RESEARCH PROSPECTUS
SCREENING FOR CERVICAL CANCER

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~~Prepared by~~

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1. Purpose

From our proposed study on screening for cervical cancer, we expect to obtain guidelines for improving the design of cervical cancer screening programs. This can be accomplished by achieving four intermediate objectives.

a) Resolve important uncertainties in our knowledge of the natural history of cervical cancer.

b) Elucidate relations between design factors of a screening program and the composition of the population which volunteers to be screened.

c) Formulate an optimization model using information developed in the first two activities. This model would choose an optimal screening policy given an assumed steady-state population and given various levels of resources.

d) Create a simulation model (or adapt an existing one, e.g. Knox [1,2]) to study questions of time-phasing and implementation of the policies developed in the third activity.

The methods we anticipate using and the data we will require for each of the four objectives are discussed in the next four sections.

2. The Natural History of Cervical Cancer

In its simplest conception, cancer of uterine cervix is a disease that progresses through early stages (dysplasia, carcinoma in-situ) to a late stage (invasive cancer). In its early stages, the disease is asymptomatic, hence women with these conditions will not ordinarily present themselves for treatment. However, cases treated early have a much better prognosis than cases left untreated until the invasive stage.

The PAP smear is a simple, painless, and inexpensive test that will detect cases of dysplasia and carcinoma in-situ with high reliability. This test has been applied to vast numbers of apparently healthy women. Large numbers of cases of dysplasia and carcinoma in-situ have been discovered and prevented from progressing to the invasive stage. But mortality from cancer of the cervix has not been dramatically reduced, as proponants of such screening activities had predicted, even in places where virtually the entire population has been repeatedly screened.

One can explain these disappointing results, as does Ashley [3,4], by suggesting that some cases of dysplasia or carcinoma in-situ will progress very rapidly to invasive carcinoma, and hence pass through the early stages between successive screenings. Ashley also suggests that these "rapid" cases are the ones with the poorest prognosis. Certainly, the distribution of dwell times in the in-situ stage will affect the performance of a screening program.

Furthermore, Ashley [3], Green [5], and others suggest that a substantial proportion of early cases may spontaneously clear up, rather than progress to invasisve carcinoma. (This view is not universal. See, e.g. Barron & Richart [6].) We are faced, therefore, with the problem of estimating the distribution of dwell times, in-situ.

not of all cases, but only of that subset of cases which will progress to clinically invasive cervical carcinoma.

Heretofore, only the mean of this distribution has been estimated, and that from age dependent incidence and prevalence data. Such a procedure can be criticized on many grounds.

i) No satisfactory means has been proposed for independently estimating the means of those cases which progress to invasive cancer, and those cases which spontaneously undergo remission. One must assume, for example, that the mean times spent by either type of case in dysplasia plus carcinoma in-situ are identical.

ii) False negative smears can distort the incidence of carcinoma in-situ. Even when adjustments are made due to this factor,--for example by estimating incidence from cases in which a positive response was proceeded by at least two negative responses, as in [7]--the problem still exists. After all, nothing prevents the first of the negative responses from being a 'true' negative, and the second from being false.

iii) Inaccurate classification of cases of clinically invasive cervical carcinoma as cancer of the corpus uterus, or inclusion of these cases in the category "cancer of the uterus unspecified", will distort ones estimate of the incidence of invasive cancer of the cervix. Campbell [8] discusses this difficulty.

iv) The computations of mean dwell time assume that women born in different years will have the same age-dependent incidence and prevalence of both

> carcinoma in-situ and invasive cancer. There is strong evidence, e.g. [9,10] that this is not true. Incidentally, this"cohort effect" offers an alternative explanation of the data that lead Ashley to conclude that some cases undergo spontaneous remission, and that other cases become invasive with virtually no intervening carcinoma in-situ stage.

These criticisms point out the need for a direct method for computing the in-situ dwell time distribution of progressive cases (cases that progress to invasive cancer).

The most satisfactory direct measurements would be obtained by leaving women with positive smears untreated until they progress from dysplasia or carcinoma in-situ to invasive carcinoma. Ethical considerations prevent this being done, although occasionally a woman will refuse treatment and hence voluntarily provide just such a case. Spriggs [11] has collect 13 such cases, in which no treatment and no biopsy were performed,and each of which has been followed for at least three years. However, the series is small and probably biased towards cases that progress to invasive cancer.(These, since they often appear voluntarily for treatment, are easier to follow up.)

Some studies attempting
~~Other attempts at~~ direct measurements of this kind will typically treat the subjects once the the stage carcinoma in-situ is reached, rather than allowing subjects to progress to invasive cancer. This is the case in the Barron & Richart [6] study, which thus provides insight only into the dwell time distribution in the stage dysplasia. Other ~~Many~~ studies, for example Peterson [12], Jordan, Bader and Day [13], and Nieburgs [14], have followed women beyond the stage dysplasia and through carcinoma in-situ

but they have all chosen to confirm the cytologic diagnosis with a biopsy and subsequent examination of the histological sections. It is argued, however, that the biopsy may miss an already invasive cancer, especially if very little tissue is taken, or that it may remove most or all of the tumor, especially if much tissue is removed.

Supporting this last point is the fact that one form of biopsy, the so-called cone biopsy, is recommended by some as treatment for carcinoma in-situ (for example, see Boyd et al. [15], and Krieger and McCormack [16]). Evidently, unless Spriggs' [11] study can be augmented, direct measurements of this kind will not yield an estimate of the in-situ dwell time distribution of progressive cases. It is at least certain that such an estimate cannot be made soon from such data.

We believe, however, that this distribution, as well as other quantities of interest, can be estimated directly from data that is routinely collected by all screening programs. These data are the birthdate,and the dates and results of each PAP smear, for every woman who has participated in the program. Also recorded is whether and when the woman contrated invasive cancer of the cervix, despite screening.

One quantity we can estimate from those data is the false-negative rate for the PAP smear. The false-negative rate is the proportion of smears taken from women with carcinoma in-situ, which yield negative results. We estimate this quantity from the manner in which the number of cases detected per screening decreases as women are screened more and more times.

A group of women, prior to being screened for the first time, will contain a backlog of cases which have yet to progress to invasive cancer. The first screening will detect a fraction of

those equal to one minus the false-negative rate. The second screening will detect the same fraction of the cases which appear between the two screenings, plus that fraction of the remaining backlog. After many screenings each new screening will detect the same number of cases as appear between successive screenings. (Some cases that appear between screenings will be missed, but their number will be made up from cases which were missed earlier, and are detected by the present screening.) The change in the number of cases detected will be slow if the false-negative rate is high, because the initial backlog will not be depleted quickly. Conversely, a low false-negative rate implies a rapid change in the number of cases detected. A crude estimate of the false-negative rate is 0.3, based on thie idea and on the limited data given in [7].

A second quantity that we can estimate from these data is the in-situ dwell time distribution for all cases, including both progressive cases and sham cases (cases that spontaneously disappear). The method of estimation relies on the following fact. Once the false negative rate is known, then this overall dwell-time distribution could be used to estimate the numbers of in-situ cases that one would expect to be detected by the screening program. More than this, one could estimate how many of these cases should be detected if screening occurred five years apart, or two years apart, or at any other interval. A knowledge of the frequency distribution of the various screening intervals in the actual screening program would then yield an expected detection rate.

We propose to invert this relationship. Instead of using the dwell-time distribution to estimate the detection rate, we will use the rates of detection in different screening intervals to estimate the dwell-time distribution. Because the equations describing this relationship are linear, the inversion process is theoretically well-understood and computationaly feasible.

The third quantity we can estimate is the in-situ dwell-time distribution of progressive cases. For this we will use data on the few invasive cancers that occur among the screened population. Given the dwell-time distribution, one could compute the expected number of invasive cases that would occur, at each interval of time after a screening test. As before, this relation is linear and could be inverted. However, the number of these cases is very much smaller than the number of cases arrested at the in-situ stage (less than 100 cases of invasive cancer, versus thousands of cases of carcinoma in-situ in reference [17]). Thus a method that estimates only the expected value of the distribution is probably not adequate in this case. We anticipate using a Baysian estimation technique, with a uniform prior distribution for selected points on the in-situ dwell-time distribution of progressive cases.

Note that the distribution derived in this way is the dwell-time distribution for cases destined to become invasive. Cases which undergo spontaneous remission do not influence the result. Note also that the survival times of these invasive cases offer information on prognosis as a function of dwell time. (Data from [17] suggests that prognosis is independent of dwell time,

but this view is disputed by Lawson [18].) Finally, note that the same procedure can be carried out on subsets of the population, for example to test whether cases in older women tend to progress faster than those in younger women, as Ashley [4] contends.

To carry out these tasks, we will need the following data on as many women as possible. A woman is eligible to be included in the study if she has had at least one PAP smear, or if she has had cancer of the cervix, or if she has had a hysterectomy, or, of course, any combination of these. For each woman in the study we shall need:

1. Birth date
2. Dates and results of each PAP smear (if any). Possible results are:normal, dysplasia, carcinoma in-situ, smear unsatisfactory.
3. If the woman has had invasive cervical carcinoma, the date it was diagnosed and the stage (WHO classification) at diagnosis. We also would like to know the treatment used and the length of subsequent survival.
4. If the woman died of a cause other than uterine cancer, the date of death.
5. If the woman underwent a hysterectomy for reasons other than cancer, or for a cancer other than cervical cancer, we wish to know it and the date of the operation.

The sources for this data will undoubtally be one or more of the large cervical cancer screening programs. Campbell [8] suggests a number of sources in 14 different countries. The British Columbia program [17] is another possible source, as are several efforts in the United States, e.g. San Diego [7], Memphis [19], and Olmstead County [20-22]. Our personal contacts with Dr. Knox, and with Dr. Garin of WHO, make us optimistic that one can obtain access to at least some of this information.

3. Participation

One of the prime determinants of the yield of any screening program is the proportion of the target population who come forward to be screened. Experience in attracting participation, in the absence of compulsion, has varied greatly between programs, countries and demographic groups. At a recent WHO symposium [23] participants cited response rates for cervical cancer screening programs as low as 25% for women over 35 years of age. In a study of screening in general practice in the UK, however, a response rate of over 90% was achieved [24].

With rates varying as greatly as this it is clearly of importance (a) to isolate the factors affecting participation, (b) to establish the size of their effects,and (c), where possible, to estimate the cost of achieving changes in the participation rate by acting directly or indirectly on some of these factors.

Many of these factors undoubtedly interact, but, at least for analytical purposes, they can be divided into

1. Demographic Characteristics
2. Attitudinal Factors
3. Organizational and Institutional Characteristics

These category headings are somewhat imprecise but are intended to correspond roughly to three groups of which group 1 is outside the decision-maker's control;group 2 is capable of being altered, but the precise methods and effects are not too clear and the effect may not be fully felt for some time; while group 3 contains those factors which are more directly under the decision-maker's control and whose impact on the response rate is somewhat more direct and certain.

Demographic Characteristics

There is not a great deal of published data on participation

rates by demographic characteristics. In the case of cervical cancer it seems fairly well established that response rates fall off with age. In the older age groups these rates often fall to as low as one-third of those in the younger age-groups [23] [25]. It is not clear,however, that the percentage returning for a second screening varies greatly between age-groups [26].

In the case of multiphasic screening there also appears to be a tendency for participation to fall off with age, although here, too, the results are somewhat unclear [27], with the effect being more pronounced among white females and least pronounced among black females.

When measure of social class are used, participation rates are also found to decline from higher class to lower class groups, with the response to cervical cancer screening being as much as one-third lower among women whose husbands have low-status occupations [25]. A similar effect has been observed in multiphasic screening. In a Washington D.C. ~~prepared~~ prepaid group practice consisting mainly of government workers, about 50% avail themselves of annual examinations, while intensive efforts to induce members of a hardcore poverty group in Memphis, Tennessee to undergo screening examinations produced only a 20% response rate [28].

In their study of breast cancer screening, Shapiro et al. [29] found that those women who refused screening were, in general, slightly older, had a lower educational attainment and were less likely to be Jewish, to have been married or to be multiparous or premenopausal. Once again, however, rates of re-examination were influenced only negligibly by age; nor were they influenced by educational attainment, race or menopausal status.

Attitudinal Factors

For a person to present himself to be ~~screening~~ screened, he must in many cases be aware of possible illnesses, believe that a screening program may help him and be willing to come forward. This is not to say that in some cases there might not be screening programs in which a person participates because it is easier to do so than not to or that one might not have a screening program which offered large enticements to take part. In general, however, personal attitudes towards illness and medical care can be expected to play a large role in determining whether and when a person comes forward to be screened.

The Australian study found that test-seeking and worry about cancer were related. In two other studies it was found that those women who reported having a lump in their breast were more likely to have sought screening [29] [25].

This leads into the question of health education and the extent to which people's awareness of disease and their attitudes to medical care can be altered in the short or long term. Clearly, health education is a process which takes place informally as well as formally but the relationship between formal expenditures on health education and attitude changes is far from clear as are the means of increasing informal education.

Organizational and Institutional Characteristics

While health education may try to alter people's perceptions of disease and attitudes to medical care, there is usually for a given program a somewhat more humble publicity activity. The effectiveness of various forms of publicity in encouraging participation in screening preograms has not been much reported on. In the Kaiser-Permanente trial of multiphasic screening an experimental group was attracted by being telephoned at home and asked to come for a screening session, while the control group consisted of a

similar group of people not so encouraged. In the event, 60% of those telephoned came forward, while only 20% of the control group came forward in the normal way [30]. It does not seem, however, that until now experiments have been carried out to test the effectiveness of various forms of publicity in a controlled manner.

An alternative or complementary method of encouraging participation lies in payments to doctors or patients, clearly one factor affecting the extent to which doctors will attempt to persuade their patients to be screened for a condition (is the extent to which they are recompensed for doing so. UK doctors receive a special fee, for example, for carrying out a cervical cancer screening test and it is often alleged that the reason for the poor penetration of cervical cancer screening in certain groups of the population is attributable to the smallness of the fee.

In Austria, a scheme was introduced in 1974 whereby mothers are given stipends contingent on their attending a specified number of ante-natal, post-natal and child development clinics. The stipend is considerable, amounting in a year to the monthly wage of an average worker. It is expected that this will ensure near 100% participation in such cases.

A further important feature which may affect participation is the manner in which a screening program is inserted into the medical care system. Cervical cancer screening programs, for example, can be carried out by family doctors as a routine procedure or as a special effort; they can be carried out by hospitals or public health clinics; they can be carried out by medically trained persons or by paramedicals. All of these systems have advantages and disadvantages. As far as their effects on participation are concerned, however, there is much supposiiton but

little hard evidence.

Wilson [31] suggests that moves to make a screening program more acceptable by health education might be greatly aided by moves to make the test itself more acceptable and he cites the case of self-administered cervical cytology tests. Glass and Rich [32] found, however, that in the case of a "captive" population such as school children, one form of self-administered test, at any rate, produced a lower rate of participation in a screening program for bacteriuria.

There is a large amount of literature concerning the effect of distance on the use of medical care facilities. Some of this has been reviewed by Shannon et al. [33]. Little or none of this work relates to screening per se and the effect on screening may be expected to differ somewhat from consultation for illness. Girt [34], for example, found that the expected negative effect of distance on consultation was offset to some extent by the fact that individuals are likely to be more sensitive to the development of disease the farther they live from a physician. His curves relating consultation rates for various diseases to distance from the general practitioner tend therefore to have a peak at a few miles distance from the general practitioner. One might expect that the offsetting effect would be less pronounced in the case of screening and this appears to be borne out from his limited evidence.

In any case it may be expected that the location of clinics - and the time and inconvenience associated with attending - will significantly affect attendance and reattendance.

Proposals: A number of factors have been listed which may be expected to have some effect on participation in screening programs. A review of the literature indicates that in most cases little or

nothing has been done systematically to measure these factors and to relate these effects to the costs of screening for disease, although a large amount of informal experience appears to exist about the rates of participation to be expected in screening programs [35].

We would propose as a preliminary step the categorization of a large number of screening programs, principally cervical cancer screening programs, according to the demographic and organizational factors listed here. Depending on the results obtained from this preliminary survey, we would propose attempting by formal multivariate methods and informal analytical methods to relate the participation of various demographic groups in different programs to organizational and, where possible, attitudinal data. In the case of such a variable as distance sufficient variation might exist within single programs to permit estimates of its effect. It is very likely that for a number of variables there would not exist sufficient variation to permit unambiguous conclusions, but we believe that even a small improvement in our knowledge of the effects of such factors could be extremely useful in planning screening programs.

The offer of WHO to approach a large numberof cervical cancer programs for us could provide us with a very useful source of data.

4. Optimizing the Screening Policy

The purpose of the optimization model is to determine the best screening policy to adopt as a function of the population to be served, and the resources available for screening. This model will not consider problems of time-phasing, such as the capital investment needed in training facilities or the preparation necessary to convince the population to participate. Rather, it will be assumed that the program has been in operation for many years, and that the composition of the population, and the prevalence and incidence of the disease, have reached their steady-state values. Thus, this model will choose only the best steady-state situation. The simulation model discussed in the next section will help determine reasonable paths from a given initial state to the desired steady state.

The elements of the optimization model are the variables that describe the policy chosen, and functions of those policy variables that describe the impacts. Policy variables include such things as:

1) Which test should be used (e.g. cytology; enzyme)
2) Who should administer it (physician, nurse, para-medical person)
3) Who should be screened and how often (see previous section)
4) What efforts should be devoted to following up positive responses to the test (e.g. send letters, make phone calls, make visits).

Impacts include:

1) Physicians' time
2) Nurses' amd paramedics' time
3) Training facilities for necessary personnel
4) Equipment for carrying out screening tests
5) Hospital beds required--(i.e. patient load due to screening program)
6) Time (and money) spent by participants in the program
7) Mortality from cervical cancer

These lists are not intended to be exhaustive.

Item 7) in the list of impacts--mortality from cervical cancer--is only one possible measure of the benefits to be derived from a screening program. Another possibility would be the expected number of woman-years of additional life due to the program. Other measures might be constructed that would reflect changes in morbidity--e.g. complications from radiation therapy or hysterectomy--with which the program would be credited.

Measures of benefit are important to the optimization process, since we intend to choose one, which we will then maximize. Which one we choose may influence the results to a considerable degree. (We also intend to investigate the sensitivity of the results to changes in the function.) For example, if we choose to maximize years of survival, the optimal policy may exclude virtually all screening activities for women over (say) 70 years. After all, these women are not expected to live very long even without cancer of the cervix. Yet to choose mortality as our measure of benefit may imply that we should concentrate our efforts on this relatively high-risk group, to the exclusion of young or middle-aged women.

We will not compute an optimal policy simply by maximizing benefits. Rather we shall constrain our policy by limiting its resource costs. Thus we may require that only a limited amount of the physician's time be take by screening activities, or that a patient not be required to travel more than 10 kilometers to receive her test, or that the total screening budget not exceed a certain number of dollars. Indeed, any impact that is a cost in the most general sense,may provide a constraint on the set of admissible policies.

Of course, these impacts will depend on the medical environment in which the screening program is implemented. For example, in a place where people are medically served only by a few large hospitals and clinics, to set up small, neighborhood screening facilities would be very expensive. But where neighborhood clinics already exist, the screening test could be offered there at little additional cost. It might prove optimal in the first case to provide a few mobile screening facilities, housed in large trucks, while it would probably be better to dispense screening tests through the existing clinics in the second case.

Data from which resource requirements can be estimated are probably best obtained directly from administrators of existing screening programs. We expect to take advantage of the offer of WHO to approach such programs for us and effect their aid in this regard. In addition, some data on costs exists in the published literature (see, for example [22,36]). Benefits, on the other hand, will be calculated using our own models of the disease process, in a manner similar to Knox[1,2].

Given an optimal policy, one would wish to explore the consequences of changing the assumptions involved in producing

it. For the policy is optimal only under the circumstances in which it is calculated. Thus we may ask whether changes in the composition of the population, or in the incidence of the disease will greatly degrade the performance of the screening system. Or we may explore the effect of assuming a higher (or lower) false negative rate of the screening test. We would hope to find policies that are not only optimal, or nearly optimal, but which remain nearly optimal when the assumptions are changed.

Such exploration can provide measures of the value of new technologies or policies that are not explicitly included in the model. Thus, one may ask how much one should pay to improve the prognosis of cases of invasive cancer by a stated amount. If the prognosis is improved, one will be able to reduce the size (and hence the cost) of the screening program while maintaining the total benefit (e.g. reduced mortality) unchanged. The reduction in screening cost is then a measure of the value of improving the prognosis.

Or one may estimate the value of techniques for enticing exactly the desired groups within the population to participate. One first solves the problem allowing oneself to choose any such population at all from among the whole population. Thus, one may specify that every woman over 45 years of age with an income (or family's income) under $6000 per year shall be screened at one year intervals, while women of the same ages but richer would be screened every eighteen months. Then one can solve the same problem, but permit participation only by groups of realistic composition (see previous section). The resources used in the two cases would be adjusted until the benefits were equal, and the difference in the resources would be the value of an ability to reach exactly the desired population.

Finally, a question of equity arises. It may be the case that two different groups of women will be similar in terms of risk of cervical cancer, and similar in terms of socio-economic status, but that it will be optimal to treat them differently. For example, to screen the rural population may require a mobile clinic that can accomplish only a few dozen screening tests a day, due to the time spent travelling. The same mobile clinic might accomplish several hundred tests among comparable women in an urban region and hence be "better" employed there. But is this fair? Although we have no magic method for resolving this question, we can at least calculate how much reduction in benefits or increase in cost an attempt to be fair will require.

5. Time-Phasing and Implementation

We propose to construct or adapt a simulation model (e.g. the model of Knox [1,2]) to study questions of time-phasing and implementation of a screening program. These questions include:

- o How, and how quickly, are the necessary resources (e.g. cytologists and cytology facilities) to be mobilized?
- o How quickly are efforts to attract participants in the program to be implemented?
- o What will be the changing needs of the program from the first ~~four~~ few years, when it is dealing with the backlog of prevalent cases, to later years, when it is locating only the incident cases?
- o What will be the impact on the program of variations in the incidence of the disease or participation in the program?

Questions of this kind are not dealt with in the framework of the optimization problem, because to do so would require that the model be too large. Instead, we will indentify prefered policies using the optimization model and assuming a steady-state (hence constant) participation, level of screening effort, and disease incidence. Then, to explore possible difficulties in arriving at those policies, and potential problems in returning to a steady state following a perturbation, we resort to a simulation approach.

Mobilize Resources

Depending on the situation in the region setting up a screening program, one or another of the needed resources may govern the rate at which the screening service can expand. For example, this critical resource could be trained cytologists.

The rate at which such people can be made available will generally depend on the size of the existing training facilities, and the rate at which those facilities can be augmented and staffed. Models treating such a situation are well-known (for example, see [37], p. 57 and [38], p. 183). Other resources are cytology facilites, personnel and facilities for carrying out the screening test, and personnel and facilities for following up those women whose tests are positive.

We have been writing as though the test to be used is the PAP smear. Of course, other tests are possible - e.g. for the enzyme 6-phosphogluconate dehydrogenase [39] - and, if used, would require that somewhat different resources be mobilized. However, the problem will be the same in principle, regardless of the test employed.

Attract Participants

The time dimension is involved in attracting participants into the program as well. First, measures taken to attract people (e.g. educational advertizing campaigns, see section 3) will require some time to take effect. That is, there is a practical limit to how fast participation can be increased. Second, one must take care that these measures do not cause participation to exceed the capacity of the system. This could discourage many from joining the program later, when facilities become adequate. In short, one should coordinate the technical aspects of setting up the program - i.e. mobilization of resources - with the social aspects - i.e. attracting participants.

This requirement for coordination might best be met by constantly expanding the target population of the screening program. While the program is small, one might aim it only at those people who are both at greatest risk from the disease and

most accessible to the screening facilities. As the program grows, both those at less risk and those less accessible would more and more be enticed into the program.

Approach to Steady-State

Prior to the start of the screening program, there will exist in the population a pool of early cases that in the usual course of events would progress in the next several years to the late, invasive stage. When the screening program is first implemented, it will discover the cases in this pool. The treatment required by these cases constitutes an unaccustomed burden upon the health care system. At the same time, those cases of invasive cancer that would have appeared in the absence of the screening program still appear in spite of its presence. For them, screening has come too late. Thus initially, the health care system must cope with its usual burden of late cases, plus the new tasks of screening and of treating early cases.

After several years, however, one expects to see a reduction in the number of invasive cases. This is due to the fact that years before, the early cases were arrested that would otherwise have progressed to today's late cases. Furthermore, the pool of early cases that existed at the beginning of the program will have been depleted. Each year, the program will need to deal only with early cases that developed the year before, rather than dealing - as the program did initially - with an accumulation of years of early cases. Thus the capacity of the health care system to deal with both early and late cases should be considerably larger early in the program than later.

The fact that benefits are delayed and that the early costs of the program are large raises another interest point. One presumes that a benefit delayed is worth less than the same

benefit achieved sooner. That is, one discounts future benefits (and costs) in comparison with present ones. If one accepts this point of view, the fact that resource costs are felt early in the program, while benefits appear only later, might lead one not to institute the program, even though the expected steady state is preferred to the present situation. Of course, such a conclusion will depend on the discount rate one chooses. A low discount rate will lead one to bear the present costs in order to receive future benefits; a high rate will cause one to forego both. A discount rate of 10% per year is widely accepted for decisions in which benefits and costs are all monetized (see [40], p. viii), but who is to say the same rate is applicable to years of survival [41]?

Uncertainty

At the beginning of a screening program, plans will be drawn up on the basis of assumed or expected rates of incidence of carcinoma in-situ among different segments of the population. These estimates will undoubtedly include some error, and perhaps a great deal. During the course of the program, direct measurements of incidence will be made, and will no doubt call for adjustments in the screening policy. Those adjustments can be made relatively painless by choosing an implementation strategy that takes into account their likelihood.

Furthermore, one should expect that incident rates will change from one cohort to women to another [9,10]. Even after the program has been in effect for many years, continued adjustments to the changing incidence rates must be anticipated.

Participation rates will also change from time to time. Witness, for example, the recent increase in screening for breast cancer in the United States. This increased interest is surely the

result of Mrs. Ford's and Mrs. Rockefeller's operations, and can be expected to die away over the next few months or, at most, the next few years.

Financial support for the program might also suffer sudden changes. The appearance of sudden interest in a program might yield increased private donations or, more slowly, increased government support. Similarly, if a program's results fall short of expectation, its funding might suffer. The screening program should be designed so that such shifts will not cripple it.

Dynamic Nature of Circumstances

Few things in human experience are constant. We must be prepared to cope not only with the average or expected situation, but with the variations in the situation that we know will occur. The optimization model that we proposed in section 4 deals only with the average situation. It requires a simulation model to ensure that policies considered optimal in section 4 will still be good policies in the real world.

6. Applications of This Research

The purpose of the research prospectus outlined here is to describe a number of studies which we believe would aid the formulation of policy towards screening for cervical cancer. These studies would contribute to models which would be useful for countries which have already created screening programs or in which screening programs have grown up without conscious political decisions. The models would be useful also for countries which are contemplating cervical cancer programs. Finally the models could serve as prototypes for other diseases where screening programs are under contemplation.

The models we hope to develop are ones by means of which the consequences of changes in policy could be tested. For countries in which cervical cancer screening programs exist already the "political" costs and benefits of reducing or expanding the program will probably be only too evident to medical policy-makers. What they may not know are the medical and economic consequences of such decisions. Models which trace through such consequences should make a vital contribution to policy discussions.

Administrations or organizations contemplating the establishment of cancer screening programs also need to know what consequences are likely to flow from such a decision and can they design a program which will best meet their objectives subject to the constraints on manpower and physical resources with which they are faced? Should they introduce a program at all? If so, how quickly should it be introduced? These are questions which can best be answered by testing and evaluating a number of alternatives.

Many of the problems raised by cervical cancer screening programs occur also in connection with screening for other diseases. One problem in particular is that of estimating the period of time

during which a particular condition remains at a pre-critical level as is the case in cervical cancer. This piece of information as we have indicated is vital to the design of screening programs, especially the determination of the screening interval. Establishment of such information by randomized controlled trials is often very costly and slow, if not impossible. The development of a methodology for estimating the natural history of the disease in its pre-critical stage by methods other than those of a purpose-built trial could be a most useful product of this work and might have application in other diseases (e.g. chronic simple glaucoma).

All screening programs encounter the problem of inducing public participation. Yet there is little evidence on the effectiveness and efficiency of various methods of encouraging participation in screening programs among various groups of the population. Clearly, however, it is difficult to make planning decisions without such information. Our research prospectus proposes that we consider systematically methods of obtaining such data, especially in the case of cervical screening.

The simulation and optimization models provide the frameworks for analyzing both the best choices given our objectives and constraints and the problems involved in reaching the preferred solutions. Although simulation models have been applied to the analysis of screening programs for cervical cancer, this is not the case, as far as we can ascertain, for an optimization model. Furthermore, the simulation model outlined here is far more oriented towards policy questions than earlier examples.

Of course, attempts to model complex policy questions are bound to be hindered by difficulties of obtaining data. We believe, however, that many of these problems can be overcome and

that the methods of overcoming them will have useful applications elsewhere - especially when it is borne in mind that screening programs, their design and implementation, are likely to be of increasing concern to health services everywhere.

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