Department of Epidemiology
School of Public Health
University of North Carolina

H. A. Tyroler

The Epidemiological Method

These notes are designed to serve as an outline for introductory lectures in epidemiology. The objective is to develop a conceptual frame upon which the contemporary uses of epidemiology can be structured. The content is designed to be general enough to be of interest to professional health workers of diverse backgrounds, and detailed enough in specific illustrations to be meaningful and relevant. The introductory nature of these notes is to be emphasized. Sophisticated, specialized techniques will not be considered. There will, however, be no sacrifice of rigor in the fundamental principles presented. Substantive detail will be of illustrative interest only.

The major concept to be developed is the common nature of the formal structure underlying diverse types of epidemiological investigations. That which is common to these activities in the presence of their diversity will be illustrated by examples of experimental, analytical and descriptive surveys.

The epidemiological technique can best be approached by a flow diagram presentation of the clinical trial of treatment for a disease. (Figure 1).

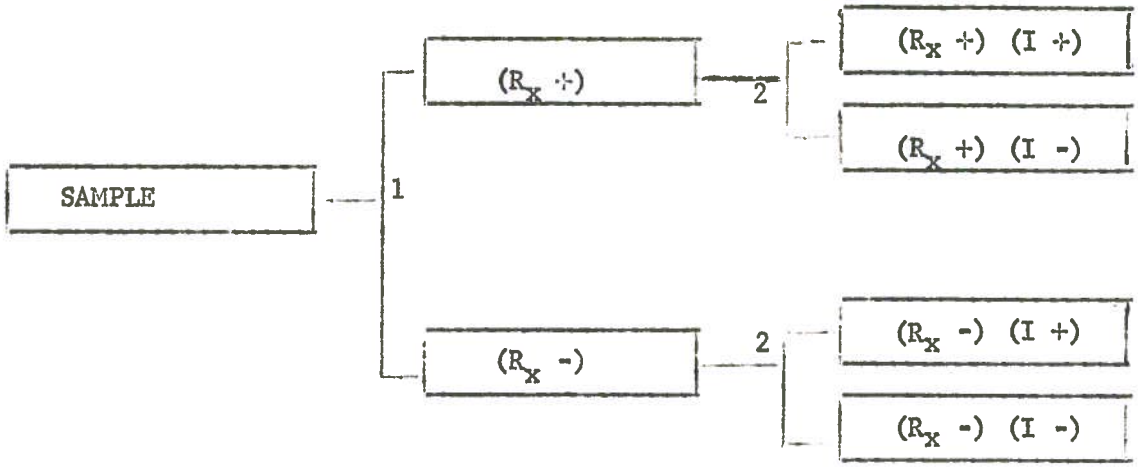


Figure 1

A defined sample of initially comparable patients are assigned (1) into a treatment group (R_x +) and a control non-treatment group (R_x -). After a period of time the individuals in each group are re-evaluated (2) and classified into groups of those either with improvement (I +) or without improvement (I -). The simpliest and most direct question asked of this experiment is whether or not there is the same proportion of improved patients in the treated as in the control group.

Let us illustrate this with a factual example. One of the first scientifically designed clinical trials was performed as recently as 1946 in evaluating the efficacy of streptomycin treatment of pulmonary tuberculosis.[1] The investigators chose patients of a restricted age range presenting with similar disease states. The investigator's resources were limited and "it was desired to eliminate as many of the

---

[1]British Medical Journal 1948 ii, 769.

obvious variations as possible"...."The type of case to be investigated was defined as follows: Acute progressive bilateral pulmonary tuberculosis of presumably recent origin, bacteriologically proved, unsuitable for collapse therapy, age group 15 to 25 (later extended to 30).

The selection of this type of disease constituted full justification for having a parallel series of patients treated only by bed-rest. Since up to the present this would be considered the only suitable form of treatment for such cases."

Patients fulfilling these criteria were selected, randomly allocated to either the streptomycin and bed-rest treatment group or the bed-rest only control group. Patients were not informed of the investigation under way. Periodic evaluations were performed using objective criteria and wherever possible the observers were unaware of the treatment status of the patients. These two techniques--random allocation to treatment groups, and the "double blind" approach are central to the experimental nature of the clinical trial. More will be said of them later.

Monthly evaluations were recorded and one objective criterion of response was the "Assessment of Radiological Appearance at Six Months as compared with appearance on admission". A modification of Table 2 of the original report including the numbers of patients in each category would look as follows in the form of our schematic outline.

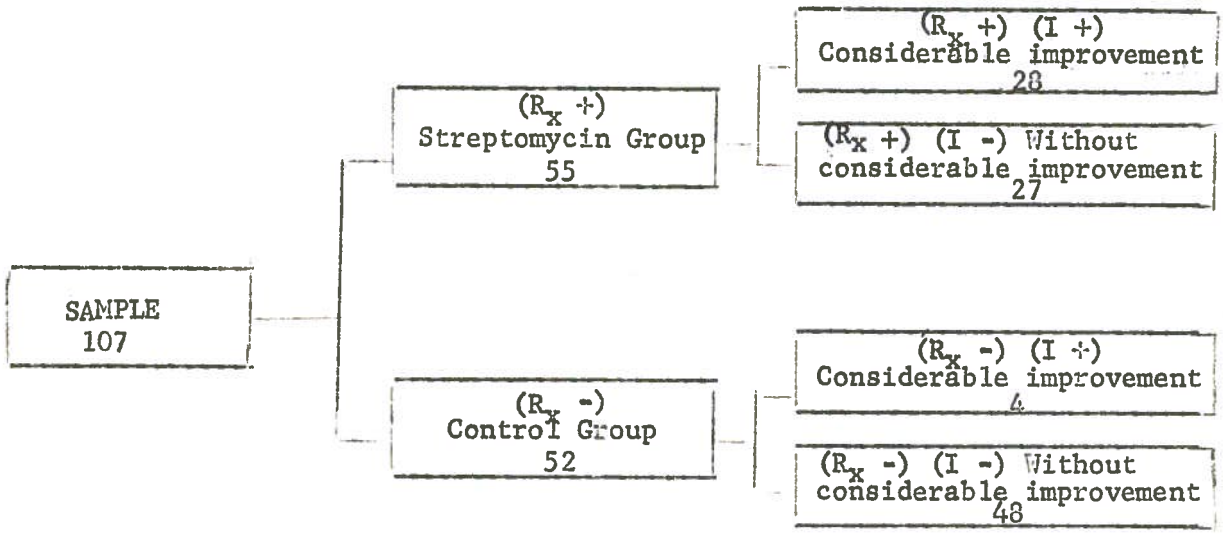


Figure 2

Returning to the basic question: is the proportion of improved patients the same in the treated and control groups? The question now becomes a simple numeric comparison.

$$\frac{(R_x +)\ (I +)}{(R_x +)} \stackrel{?}{=} \frac{(R_x -)\ (I +)}{(R_x -)}$$

$$\frac{28}{55} \stackrel{?}{=} \frac{4}{52}$$

$$0.51 \stackrel{?}{=} 0.08$$

Obviously the proportions are not equal. We now ask two questions. First, could the observed difference be a random happenstance likely to have occurred by chance and not necessarily to be expected again if we treat another series of patients. The design of the clinical trial permits us to approach this question by biostatistical techniques. The patients were initially comparable in age, duration and severity of disease. The random allocation to treatment and control

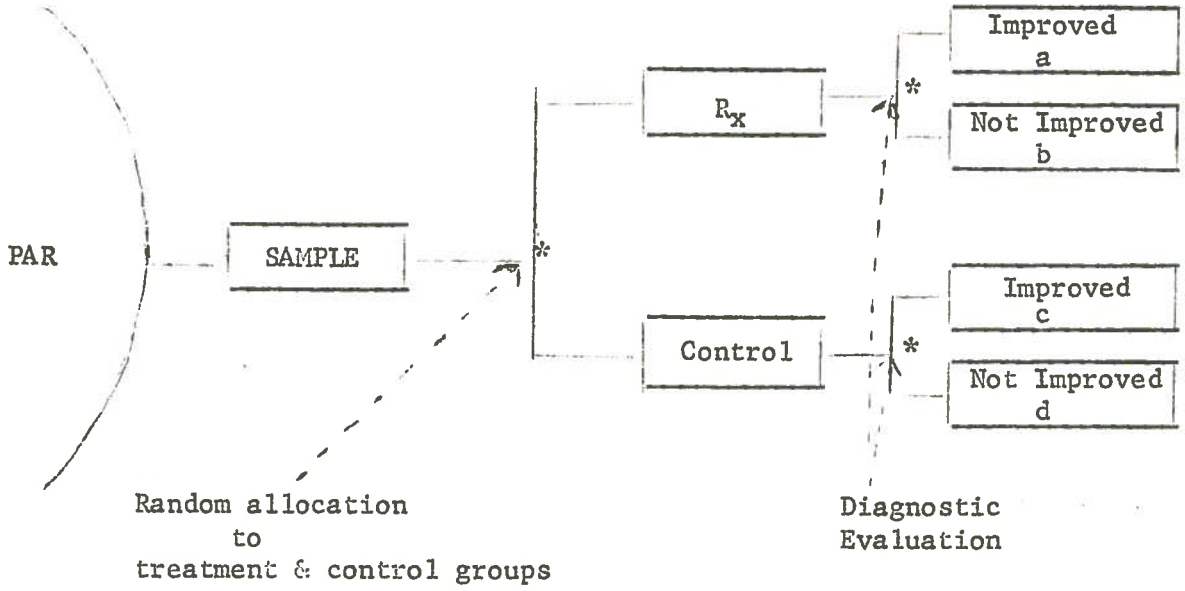
groups made measurable the probability of chance assignment of individuals to groups with these different ratios of improvements (0.51 vs. 0.08). The authors utilized statistical techniques to compute this probability, and found that the probability of this difference or a larger one occurring by chance alone is less than one in a million.

The second questions is whether or not the statistically demonstrated superiority of drug treatment over the bed-rest control treatment is medically meaningful. In this example the magnitude of difference of improvement ratios is sizeable as well as statistically significant. In other instances relatively small differences will be statistically significant. In all trials medical considerations of costs, sequalae, side effects and toxicity must be appraised against the statistical improvement ratio. In addition we must keep in mind that the results of our experiment on a sample are generalizable only to the population of which the cases studied are a sample. In the clinical trial of streptomycin treatment the results are generalizable only to hospitalized patients with age and disease characteristics as defined. Younger or older patients, those with more or less severe disease may or may not have the same response to streptomycin. Whatever their response may be it is not necessarily predictable from this experiment alone.

We are now able to set up a general outline of the structure of the clinical trial.

Steps in the Experimental Epidemiological Method as Illustrated by the Clinical Trial

1. Schematic Outline:



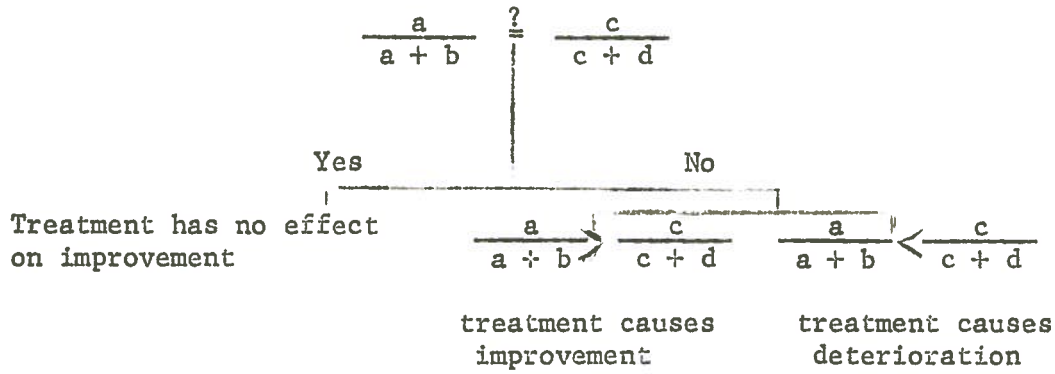
*Points at which double blind technique maintained (Patients and observers unaware of treatment category)

2. Data processing:

Collection, recording, tabulation and display of data.

		Evaluation		
		Improved	Not Improved	
Treatment	Drug	a	b	a + b = all in R_x group
	Control	c	d	c + d = all in control group
		a + c = all improved	b + d = all not improved	a + b + c + d = total sample

3. The quantitative comparison:



4. Statistical analysis.

5. Medical interpretation.

Data Processing

It has been found useful for the purposes of this introductory series to provide practical experience in data processing. Material from the streptomycin evaluation clinical trial has been recorded in punch card form. Utilizing the optical coincidence technique permits each student to have his own deck of cards and to perform data processing and table generation exercises without the use of any ancillary equipment.

The basic principle of optical coincidence data processing is simply that of having a separate document (or punch card) for each attribute measured. For example, one card would represent patients in the streptomycin group, another patients in the control group. The set of cards must represent mutually exclusive and exhaustive attributes of a characteristic. In the instance of treatment each individual is uniquely assigned to either the streptomycin or control group.

Similarly for evaluation status there would be one card for considerable improvement and one card for absence of considerable improvement. Each patient would uniquely be represented in one of these categories.

The code involves both physical location on the card and the presence or absence of a punch. The location uniquely identifies a patient. It can be thought of as the "address" in cartesian coordinates of an identification number. Mr. Jones, case number 26, can be located in Row 2, Column six on each attribute card. The presence of a hole punched on an attribute card in location Row 2, Column 6 signifies that Mr. Jones has the attribute represented by that card. Using a standard card with twelve rows and 80 columns permits simple analysis of a series of 960 patients.

Superimposing two attribute cards tests for the joint presence of two attributes in the same patients. The light transmitted through both the cards "streptomycin" and "considerably improved" identifies those, and just those patients who had the joint attributes of streptomycin treatment and considerable improvement. These can be counted and represent group "a" of our schematic outline (Figure 2). Similarly superimposition of "control" and "considerably improved" documents permits quantification of group "c". The completion of the tabulation of this data should be obvious.

Attributes need not be restricted to two in number in the use of this technique. Any number satisfying the criterion of a mutually exclusive and exhaustive nature can be utilized. For example, the original report of the clinical trial of streptomycin Table 2 does not divide radiological assessment into "considerable improvement" and "not considerable improvement." Rather what we have grouped together as "not

considerable improvement" consisted in the original report of the categories "moderate improvement", "no change", "moderate deterioration", "considerable deterioration" and "deaths".

An optical coincidence deck has been prepared permitting the student to generate Table 2 of the original report. (See attachment).

Table 2. Assessment of Radiological Appearance at Six Months as Compared With Appearance on Admission

Radiological Assessment	Streptomycin Group		Control Group	
Considerable improvement	28	51%	4	8%
Moderate or slight improvement	10	18%	13	25%
No material change	2	4%	3	6%
Moderate or slight deterioration	5	9%	12	23%
Considerable deterioration	6	11%	6	11%
Deaths	4	7%	14	27%
Total	55	100%	52	100%

The exercise developed to this point documents the utility of the experimental clinical trial in appraising the efficacy of streptomycin treatment. In addition Table 2 contains interesting information of a descriptive epidemiologic survey nature. Both the control and treatment groups exhibit marked variability in the course of the disease. The control group, in particular, with no treatment but bed-rest is illustrative of the so called natural history of the disease. In directing attention to populations the survey technique often is the only practical approach. In contrast to the experiment, factors under study cannot be randomly nor experimentally assigned to patients. The problem becomes one of appraising and disentangling multiple causative and determinative factors

as they present themselves to observation rather than to experimental manipulation and control. For example a question often asked is what distinguishes patients showing considerable improvement from those progressing on to death given the same treatment regimen. Asking and answering questions of this type referrable to populations of patients is an illustration of the analytic epidemiologic survey.

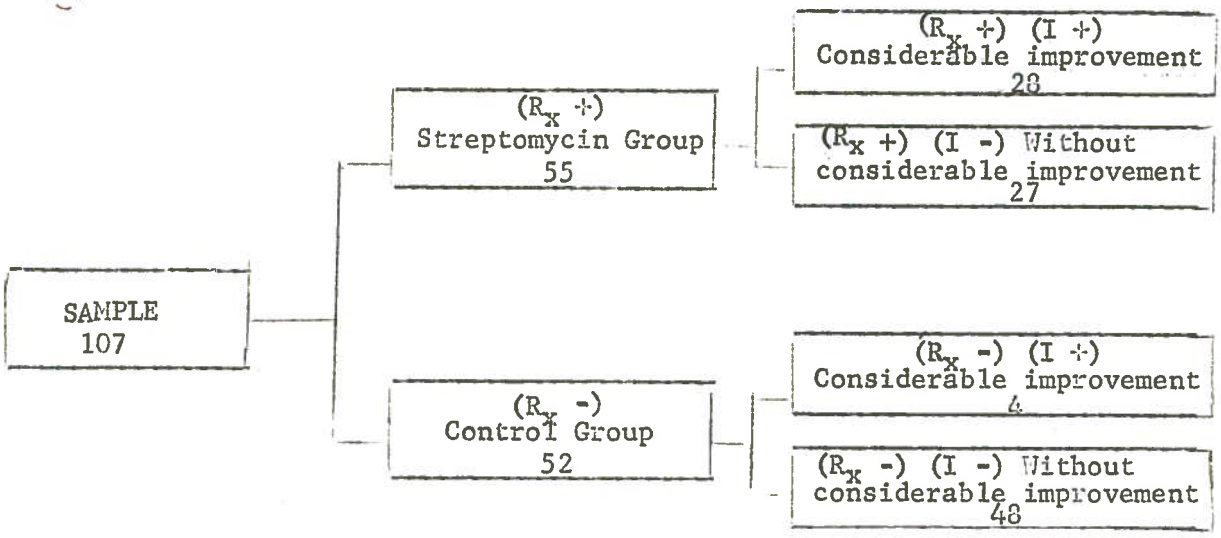
An example is provided by the streptomycin clinical trial in which the six month status of both the control and streptomycin groups is related to the presence of cavitation on admission. Continuing with the optical coincidence technique of data processing, students can generate Table 4 of the original report.

Table 4. Radiological Assessment at Six Months Related to Presence or Absence of Gross Cavitation on Admission

			Radiological Assessment at 6 Months					
			Improvement		No Change	Deterioration		
X-Ray on Admission	Group	Total Cases	Considerable	Slight or Moderate		Slight or Moderate	Considerable	Deaths
Cases with large or multiple cavities	S	32	11	7	2	4	4	4
	C	30	1	8	2	6	2	11
Other cases	S	23	17	3	0	1	2	0
	C	22	3	5	1	6	4	3

In addition to streptomycin efficacy Table 4 shows evidence of much poorer prognosis for each group if cavitation is present on admission. There is little difficulty in understanding and interpreting this relationship. In this instance it is so evident as to be trivial--the more

advanced the pathological changes on admission the more likelihood of deterioration or death. The initial condition obviously influences the outcome. Nevertheless it is important to recognize the difference between appraisal of the influence of the "initial condition" and the "efficacy of streptomycin". Streptomycin was experimentally administered, the initial clinical condition was not. Research design permits statistical analysis in one instance; the other requires knowledge of pathology for interpretation.



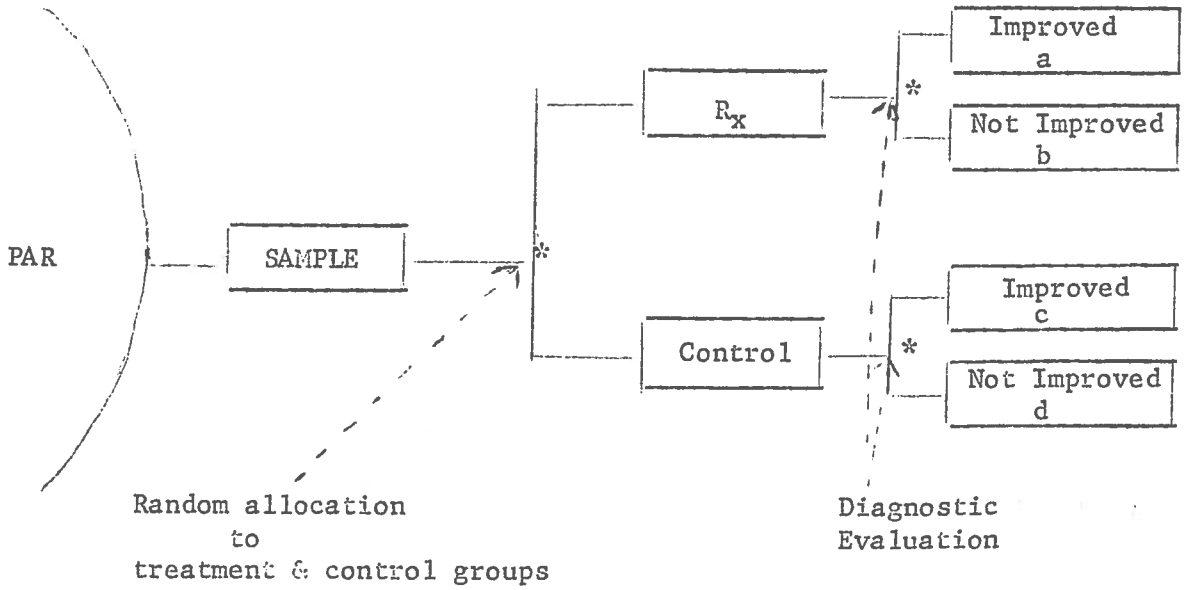
$$\frac{(R_x +)\ (I +)}{(R_x +)} \stackrel{?}{=} \frac{(R_x -)\ (I +)}{(R_x -)}$$

$$\frac{28}{55} \stackrel{?}{=} \frac{4}{52}$$

$$0.51 \stackrel{?}{=} 0.08$$

Steps in the Experimental Epidemiological Method as Illustrated by the Clinical Trial

1. Schematic Outline:



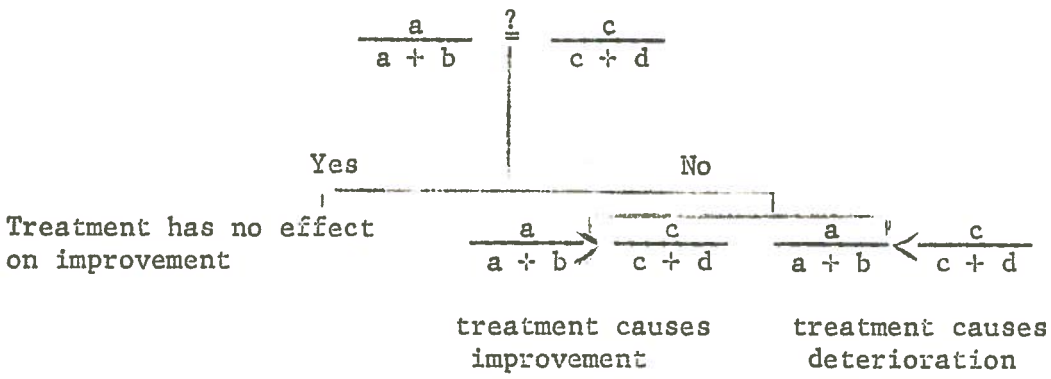
*Points at which double blind technique maintained (Patients and observers unaware of treatment category)

2. Data processing:

Collection, recording, tabulation and display of data.

		Evaluation		
		Improved	Not Improved	
Treatment	Drug	a	b	a + b = all in R_x group
	Control	c	d	c + d = all in control group
		a + c = all improved	b + d = all not improved	a + b + c + d = total sample

3. The quantitative comparison:

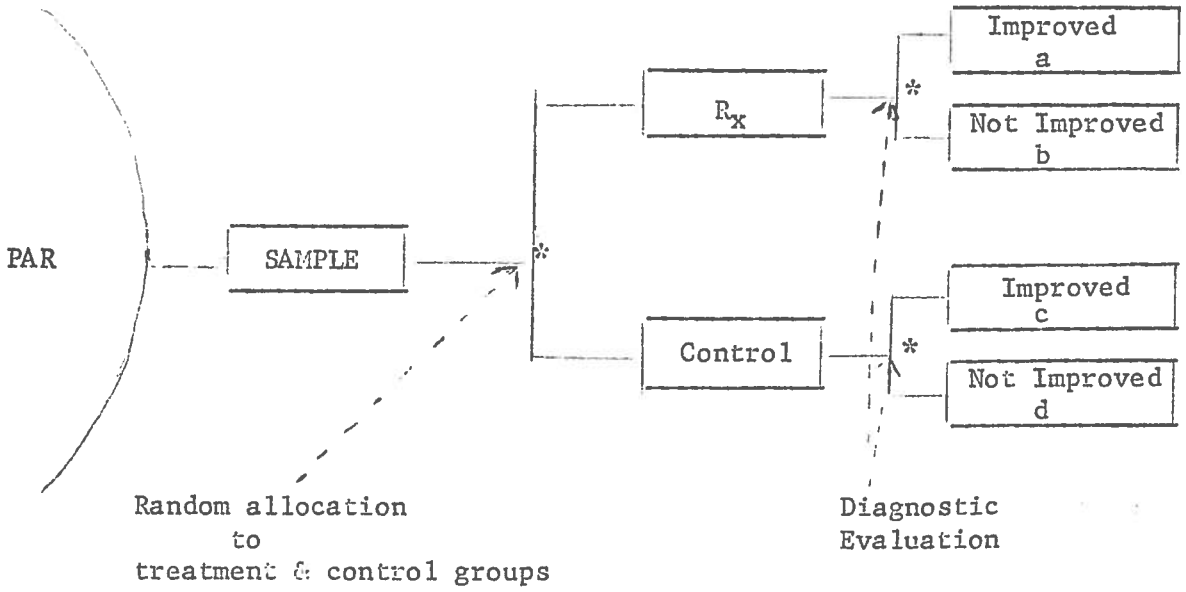


4. Statistical analysis.

5. Medical interpretation.

Steps in the Experimental Epidemiological Method as Illustrated by the Clinical Trial

1. Schematic Outline:



*Points at which double blind technique maintained (Patients and observers unaware of treatment category)

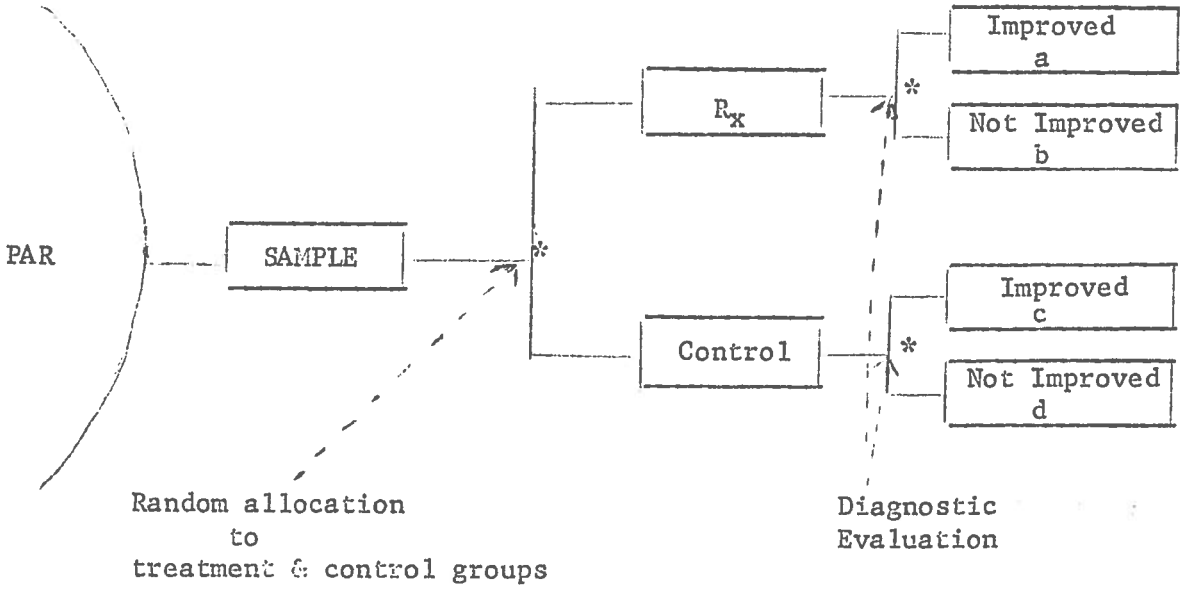
2. Data processing:

Collection, recording, tabulation and display of data.

		Evaluation		
		Improved	Not Improved	
Treatment	Drug	a	b	a + b = all in R_x group
	Control	c	d	c + d = all in control group
		a + c = all improved	b + d = all not improved	a + b + c + d = total sample

Steps in the Experimental Epidemiological Method as Illustrated by the Clinical Trial

1. Schematic Outline:



*Points at which double blind technique maintained (Patients and observers unaware of treatment category)

2. Data processing:

Collection, recording, tabulation and display of data.

		Evaluation		
		Improved	Not Improved	
Treatment	Drug	a	b	a + b = all in R_x group
	Control	c	d	c + d = all in control group
		a + c = all improved	b + d = all not improved	a + b + c + d = total sample