



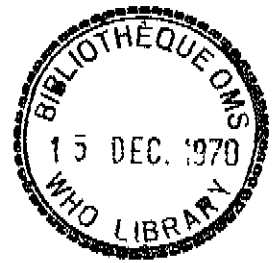
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AUTOMATED MULTIPHASIC HEALTH TESTING (AMHT) IN RESEARCH

by

Dr Aubrey Kagan
Chief, Epidemiology of Non-Communicable Diseases
Division of Research in Epidemiology and Communications Science, WHO



I. THE PROBLEM

My remarks are confined to studies of disease and its control in groups of people - epidemiological research.

Some of us have been concerned that since the end of World War II more money, time and effort has been spent on epidemiology than ever before and that the return in knowledge and efficient services has not been commensurate. There is room for increasing the efficiency and effectiveness of epidemiology both in the field of service and the field of research.

The Cause

This situation is due to inherent difficulties in the problems to be tackled that are unlikely to be met without modification of traditional methods.

The usual process of discovery depends upon thought, observation and experiment. Thought directs observation along a particular pathway. Observation sends thoughts in a particular direction. These processes lead to a hypothesis which is then tested. The results of this lead to an acceptable theory or one that needs further test, or a change in hypothesis, or a set of observations is indicated - and so on.

There is an element of chance in choosing the right observation, the right hypothesis, the right conditions for observation and the right test situation. That is why the majority of ideas and hypotheses prove to be sterile and chance observations may be productive.

A negative result is only useful if the false hypothesis is in some way related to the correct hypothesis and its disproof directs attention to the latter, or, if by excluding one of a few possibilities attention is directed to the others. In any event, unless the first hypothesis is luckily correct, observation and experimentation have to be repeated.

This process has succeeded and is tolerable when the procession between thought, observation, experiment and back again is fast and inexpensive. A train of thought can be followed, modified, re-tested or cast aside, and a new idea can then be put through the same process. Under these conditions the process results in discovery sufficiently often to receive acclaim and acceptance and to have resulted in the undoubted advances of science that we now experience.

When the process is slowed down - e.g. smaller chances of getting the right idea, or need for large scale prolonged observation and tests - the frequency of getting useful results is greatly diminished. The expense of procession becomes great and the expense of repetition enormous in terms of manpower, materials and time.

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The latter describes the predicament of many epidemiological problems particularly, but not exclusively, of non-communicable disease. Here the number of factors suspected, and therefore to be observed, is great. Observation of representative samples of large numbers of human beings under habitual conditions is required. This is difficult and expensive to arrange and slow to complete. Observations are often inaccurate and lead to confusion rather than clarification. The number of possible associations is great because not only are the number of suspect factors large but it is likely that combinations of factors should be examined. The number of hypotheses arising is large. Tests of hypotheses of prevention of disease seldom take less than two years and often take longer. When, as is usually the case, the disease is infrequent (e.g. an incidence rate of about one per cent. per year) large numbers of subjects must be studied. Discovery is the exception. False hypotheses leading to sterile results are the rule. Repetition of the process becomes necessary but inexpedient in terms of effort, time, and money.

We cannot do without the iterative process of "thought, observation, test". We must make it more effective. This might be achieved by:

- (i) improving study designs
- (ii) better forms of mathematical analysis of data
- (iii) greater, and known, precision of observation
- (iv) assessment of larger numbers of subjects
- (v) multipurpose action

II. FEATURES OF AMHT RELEVANT TO RESEARCH

AMHT is a data acquisition system. It can be used to obtain data on a large number and variety of factors, in a large number of subjects. The observations can be in the form of answers to questions, physiological investigations, biochemical and other laboratory tests. The subject, or material to be assessed, has to come to the "system". Physiological and biochemical tests can be made on the subject as it is, or under "load", e.g. blood pressure on arrival or after exercise; blood glucose on arrival or after glucose load.

The advantages are: (1) many observations can be made on many subjects and generally speaking the cost per subject falls with an increase in the number of subjects examined; (2) observations can be made with unskilled personnel (but these must be specially trained and supervised); (3) the degree of precision of observation can be monitored; (4) data is transformed and stored in a computer compatible form; (5) observations on satisfactoriness of the data can be made before the subject leaves the premises; (6) re-examination or special examination can be made of some of the subjects as required and decision to do this can be based on the results of previous routine observations; (7) the system can be made in a transportable form.

The disadvantages of AMHT are: (1) the cost depends to some extent on the nature and number of the tests, but even with only one or two it is still high. It is unlikely to be economical with less than 500 subjects on average per week and to obtain real economic effects it would be desirable to double or treble this number; (2) observations cannot be made on habitual micro-environment or habitual physiological responses over a long period of time; (3) service, maintenance, and repairs are likely to be difficult, expensive, or both.

If we now revert to our five requirements for increasing effectiveness of epidemiology we see that AMHT is no substitute for the first two (study design and methods of analysis). It is particularly suitable for the third, fourth and fifth. The fourth (larger numbers of subjects) has been discussed enough. We have indicated that AMHT does not necessarily

imply precision,¹ but it does provide a convenient system for assessing precision and ensuring that methods with the desired degree of precision are used.

The possibility of multipurpose action stems from the frequency with which expensive research necessities - choice of samples of subjects, personnel, time and place of observation, types of observation - can overlap to a high degree for studies of different health problems, if these are carefully chosen. A system which can be adapted to study a large increase in number of subjects and more types of observation will permit several studies to be made simultaneously. AMHT, under some circumstances, has the potential for doing this at little additional expense. We give "guesstimates" of examples below.

III. TYPES OF RESEARCH PROJECT FOR WHICH AMHT MIGHT BE USED

Assuming that the research proposed is desirable and can be funded and carried out, AMHT should be used: (1) if there is no other way of doing it; (2) if there are other ways, but AMHT is more effective and at least as efficient, or equally effective and more efficient.

Examples

A. Evaluation of effectiveness of early diagnoses

One of the factors limiting the rational use of AMHT in service is the lack of knowledge on the usefulness of treatment.

Below are stated a number of hypotheses of this type, that are of immediate relevance to the service use of AMHT in developed countries and could be of importance to its use in developing countries.

Each is a problem in its own right that needs to be solved before a screening preventive programme can be rationally initiated.

I will try to show the requirements for each study separately and then to examine the likelihood of increasing effectiveness by multiple studies of varying proportions. (See summary in Table 1).

The estimates are guesses based on some known United States and European costs, and some projections made as a result of informal and unpublished discussions two years ago on measurement of a very large number of factors by use of AMHT for research purposes.

1. Hypothesis

(a) Treatment of asymptomatic bacteriuria in pregnancy prevents maternal and foetal disease.

REFERENCES

- Kass, E. H. (1960) Archives of Internal Medicine, 105, 194; Treatment reduces risk
Little, P. J. (1966) Lancet, 2, 925; Treatment doesn't reduce risk, it might increase it
Smith, P. Kincaid (1965) Lancet, 1, 395, 1966; Progress in Pyelonephritis, page 11-26
Rosenheim, M. L. (1965) Ibid, page 369; Renal disease in late life is due to infection in infancy or childhood

¹ "The Use of AMHT for Health Services with Particular Reference to Developing Countries", Dr Aubrey Kagan and Dr Pierre Mansourian

Screen 50 000 women three to six months pregnant for bacteriuria.
1000 cases divided at random into treatment and placebo group.
Follow women for 18 months, child for one year.
Follow other women for 18 months, child for one year.
Note subsequent bacteriuria, renal, pregnancy, foetal, infant, maternal - disease.

(b) Determine the characteristics of women who benefit and who don't benefit from treatment as in (a).

As for (a) but: increase number of markers recorded, increase number of subjects studied times two.

(c) Determine pre-natal indicators of risk to pre-natal mortality, morbidity; maternal mortality, morbidity; foetal wastage.

Screen 5000-25 000 women of child-bearing age (number depends on pregnancy rate) for pregnancy.

Assessment of those becoming pregnant.
Follow up all pregnant, repeat pregnancy test, other tests.
Follow up post labour and the infant for one year.

2.

(a) Non-invasive carcinoma of the cervix remains non-invasive or resolves. Invasive carcinoma of the cervix is preceded by abnormal smears. Knox, E. G. (1966) Problems of Progress in Medical Care, Editor M. McClacian, London, page 277.

Screen 100 000 women aged 35-64 years three times in five years.
Assess natural history, incidence, prevalence and error rates.

(b) High risk of carcinoma of the cervix. Relation to intra-uterine device

As above, but more markers.

(c) Effect of screening and treatment of carcinoma of the cervix.
Incidence of carcinoma of the cervix.
As for (a) but follow up 100 000 unscreened women as well.

3.

(a) Screening doesn't reduce mortality from carcinoma of the breast. Incidence of carcinoma of the breast.

REFERENCE

Shapiro, S., Strax, P. & Venett (1966) Journal of the American Medical Association, 195, 631. A higher proportion of carcinoma found on screening without nodes than found without screening. Prevalence one to three per 1000 women at the age of 33 or more

Screen 40 000 women¹ aged 35-64 - clinical and mammography.
Follow with repeated screening for five to seven years.

¹ A study with 30 000 subjects in each group is being carried out. See also Strax, P. et al. (1967) Cancer, 20, 2184. Mammography and Clinical Examination in Mass Screening for Cancer of the Breast. Venet, L. et al. (1969) Ibid, 24, 1187, Adequacies and Inadequacies of Breast Examination by Physicians.

Follow 40 000 women¹ ages 35-64 unscreened.
Diagnose and treat as needed.

(b) High risk of carcinoma of the breast. Who benefits from treatment?

REFERENCE

Bullbrook, R. D. et al. (1962) Lancet, 2, 1238, Hormone high risk

As for (a) but additional markers.
Unscreened subjects unnecessary.

4.

(a) Screening for diabetics and borderline glucose intolerance followed by treatment reduces chance of - fundal, peripheral arterial, cardiac, renal, cerebral - complications; chronic infection; all mortality and morbidity.

Identify those who will benefit and those who won't.

Screen 50 000 men and 50 000 women aged 35-59 for glucose intolerance.

Assess markers in all.

Follow up the glucose tolerant with annual tests for five years.

Follow up the glucose intolerant: α diabetics, 2000 men and 2000 women treated to reduce glucose intolerance - for five years; β borderline, 3000 men and 3000 women divided into treated and placebo groups - for five years.

Follow up the rest for notification of illness, death and rescreen annually.

Follow up 25 000 men and 25 000 women unscreened - for diabetes notification and outcome.

Examine notified, five years.

Autopsy at death.

(b) Similar for hypertensives.

(c) Similar for hypercholesterolaemics.

(d) Similar for combinations.

Additional problems can be added to 2, 3, or 4 for little extra cost, e.g. preventive trials of endogenous depression.

High risk factors for endogenous depression.

Cost added \$ 200 000 (cost separate, \$ 5 million).

Retrospective studies of high risk to carcinoma of the bronchus, chronic bronchitis.

Cost when added \$ 200 000 (cost separate \$ 500 000 each).

Prospective study of high risk to alcoholism.

Cost added \$ 200 000 (cost separate \$ 5 million).

If children and young adolescents are studied: retrospective study of rheumatic heart disease would probably cost about \$ 200 000 (and about \$ 500 000 separately).

¹ A study with 30 000 subjects in each group is being carried out. See also Strax P. et al. (1967) Cancer, 20, 2184. Mammography and Clinical Examination in Mass Screening for Cancer of the Breast. Venet, L. et al. (1969) Ibid, 24, 1187, Adequacies and Inadequacies of Breast Examination by Physicians.

All these studies together would cost about \$ 9 million. If they were each done separately they would cost about \$ 33 million.

These costs, of course, are rather rough. They do not include development and feasibility studies, but for most of them AMHT methods are available. For 2, development is needed.

Because of the large numbers of subjects and factors to be studied AMHT would be ideal.

Some costs of past and present single purpose studies are given below for comparison:

1. Framingham: Observational-analytical coronary heart disease study - about \$10 million.
2. Heart drug study, secondary prevention by several drugs on coronary heart disease - about \$7 million +.
3. Tecumseh: semi-multipurpose study - about \$12 million.
4. Clofibrate single factor primary prevention coronary heart disease - about \$5 million.
- B. High risk to disease

This somewhat over-used term refers here to three related objectives:

identification of powerful predictors of susceptibility before disease occurs;

conception of new hypotheses of control of disease;

determination of norms.

The requirements are identification and examination of a large number of subjects; assessment of a large number of factors; record, storage, retrieval of data in a form suitable for analysis; storage of material; follow-up and occasional re-examination of subjects over a period of two to five years.

AMHT, if suitably adapted, would be essential for the preliminary biological assessment. It is an excellent mode in which to develop and use a subject identification procedure. It provides an excellent data storage and retrieval system. It might be the best system for re-examinations.

C. Determination of needs for comprehensive health care

Rational decision on the nature of a health service for a population depends, amongst other things, on a knowledge of the present state of health of the community.

Flimsy information on this is often accepted as the basis for decision on expenditure of large sums of money. This can seldom be rational and makes it difficult, if not impossible, to learn how to make better decisions and what information is needed for this.

In my opinion, in the present state of our ignorance, it is desirable to obtain a great deal of information on the present stage of health of people before planning either a service or research programme. This health "situational analysis" might well be carried out by means other than AMHT. The possibility of it being more effective or efficient by means of AMHT should be considered in each case.

IV. COST OF AMHT IN RESEARCH AND CONCLUSIONS

I have referred to research in commendatory terms that may cost \$5-\$50 per person examined, and earlier¹ indicated that service at 5 per person might not be acceptable in some countries.

There is, of course, a difference. The cost of the former is per person examined. That of the latter is per person in the population. In the research programme samples of population will be examined. If, as one would hope, the results will be extrapolated to at least 100 times as many people as are studied, the cost per person who stands to benefit is at most one-hundredth of the cost per person examined.

This is because the research is related to health service and can be regarded as part of the capital cost of the latter.

Although I have been talking about quite large sums of money for research - \$5-\$20 million - this is small in comparison to the cost of a health service - e.g. India, about \$250 million; United Kingdom, about \$5000 million per year.

Research is likely to result in a saving, e.g. by indicating that some of the accepted methods of screening or "treating" precursors of disease are ineffective or that other methods are effective. This saving is operative over a long period of time and likely to be applicable to many communities. It is therefore likely to be large.

All this discussion is applicable to both developed and developing countries.

From the argument in "The Use of AMHT for Health Services with Particular Reference to Developing Countries" by Kagan and Mansourian it can be inferred that in the present state of our knowledge an AMHT system given as a gift to a developing country is likely to incur additional expense that could not be afforded and to be insufficiently effective for service purposes.

The reverse can be said of AMHT in research. Certain kinds are likely to be made possible and/or more effective and efficient by use of AMHT. A gift for research might result in affordable and effective service.

The place for research has to be selected with care. Providing it is suitable the results are likely to be beneficial far beyond the bounds of the country in which research is done.

The situation is summarized in Table 2A and 2B.

¹"The Use of AMHT for Health Services with Particular Reference to Developing Countries" by Dr Aubrey Kagan and Dr Pierre Mansourian

TABLE 2A. AMITT IN RESEARCH

I Function	II Actual needs	III Limits of present provision	IV Usability	V Can/can't provide needs	VI Suitable action follows	VII Reliability precision	VIII Costs	IX Effectiveness	X Future
<p>A. Test Effectiveness of Early Diagnosis</p>	<p>1. Screen large numbers of subjects for (a) early diagnosis (b) precursors (c) other risk factors 2. 'Treated' 'control' design. 3. Follow up for change and end points</p>	<p>Possible but expensive. Large numbers a limiting factor.</p>	<p>Transportable system ideal</p>	<p>II.1.1.b & c Many possible now II.1.1.a. Some possible now. Development needed. Large numbers not limiting factor</p>	<p>Unsuitable action prevented. Information aids discussion on 'optimal' action</p>	<p>Often poor but system ideal for improving, assessing, and controlling</p>	<p>\$5-\$50 per head but reduced by whom resists extra-polatable (≈ 1/100)</p>	<p>1. Makes multipurpose testing possible. 2. May be only practical approach</p>	<p>1. Some aspects need development (record and identification; assessment of some factors). 2. Could become quick, humane, rational substitute for slow and natural (and disappearing) method of survival of the fittest.</p>

TABLE 2B. AMHT IN RESEARCH

I Function	II Actual needs	III Limits of present provision	IV Usability	V Can/can't provide needs	VI Suitable action follows	VII Reliability precision	VIII Costs	IX Effectiveness	X Future
<p>B</p> <p>Define Characteristics of High Risk.</p> <p>1. Identify predictors.</p> <p>2. Conceive new hypothesis.</p> <p>3. Determine 'norms'.</p>	<p>1. Identify and examine large numbers of subjects for a large number of factors.</p> <p>2. Record storage and retrieval of data.</p> <p>3. Follow up.</p>			<p>Additional information not obtainable by AMHT but needed e.g. environmental, habitual, exposure and reactions.</p> <p>Facilities available.</p>					
<p>C</p> <p>Identify needs for comprehensive health care.</p>	<p>Assessment of many factors in moderately large numbers of subjects.</p>			<p>Use of facilities.</p>				<p>May be most effective especially if combined with other purposes but each case needs consideration on its own merits.</p>	<p>Multipurpose mobile research system to cover large areas.</p>