a third of the patients will be assigned to a parallel control group which receives no additional intervention. This group is included to cover the possibility that the compliance rate has not stabilized as expected at the six month mark of the study. Additionally, it will permit the assessment of any side effects induced by increasing compliance in the intervention groups.

The health attitudes questionnaire will be omitted from the ninth month evaluation as it is anticipated that the temporal proximity of this assessment to the sixth month evaluation will result in stereotyped responses to the questionnaire.

The final assessment will also include a re-evaluation of end-organ status, other morbidity, absenteeism, and mortality. This will be performed by a clinician who is "blind" with respect to the location of the subject's care and the nature of compliance-intervention measures, if any.

In addition to the above measures, it also planned to obtain precise cost factors for the components of clinical evaluation of these hypertensives, their clinical management, and the clinical strategies for modifying their compliance with therapy. This economic analysis will permit an assessment of the benefits, in terms of compliant, controlled hypertensives, and the costs (including possible increases in short term absenteeism) of the intervention programme.

Several points in the design as described bear further scrutiny. For example, is five to six months a sufficient time period to demonstrate any differences between community and industrial care? It is felt that any differences in the number of patients treated and under adequate blood pressure control which fail to appear by six months are likely not clinically important. However, a second question might be of more relevance: if differences in results appear

for the two sources of therapy, how long can they be sustained? Obtaining the answer to this question is partially confounded by introducing the compliance-intervention techniques six months after the trial begins. However, only those patients whose blood pressure is not controlled and who are not compliant will enter Phase II and of these one-third will be assigned to a control group which will not be subject to compliance-intervention. Thus the design flexibly adapts to the relative success or failure of the Phase I treatment modalities and a proportion of patients including a control group of non-compliers will be followed without interruption for up to one year.

Taking the opposite perspective, does it make sense to wait six months before utilizing the strategies designed to achieve compliance? Why not give patients a "head start" and prevent them from slipping into poor compliance patterns? There is perhaps no clear cut solution to this "preventive" versus "remedial" treatment issue. The decision favoring a remedial approach is based on three points. First, if patients who will utimately prove to be non-compliant cannot be identified prior to the initiation of therapy, then compliance-inducing techniques must be applied to all patients, incurring inefficient use of expensive resources. Second, tailoring and behavior modification are to be used to induce compliance to a specific treatment schedule (as prescribed by the individual's physician) and their introduction before

a somewhat stable schedule is achieved would necessitate changes in their application which would be confusing for both staff and patients. Finally, the strategies themselves are to be evaluated: the sample sizes required to demonstrate any effect are reduced by eliminating those whose compliance is already adequate because this reduces variance within the sample and increases the potential gain in compliance.

4.3.5 Sample Sizes

The calculation of appropriate sample sizes for the study is based on data collected from preliminary studies at DOFASCO and on a number of assumptions and clinical judgments as outlined below:

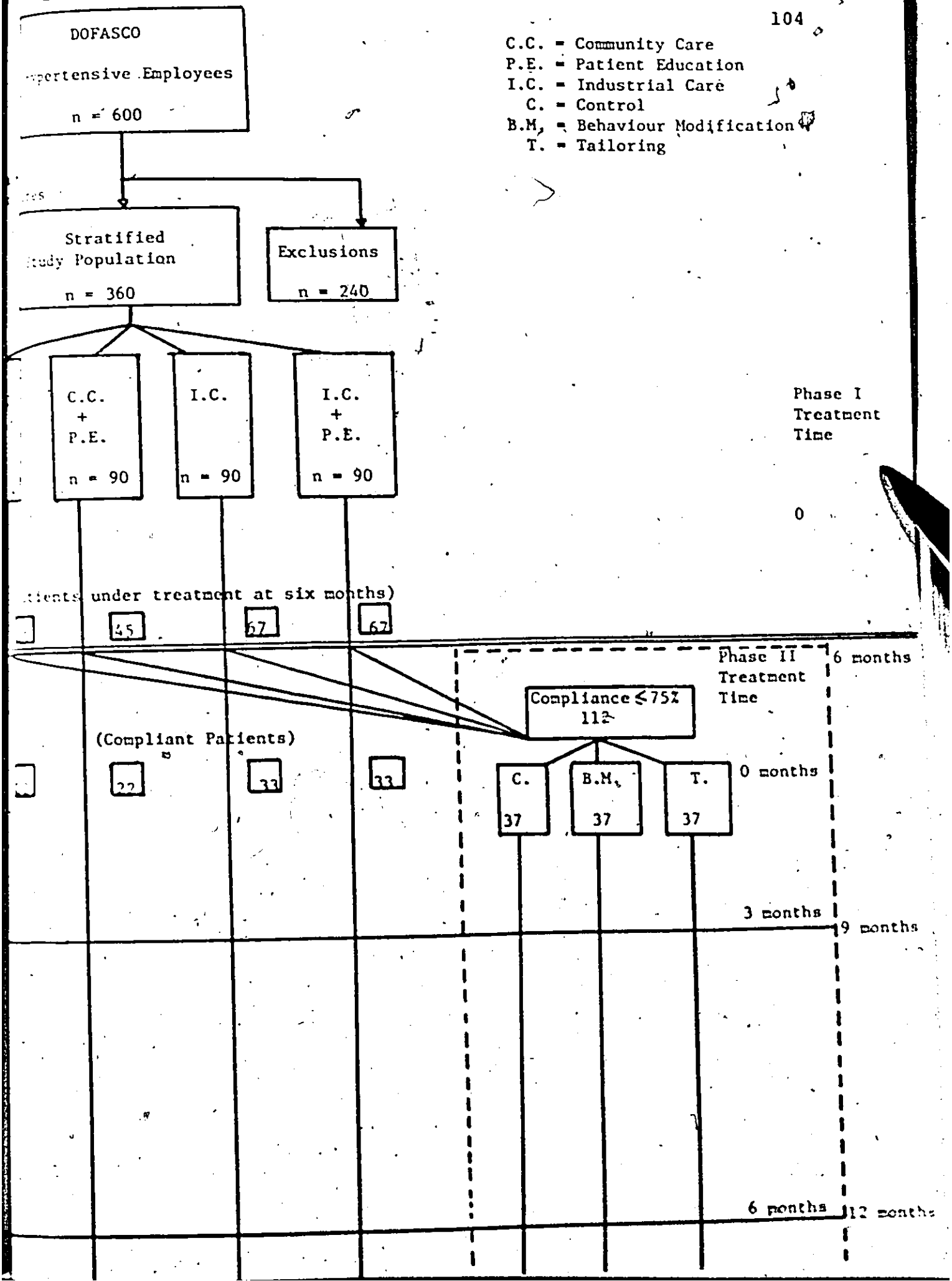
1. Of the 600 known hypertensives at DOFASCO approximately 10% are under active treatment. This is the best estimate of Dr. E. Gibson, one of the DOFASCO physicians. This would leave about 540 potential candidates for the study population.

2. Of these 540 potential candidates, approximately one-third will be excluded by the admission criteria (see figure 3). Those still eligible would then number 360. Thus for treatment groups of equal size, each of the 4 Phase I groups would have 90 members.

3. Of those patients who are referred to community physicians approximately 50% will receive antihypertensive medication. There is no way to estimate this figure with great confidence. Previous experience at DOFASCO indicates that less than 20% of referrals are ever seen. However, for

STUDY OUTLINE:

Figure 3



the purposes of the study, the active participation of the community physicians will be sought and an initial appointment will be set up for each patient. Even given full participation on the part of community physicians, however, some patients may not keep this initial appointment, others may drop out after initial visits, and still others may experience a blood pressure reduction without therapy. If it does occur that 50% of referred patients are eventually placed on antihypertensive medication, then 90 of the initial 180 patients assigned to community care will reach Phase II within the treatment programme, assuming no positive effect of patient education. (Any positive effect of patient education would increase this figure.)

4. Of the patients referred to care at DOFASCO, it is expected that 75% will be placed on antihypertensive medication. Patients who refuse therapy or whose blood pressure falls without drug treatment would, of course, not be under therapy at the start of Phase II. However, the convenience of the DOFASCO clinic and the stated intention of the DOFASCO physicians to place everyone on therapy when it is medically indicated favour a higher proportion of patients treated pharmacologically. If these figures apply 135 of 180 patients assigned to industrial care will be under treatment at the sixth month evaluation. Any positive effect of patient education would increase this figure.

5. For those patients begun on antihypertensive medication it is estimated that 50% will be "compliant", defined here as taking more than 75% of prescribed medication. Compliance rates in Davis' review of the literature [23] ranged from 15% to 93% and in Marston's review [70] from 0% to 96%. Several studies show that somewhat under 50% of patients are compliant [78,88,94,109]. The 50% figure has been adopted because a. it safeguards against overestimating the number of patients available for Phase II studies and b. it maximizes the variance to be used in calculating the necessary sample sizes required to demonstrate differences in the proportion of compliant patients (assuming a binomial distribution). The same compliance rate is assumed to apply to both community and industrial treatment groups. More rigorous treatment in one group or the other may well be met by increased resistance on the part of the patients whether for increased side effects or inconvenience, despite increased supervision.

6. In order to attain a clinical conclusion that "patient education" is successful in improving compliance it is felt that an absolute increase of 25% in the proportion of patients rated compliant should be achieved. Thus, if 50% of the patients in the comparison group are compliant, the proportion among those receiving special education should be at least 75%.

7. At the sixth month check the average compliance rate of those patients found "noncompliant" (≤ 75% of pills

consumed) will be 40% of pills consumed. Again it is not possible to predict an average compliance rate so a figure has been chosen which seems reasonable and which very nearly maximizes variance and thus maximizes the number of patients required to demonstrate differences between the compliance-intervention techniques and the control group.

8. It is judged that a meaningful improvement in compliance rate in the two groups, tailoring and behavior modification, is 25%. Thus if the average compliance rate in the control group is 40%, the rate among those receiving tailoring or behavior modification should be at least 65% if the techniques are to be termed successful. Using assumptions 1. through 5. the number of patients available for each part of the study are recorded on figure 3. It should be emphasized that these are felt to be the minimal numbers available.

The number of patients in each treatment group required to establish the clinically meaningful changes cited above, may be calculated as follows:

a. Community Care versus Industrial Care

To evaluate the proportion of patients brought under treatment, the minimal number of patients available for the appropriate comparison groups is 180 in each. If significance is tested at the 5% level ($\alpha = .05$) with a probability of success of 80% ($\beta = .20$, a 25% difference in the proportion of patients brought under treatment can

be demonstrated with a sample size of 45 (for a difference between 50% and 75%) in each group.

To test the proportion of patients brought under control (diastolic blood pressure < 90 mm Hg) among those treated $\alpha = .05$, $\beta = .20$, a 25% difference (50% - 75%) can be demonstrated with sample sizes of 45. As shown on figure 3, the minimal numbers available are 45 and 67, ignoring the patient education groups.

b. Patient Education

Again with $\alpha = .05$, $\beta = .20$, to detect a meaningful difference of 25% in the proportion of patients compliant with therapy, (50% to 75%) sample sizes of 45 would be necessary. The available numbers, shown on figure 3, are 45 and 67, in the respective treatment groups.

c. Tailoring and Behavior Modification

Here individual average compliance rates, rather than proportion of patients compliant, will be studied. It is assumed that individual compliance rates, among the patients found noncompliant, are normally distributed from 0% to 75% (the defined cutoff point) with a standard deviation of 15%. The standard error of the means of each of three groups (control, behavior modification, and tailoring) with n = 37 would be about 2.5. For pairwise comparisons, of the intervention groups and the control group, the standard error of the difference of the means would be approximately 4 which means that the 25% difference being

sought on clinical grounds would be detected with ease. Actually, patients may be used as their own controls, since their compliance rates before intervention will be known, and within-group comparisons will greatly increase the sensitivity of the comparisons, permitting much smaller differences than 25% to be detected. This, however, would be of academic rather than clinical interest.

The foregoing determinations clearly indicate that all aspects of the study are feasible.

It should be noted that the expected size of the study population, about 360 men, is insufficient to demonstrate a significant difference between the various treatment groups in terms of morbidity and mortality over the 12 months of the study. In the Veteran's Administration studies, for example, the difference in morbidity between the treatment and placebo groups for diastolic pressures in the 90-114 mm Hg range was accumulated at a rate of about 10% per annum [61]. In this proposed study, if compliance rates are relatively similar in the community and industrial treatment groups, any differences in morbidity would relate to differences in numbers of patients brought under treatment and differences in blood pressure control; it is not anticipated that these differences will result in a significant difference in morbidity at least in the short term of the trial.

d. Significance of this Research

The importance and relevance of the proposed research is underscored by a consideration of the following issues:

1. Hypertension is a disorder of high frequency (10 - 18% of North American male population) which is a major contributor to disability and untimely death.

2. Although the efficacy of antihypertensive therapy has been established, the effectiveness of clinical treatment is impaired, in large part, because of the failure of hypertensives to comply with therapeutic regimes.

3. The multi-center trial of stepped-care in hypertension (HDFP) being conducted in the U.S., although promising to provide additional evidence for the effectiveness of antihypertensive therapy, does not systematically explore strategies for improving compliance with drug therapy.

4. The results of the project proposed here would be directly applicable to the clinical management of substantial numbers of Canadians.

5. STATISTICAL ANALYSIS

The first part of the trial, Phase I, is designed in a two-by-two factorial fashion. That is to say two factors, source of care and special patient education, are to be measured for their effects on the outcome variables, namely, blood pressure control, compliance with prescribed medication, side effects, absenteeism and psychosocial adjustment.

This design is statistically economical. For example, if one observation, say of compliance, is made at six months on each patient for each of the source-education combinations, comparisons of the mean effect of the source of care can be made on the basis of observations made on patients assigned to both education and no education, that is all patients in the trial. Additionally, comparisons of the mean effect of patient education can be made on the basis of observations on all patients. To get the same precision with a non-factorial design one would have to choose one source of care and make observations on a sample size of patients equivalent to the entire study complement. This would give no information about source of care and a second experiment of equal sample size would have to be performed to give this information.

Thus many more patients than in the factorial design would be required. Furthermore, the two experiments would not yield direct information about the interaction between source of care and patient education.

Perhaps the most appropriate statistical tool for the factorial design as outlined here is termed "analysis of variance". It is inappropriate to use simple pairwise comparisons of the four group means for at least two reasons. First, six pairwise comparisons are possible for four means but only three such calculations can represent independent orthogonal comparisons, with any further comparisons constituting re-use of the data. The use of linear contrasts with analysis of variance permits the selection and analysis of the three most appropriate comparisons, in this case patient education versus no patient education, community care versus industrial care, and interactions between source of care and patient education. Second, the precision in estimating the variance gained by the use of the factorial design will be diminished if only those measurements in the two groups being compared are used. This loss is regained by the use of a pooled variance as is permitted by the use of analysis of variance techniques (provided, of course, that variances within the groups are similar when the end points are assessed at six months).

In analysis of variance, the overall variance of all observations is separated into parts, each of which measures variability attributable to a specific source,

here within each of the four study or "treatment" groups and among the groups. The dispersion of variances is due to any differences in the means of the study groups since it is assumed that the variances of groups from the same population are equal and normally distributed.

Statistically significant dispersion is evaluated through the "F" distribution. That is, depending upon which comparisons are of interest, the variances of the appropriate groups are compared to the pooled within-group variance and the ratio of the variance is compared to an F distribution with k-1, N-k degrees of freedom where k is the number of groups compared, N is the total number of observations, k-1 is the degrees of freedom due to the groups, and N-k is the degrees of freedom within all k groups. Examples of this mode of analysis are contained in Appendix 1. Here ficticious data are presented for 10 study subjects in each of the four study groups for individual compliance rates at six months and analysis of variance tables are calculated accordingly.

The use of analysis of variance techniques requires two conditions aside from those mentioned. First, the numbers in each treatment group must be approximately equal. The randomization process used in the trial ensures that this standard will be met. Second, the variables to be analysed must be continuously distributed and their components must be additive. Most of the study variables

satisfy these criteria. However, compliance rates are expressed in terms of proportions. As such they are distributed between 0 and 1 and violate both criteria: they may not be continuously distributed and cannot be partitioned into additive components save, as an approximation, when each proportion is near 0.5. While the average compliance rate may be expected to be close to 0.5, the proportions for individual patients can be expected to vary widely (in fact, from 0.0 to 1.0). However, this problem can be obviated by transforming the proportions to a scale where the effects are likely to follow a linear law. A number of simple transformations are available and an arcsine transformation has been chosen for the example in Appendix 1.

In the second part of the study, Phase II, the original factorial design is abandoned. The study population is assessed for rate of compliance and two populations, "compliant" and "noncompliant" are formed accordingly. Stratification prior to randomization will ensure the even distribution of compliance rates and source of care among the intervention groups for the noncompliant population and the design is again, at least potentially, factorial, with the factors being source of care and compliance-intervention technique.

If the Phase I groups yield equal numbers of noncompliant patients then factorial integrity will be

achieved and analysis of variance methods will once more be applicable. However, drop-outs can be expected to be more numerous in the community care groups and it may be that compliance rates with medication may differ among the groups for those who remain under treatment. Additionally, the pre-randomization stratification does not take into account the use of patient education in Phase I, on the assumption that this will have no effect; if it does have an effect, the yield from the patient education groups will differ from that of the other groups. Furthermore, the group sizes for the intervention part of Phase II can be expected to be small (approximately 40 in each) so that the formation of source of care cells (and patient education cells) within the intervention groups would necessitate comparisons of small numbers of patients. Finally, comparison of the intervention groups with those groups within the compliant population are desirable but the design can no longer be considered factorial for the purposes of statistical analysis when these non-intervention groups are included because the assumption of random assignment is violated.

Analysis could proceed along several different lines depending upon the outcome of these eventualities. For instance, if sample size permits and the comparison cells are of roughly similar size, analysis of variance techniques would still be appropriate. Any effect of patient

education could be accommodated by pre-randomization stratification, with randomization designed to create even distribution of the "education" and "no education" patients among the intervention and control groups. If cell sizes prove to be very small it may be possible to combine cells within groups for the purposes of analysis. For example, it may be found that source of care has no effect on those patients found noncompliant. In this event, source of care can be dropped from the analysis and these cells combined. Alternatively, non-parametric tools such as chi-square can be exercised if the numbers are small. It should be noted here that assessment of compliance prior to entry into the intervention groups and re-assessment following intervention permit before-after comparisons within each of the intervention groups; this will greatly increase the sensitivity of analysis to detect changes in compliance rates.

Numerous alternate methods are available for the assessment of data generated by the study. For example, if numerous factors prove to be of importance in the determination of compliance, the use of multiple regression analysis is appealing. However, it is the avowed intention of the author to keep the analysis of these data as simple as is consistent with statistical and clinical relevance.

6. SUMMARY

Compliance with prescribed therapy when that therapy is to be self-administered is a problem of substantial magnitude in virtually all outpatient circumstances as is attested to by a growing scientific literature. While concern is mounting about the attendant decrease in effectiveness of therapy due to lack of compliance, methods of intervention are presently inadequate, impractical or insufficiently tested.

Three strategies for compliance-intervention are described in the preceding text and a proposal for their testing among hypertensive employees of a steel mill is presented. This research design is presently being implemented.

Effective and practical methods of compliance monitoring and intervention hold the promise of improved clinical management of those medical conditions for which efficacious self-administered treatments exist.

APPENDIX 1

Examples of Statistical Analysis

Table 14 which follows contains fictitious data for the compliance rates for ten subjects in each of the four Phase I study groups. The appropriate calculations and analysis of variance table (Table 16) follow thereafter.

The experimental hypotheses would be tested in the following fashion:

1. Hypothesis: The population means in the study groups are equal.
2. H: $\mu_1 = \mu_2 = \mu_3 = \mu_4$, the means for all four groups are equal.
3. Level of significance: $\alpha = 0.05$.
4. Test statistic is F, the ratio of the mean square for means ("among", Sp^2) to the mean square for within groups (Sm^2).
5. On the assumption that the observations are randomly selected from normal populations with $\sigma_1^2 = \sigma_2^2 = \sigma_3^2 = \sigma_4^2$ (homogeneous variance) and that the hypothesis is true, the distribution of $F = F(K-1, \Sigma n_i - K)$.
6. The critical region is $F > F_{1-\alpha}(K-1, \Sigma n_i - k)$.
7. Compute F and see whether or not it falls within the critical region.

8. Accept or reject the hypothesis.
9. State the conclusions for the experiment.

For example, for the transformed compliance rates as shown in Tables 14 and 16:

1. Hypothesis: The population mean compliance rates in the study groups are equal.
2. H: $\mu_1 = \mu_2 = \mu_3 = \mu_4$
3. $\alpha = 0.05$.
4. Use $F = S_m^2/S_p^2 = .12138 / .41363 = .29345$ (from Table 16).
5. If the assumptions are satisfied, the sampling distribution of F is F(3,36).
6. Reject if F>3.54, the 95 percent value of F(3,36).
7. F is not in the critical region.
8. The hypothesis is accepted.
9. There is not sufficient evidence to reject the hypothesis of no difference in the mean compliance rates of the study groups.

Similarly the source of care, patient education, and interactions between source of care and patient education can be assumed to have no effect as is demonstrated in Table 16.

For added clarity, a table of means (Table 17) and visual display (Graph 1) finalize the analysis.

Table 14

(Fictitious) Compliance Rates Among the Four Phase I Treatment Groups for Ten Subjects

	Community Care				Industrial Care			
	Without Education		With Education		Without Education		With Education	
	% compliance	2 arcsine $\sqrt{p}$	% compliance	2 arcsine $\sqrt{p}$	% compliance	2 arcsine $\sqrt{p}$	% compliance	2 arcsine $\sqrt{p}$
	80	2.21	96	2.74	80	2.21	85	2.35
	60	1.77	80	2.21	30	1.16	90	2.50
	50	1.57	70	1.98	96	2.74	96	2.74
	90	2.50	40	1.37	100	3.14	98	2.86
	70	1.98	50	1.57	80	2.21	88	2.43
	0	0	90	2.50	88	2.43	90	2.50
	70	1.98	94	2.65	70	1.98	92	2.57
	92	2.57	94	2.65	80	2.21	30	1.16
	90	2.50	70	1.98	84	2.32	40	1.37
	88	2.43	30	1.16	30	1.16	50	1.57
T_i	690	19.52	714	20.81	738	21.58	759	22.04
n_i	10		10		10		10	
$\bar{y}_i$	69.0	1.952	71.4	2.091	73.8	2.158	75.9	2.204
S_i		43.371		46.201		49.999		51.861
T_i^2/n_i		38.104		43.301		46.557		48.580

$T = \Sigma T_i = 83.95$ $\quad$ $CF = T^2/N = 176.177$

$N = \Sigma n_i = 40$

where: 2 arcsine $\sqrt{p}$ represents the transformation of the proportional compliance, p.

T_i = column total

n_i = number of observations in each column

$\bar{y}_i$ = mean of column observations

T = grand total

N = number of all observations

CF = correction factor

S_i = sums of squares of observations in each column

Note: all calculations are with 2 arcsine $\sqrt{p}$ to 4 decimal places: table values were rounded after calculation

Calculations for Data in Table 14.

Linear contrasts, as follows, may be utilized to simplify the calculations for comparisons of interest:

TABLE 15: Linear Contrast Coefficients

Effects	CC		IC	
	$\overline{PE}$	PE	$\overline{PE}$	PE
SC	+1	+1	-1	-1
PE	+1	-1	+1	-1
SCXPE	+1	-1	-1	+1

where:

CC = community care
IC = industrial care
PE = patient education

$\overline{PE}$ = without patient education
SC = source of care
SCXPE = interaction between source of care and patient education; the signed numbers in the table represent linear coefficients (c_i)

for which $\Sigma c_i = 0$ for any one effect.

-the sum of squares for a given effect (SS effect) is given by:

$$SS\ effect = \frac{(\Sigma c_i T_i)^2}{r \Sigma c_i^2}$$

where T_i = column total as defined for Table 14.
r = number of replicates (observations).

Thus the following calculations may be made:

Main effects and residual

1. Source of care $SSSC = \frac{(19.5203 + 20.8088 - 21.5730 - 22.0408)^2}{(10)(4)}$

$= .27039$

2. patient education

$$SSPE = \frac{(19.5203 - 20.8088 + 21.5770 - 22.0408)^2}{(10)\ (4)} = .07676$$

3. interaction

$$SSI = \frac{(19.5203 - 20.8088 - 21.5770 + 22.0408)^2}{(10)\ (4)} = .01700$$

4. among groups

$$SSBG = \frac{(19.5203)^2 + (20.8088)^2 + (21.5770)^2 + (22.0408)^2}{10} - CF$$

$$= 176.54120 - 176.17705 = .36416$$

5. Total sum of squares

$$SST = 191.43184 - 176.17705 = 15.25479$$

6. Within groups

$$SSR = 15.25479 - .36416 = 14.89063$$

TABLE 16: Analysis of Variance for Compliance Data

Source	df	ss	ms	F	
among groups	3	.36416	.12138	.29345	NS
SC	1	.27039		.65370	NS
PE	1	.07676		.18558	NS
SCXPE	1	.01700		.04110	NS
within groups	36	14.89063	.41363		
Total	39	15.25479			

where: df = degrees of freedom ms = mean square = ss/df
F = variance ratio
NS = not significant
SC, PE, SCXPE as for Table 15

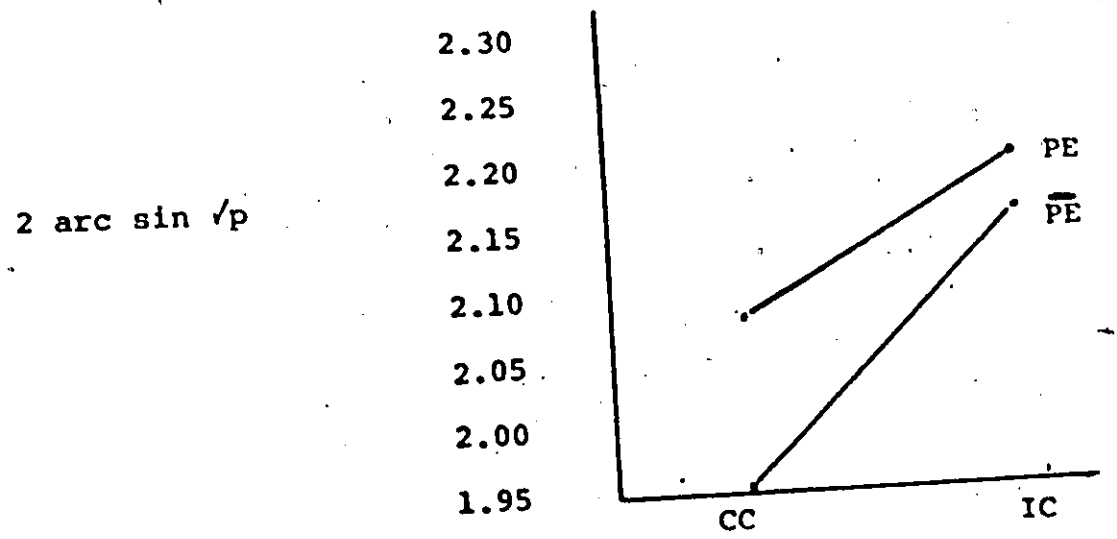
TABLE 17: Table of Means for Compliance Data

CC				IC			
PE		$\overline{PE}$		PE		$\overline{PE}$	
2 arc sin $\sqrt{p}$	%	2 arc sin $\sqrt{p}$	%	2 arc sin $\sqrt{p}$	%	2 arc sin $\sqrt{p}$	%
1.95203	69.0	2.08088	71.4	2.15770	73.8	2.20408	75.9

where CC, PE, $\overline{PE}$, IC, 2 arc sin $\sqrt{p}$ are as for Tables 14 and 15.

FIGURE 4

Comparison of the mean compliance rates by source of care and patient education.



where: p = proportional compliance rate

CC, IC, PE, $\overline{PE}$ as for Table 15.

APPENDIX 2.

Stepped Care Antihypertensive Therapy

The National Heart and Lung Institute Hypertension Detection and Follow-up Programme (HDFP) is using an approach to therapy which it terms "Stepped Care". The features of this method include:

1. A drug protocol which, while preserving some flexibility in therapy, determines the choice of specific pharmacologic agents, the dosages available, and the period of time allowable before sequential adjustments in therapy are required, in view of current blood pressure status.

2. A number of measures designed to increase the patient's motivation to participate in therapy and to increase adherence to prescribed drug therapy.

3. A standardized approach to advice and counselling of the participant with respect to cigarette smoking and alteration of diet in relation to intake of fats, total calories, and salt.

In the HDFP studies, the main thrust is comprehensive treatment of hypertensive patients with matters of compliance a secondary issue. In the proposed DOFASCO studies, compliance shares equal status with therapy and specific measures to improve compliance are to be tested.

Furthermore the problems of diet and smoking will not be dealt with in the DOFASCO studies beyond whatever advice or treatments are recommended by the attending physicians.

Thus the DOFASCO trial will utilize the drug protocol portion of the HDFP stepped care plan for those patients assigned to industrial care but will deal with matters of compliance rather more specifically and matters of diet and smoking less specifically. The drug protocol as outline below, is a biologically sensible approach to titrating medication types and levels according to blood pressure response employing a standardized format which facilitates analysis.

Drug Protocol:

Each participant allocated to Industrial Care (Stepped Care Group) will be given an appointment for his initial treatment visit as soon as possible after contact with his private physician, when appropriate, and in any case within two weeks of the second screening visit.

At this initial treatment visit information from the baseline history, physical, laboratory and other special examinations will be reviewed with the participant. Any additional diagnostic studies required will be explained to the participant and arrangements made for obtaining them. The necessary consent forms will be discussed and the participant's signature requested.

The "goal diastolic pressure" will be an average of Readings 2 and 4, sitting position, below 90 mm Hg. This goal may not be attainable in cases where unacceptable side effects intervene, but every effort should be made to get as close to the goal pressure as is feasible. The least amount and number of antihypertensive agents necessary to attain the goal blood pressure will be used. Use of well-tested, approved antihypertensive drugs is to be the major means to achieve the goal diastolic blood pressure.

The basic plan of the Stepped Care therapy regimen will progress as necessary through five steps in the following manner:

(1) The first step will use a diuretic in different dosage levels as the only medication. Chlorthalidone will be the diuretic of choice unless there are contraindications to its use. Potassium supplements or addition of spironolactone may be used as required to prevent or control hypokalemia. Probenecid or allopurinol may be used to control significant hyperuricemia. If chlorthalidone is contraindicated or causes side effects, spironolactone may be used as an alternative diuretic.

(2) The second step will consist of adding an anti-adrenergic agent (reserpine or methyldopa) to the diuretic if blood pressure control has not been achieved with the diuretic alone. Reserpine (in the combination

preparation, Regroton [R]) will be the drug of choice unless there are contraindications to its use or it is found to cause intolerable side effects. If this is the case, methyldopa will be used. A range of dosages may be used for each medication.

(3) The third step will consist of adding hydralazine to the diuretic and antiadrenergic agent if goal blood pressure has not been attained in Step (2). Participants with coronary artery disease will not be given hydralazine but will bypass Step (3) and go directly to Step (4).

(4) Step (4) consists of adding guanethidine to the diuretic (Step (1)) and hydralazine (Step (3)) medications. In most cases antiadrenergic agents (Step (2)) will be stopped when guanethidine is added, since these medications work in similar ways and have little additive effect. Since guanethidine is quite potent, participants should be followed closely by a physician according to a schedule of individualized therapy until the participant is stabilized on a satisfactory dosage of guanethidine. Continued close physician supervision will also be required for as long as the participant remains on this drug.

(5) Step (5) is utilized for participants who have been advanced through the first four steps and still have not reached satisfactory blood pressure control. At this point the physician may use other agents, such as

furosemide or ganglionic blockers, to achieve adequate blood pressure control in an individualized manner according to the best judgment of the treating physician and in consultation with senior specialists as indicated. Participants in Step (5) should be followed closely by a physician throughout the course of their treatment.

Participants who have been at or below goal blood pressure on the second clinic visit and the initial treatment visit (i.e., before being placed on medications) will not be started on medication but will be followed in accordance with the schedule of contacts. In addition to monitoring their blood pressure, advice regarding mild salt restriction and weight reduction may be given to assist in keeping these participants below goal blood pressure without requiring medications. Additional help with dietary advice to lower cholesterol and assistance in stopping smoking may also be offered when appropriate.

If a participant is above goal at the initial treatment visit, or subsequently he has a diastolic blood pressure as high as 100 mm Hg at any one or 90 mm Hg at any 2 or 4 consecutive visits he will be started in the Step-Up schedule according to the general principles described below.

The general principles of Stepped Care include the following:

Medications are increased in a stepwise manner beginning with the least toxic drugs adding more potent

(and potentially more toxic) medications as necessary to bring the participant to the goal blood pressure of less than 90 mm Hg diastolic, or as close as possible to this goal without intolerable side effects, always the least number of medicines possible.

Physicians are allowed some flexibility within a range of dosages for each medication. The physician may choose the dosage level at which he wishes to start in each Step and may adjust the dosages within the prescribed range as he feels is appropriate for an individual participant. In certain instances there may be more than one alternative pattern of medication for a given situation: for example, for a participant with hypokalemia on chlorthalidone, the physician may add KCl solution, add spironolactone, or switch to spironolactone alone, according to his judgment in the interest of the given participant.

Ideally medications should be advanced either to a higher dose within a Step, or the next Step drug added, as soon as a given drug level has reached optimal effect, if the goal blood pressure has not been reached.

For diuretics - usually peak blood pressure lowering effect is reached in three to four weeks.

For reserpine - usual peak blood pressure lowering effect is in six to 12 weeks.

For methyldopa and hydralazine (which are much faster-acting) - peak blood pressure lowering effect is usually in one to two weeks for a given dose.

For guanethidine - peak lowering effect may take one to two weeks but the participant should be seen weekly until goal blood pressure is reached. If a participant has not reached the goal blood pressure on a given dosage of medicine when that medication had been given long enough to reach its usual peak blood pressure-lowering effect, the medication must be increased in dosage, or the next Step medication should be added, unless there are serious contraindications in the physician's judgment. In such circumstances the physician should state in the clinic revisit record his justification for not advancing the drug programme despite lack of adequate control.

If all drugs within a given Step are contra-indicated or have caused intolerable side effects, that Step is bypassed and the participant proceeds on to the next higher Step.

Weight reduction and moderate salt restriction may be recommended as an aid to the primary drug therapy when appropriate - but regular drug therapy remains the primary treatment modality for all participants except those who can be maintained at goal blood pressure without medications.

Participants with more severe elevations of blood pressure (e.g., greater than 115 mm Hg) or those who are already on drug therapy may be started off at a level higher than Step (1) and advanced more rapidly than others, at the discretion of the treating physician.

APPENDIX 3

BUDGET

The following budget was submitted along with the research protocol to the Medical Research Council of Canada (MRS) on April 1, 1973. The project was subsequently approved and was allocated funds in the amount of $36,900.00 for Phase I and $29,500.00 for Phase II. Assignment of the latter funds was made dependent upon the actual generation of the predicted numbers of patients for Phase II intervention. As is MRC custom, the funds were not designated for specific categories of expenditure and no mention was made of which budget items were found excessive. In any event, experience in the initiation of the trial has indicated that the original estimates were accurate in quantity if not in detail and submission for increased funding from MRC or alternate sources is contemplated.

	Fiscal Year Ending March 31:	
	1974	1975
	$	$
A. Salaries		
1. Clinical Personnel		
a. Physician Services -initial and final asses. (OHIC)	nil	nil

	Fiscal Year Ending March 31: 1974 $	1975 $
1. a. Physician Services (cont'd)		
-community physicians (OHIC)	nil	nil
-industrial physicians (DOFASCO)		
R.H. Martin, M.D.	nil	nil
E. Gibson, M.D.	nil	nil
L.A. Hargot, M.D.	nil	nil
b. Nurse (behavioral modification programme) 9 mos., part-time	800.	1600.
c. Pharmacist - 15 mos., part-time	3000.	2000.
2. Professional Assistants		
a. Research associate (M.Sc. level) 18 mos., full-time	9750.	9750.
3. Technician		
a. Blood pressure technician -15 mos. half-time	2250.	1500.
4. Support Personnel		
a. Assistant (tailoring programme) 9 mos., part-time	1000.	2000.
b. Assistant (patient education programme) 9 mos., full-time	4000.	nil
c. Statistical clerk - 18 mos., full-time	4050.	4050.

	Fiscal Year Ending March 31: 1974 $	1975 $
4. Support Personnel (cont'd)		
d. Accountant (MBA or CA student, part-time	750.	750.
e. Bookkeeper -15 mos., part-time	1875.	1250.
f. Secretary -18 mos., half-time	1875.	1875.
g. Clinic coordinator -15 mos., full-time	3750.	2500.
5. Interviewing Services	7000.	3000.
	40100.	30275.
Employee benefits (15% of full-time personnel	3230.	2445.
	43330.	32720.
B. Equipment		
1. Garrow Random Zero Sphygmomanometer - modification of existing equipment - 2 sets	300.	
2. Sphygmomanometers for behavioral modification program -25 Avenue Exacters aneroid hand model, $25. each	625.	

	Fiscal Year Ending March 31: 1974 $	1975 $
B. Equipment (cont'd)		
3. Stethoscopes for behavioral modification program, 25 Douglas single stem, $6.50 each	162.	
4. Typewriter, IBM Selectric	650.	
5. Slide-tape playback systems (2 Coxco Slide/Sound Projectors, $275. each)	550.	
6. Desk Calculator (Wang)	400.	
	2687.	
C. Material, Supplies, and Services		
1. Stationery, office supplies	400.	
2. Duplication of forms	300.	
3. Miscellaneous	300	
4. Translations of questionnaires, slide-tape shows (Italian, Yugoslavian)	500.	
5. Production of audio-visual educational media	300.	
6. Keypunching	1000.	
7. Computation	1000.	2000.
	3800.	2000.

	Fiscal Year Ending March 31: 1974 $	1975 $
D. Travel		
1. Recruiting expense (advtg and travel for research associate)	500.	
2. Local travel	300.	
	800.	
TOTAL	$ 50617.	$34720.

See budget justification summary that follows.

Budget Justification

Physician services at DOFASCO are supported by Company funds as they fall outside the provisions of the Ontario Health Insurance Commission. The complement of physicians at DOFASCO is not expected to increase as a result of the care of hypertensives, however, so no provision has been made in the study budget for these services. The initial and final assessments have been carefully reviewed and are considered to represent appropriate clinical evaluations of hypertensive patients; accordingly, financial support for these examinations will be through the usual channels for clinical care in Ontario.

A nurse will be engaged part-time for the behavior modification part of the study. She will make weekly blood pressure and compliance checks and issue the

appropriate behavior reinforcers. This will require approximately 15 hours working time per week.

The DOFASCO clinic pharmacy will require temporary expansion and the part-time services of a pharmacist throughout the study. (A pharmacist is required by law in Ontario for these services.)

A research associate with firm grounding in statistics and with organizing capabilities will be required to oversee the management of the project and deal with quality control, questionnaire development and pre-testing, and data handling and analysis. He/she will direct a statistical clerk who will insure the correctness and completeness of data collection on a day-to-day basis.

The screening, six, nine and 12 month blood pressure and compliance assessments will be performed by a specially trained technician in order to insure the standardization of these assessments.

Non-professional assistants will be employed to carry out the patient education and "tailoring" programmes. Approximately 180 patients will be involved in the former which includes an initial instruction period and subsequent follow-up. Tailoring involves about 37 patients and this would necessitate only part-time work on a continuing basis.

A senior MBA or Chartered Accountancy student will be engaged to initiate cost-accounting procedures and provide a final summary which will separate research expenses from the cost of clinical services provided at DOFASCO. This would include an assessment of physician, nurse, and support staff time and laboratory, ECG, and radiology expenses at DOFASCO connected with the care of hypertensives. This would form the basis for future cost-benefit and cost-effectiveness studies. The actual collection of accounts data will be performed by a part-time clerk with bookkeeping skills.

Data on sociodemographic items, job activity, psycho-social adjustment, knowledge of and attitudes toward pill-taking, past medical history and functional inquiry will be collected at standardized interviews by the trained personnel of the McMaster Field Survey Unit. Skilled interviewing is particularly important with respect to the psycho-social assessments. Field survey services usually include questionnaire development, pre-testing, editing, coding, keypunching, and transportation expenses in addition to the actual interviewing; the usual rate is about $22.00 per person-interview hour. In the study, all but interviewing and editing will be handled by the regular study staff and interviewing expense has thus been calculated on the basis of $10.00 per interview including waiting time and editing.

The rather cramped DOFASCO clinic will be utilized, rent free, for all assessments. However, this will necessitate careful scheduling and coordination of appointments and events at the clinic for several hundred men (on shift work). This will be carried out by a non-professional person, here termed as a clinic coordinator, working in cooperation with DOFASCO personnel.

Inexpensive hand-model sphygmomanometers and stethoscopes will be used in the behavioral modification programme. Patient education will be provided in a slide-tape format providing standardization and portability.

The three major linguistic groups at DOFASCO are English, Italian, and Croatian. Exclusion of the latter two groups would compromise sample size inordinately. Thus all questionnaires and educational materials will be translated in advance of the study to minimize the effect of linguistic barriers.

Coding, keypunching, and verifying of some ten data cards per patient for the study will be required for subsequent computer analysis. The latter would include the writing of new programmes and actual computer time.

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