details of the register, including operational details and the design of the register cards, will be published later.

Results

Data on 478 families have been collected. In 83 families the disorder in question either proved not to be genetic or the cause was unresolved. No individuals were considered to be at risk in these families. The distribution of the various types of genetic disease (see Table) among the remaining families is not representative of the population as a whole, but partly reflects the department's particular interests—for example, in the X-linked muscular dystrophies.

Of the 478 families, 249 were referred specifically for genetic counselling—50 autosomal dominant, 56 autosomal recessive, 33 X-linked recessive, 61 multifactorial, 22 chromosomal, and 27 in which the disorder was either not genetic or the cause was unresolved.

Individuals at risk of becoming affected themselves mainly concerned autosomal dominant disorders—that is, 245 out of a total of 280 subjects were considered to be at risk. This is mainly because many of these disorders were of late onset and occurred in large families—for example, myotonic dystrophy, Huntington's chorea, and polyposis coli.

Of 717 subjects at risk of having an affected child or of having a carrier daughter (X-linked recessive disorders), autosomal dominant and X-linked disorders accounted for 646. In the case of autosomal dominant disorders many were at risk both of becoming affected and of having affected children.

A total of 56 affected children ("preventable cases") were born to parents who, a priori, were at high risk of having affected offspring. There were a further 94 individuals at high risk of becoming affected, but so far they have shown no signs of the disease.

Discussion

Our results indicate that the main scope for preventing genetic disease lies with the simply inherited disorders, because in general the proportion of individuals at high risk is greater than in the case of multifactorial and chromosomal disorders. Even in simply inherited disorders, however, it will be possible to prevent only a proportion of cases, since some will occur in families in which there has been no previous history of the disease.

Only a relatively small proportion of individuals at risk of having affected children (or carrier daughters in the case of X-linked disorders) were referred specifically for genetic counselling (101 out of a total of 717, or 14%). Many affected children were born to parents who, a priori, were at high risk of having affected children but who had never been counselled and were therefore unaware of the risks. Others were referred for counselling only after the birth of an affected child which might otherwise have been prevented. At present no defined procedure for tracing such individuals exists. Herein lies the value of a genetic register system.

The first step in such a system is the ascertainment of those at risk. This could be achieved through general practitioner, hospital, and health department records linked to a genetic register. The next step is to develop procedures for contacting, through their family doctors, individuals who are found to be at risk. The final step is to provide adequate advice and follow-up for those at risk. The latter could be achieved through a genetic register system. This approach to the prevention of disease could have important implications, both for the individual and for society. Not only would such a register be of value in tracing and following up those at risk of having affected children but it might also be of value in alerting individuals with inherited susceptibilities to drugs and for detecting aid eradicating life-threatening complications of genetic disease, such as intestinal malignancy in polyposis (McKusick, 1969). The main function of such a register system, however, would be to prevent genetic disease.

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Assessing Reports of Therapeutic Trials

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Summary: A check list is described which helps the systematic assessment of reports of therapeutic trials, particularly the aspects that need to be considered in assessing their validity. The check list was used to examine 141 reports of therapeutic trials published in four British non-specialist journals in the first six months of 1966 and of 1969. Of these reports 51% were found to be acceptable and a further 16% probably acceptable; 33% were considered unacceptable because they lacked one or more of the features required in a valid report. The check list has been found useful in assessing claims made for drugs and other therapeutic measures on the basis of published reports.

Introduction

Every doctor who reads reports of therapeutic trials has to face the problem of assessing their validity and their relevance to his practice. Though much is now known about what constitutes a satisfactory therapeutic trial, only those who spend their time planning, executing, and studying such trials can efficiently assess reports of trials.

One of the earliest criteria of a satisfactory trial to be

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recognized was the use of appropriate controls, and several series of published reports have been assessed solely on this criterion (Ross, 1951; Patterson, 1962). Other important points considered in assessing reports in subsequent studies were random allocation of treatments, the use of objective measures (preferably double-blind), and the statistical analysis used (Mahon and Daniel, 1964; Reiffenstein, Schiltroth, and Todd, 1968).

TABLE I.—*Check List for Assessing a Therapeutic Trial Report*—Side 1

Author and Journal reference

Y = Yes
N = No, or not clear
D = Doubtful

Title

1. *AIM*: specific ☐, or not clear ☐; single ☐, or multiple ☐

2-4. *DESCRIPTION OF SUBJECTS, DRUG ADMINISTRATION, ETC.* ARE THE FOLLOWING SPECIFIED?

2·1	Healthy subjects or patients?	Y	N
2·2	Volunteers or not?	Y	N
2·3	Age	Y	N
2·4	Sex	Y	N
2·5	Race	Y	N
2·6	Criteria of selection	Y	N
2·7	Contraindications	Y	N
2·8	Presence of disease other than that treated	Y	N
2·9	Whether additional treatments were given	Y	N
	If they were, are they described?	Y	N
3·1	Daily dose	Y	N
3·2	Frequency of administration	Y	N
3·3	Hour(s) o'clock when given	Y	N
3·4	Route of administration	Y	N
3·5	Source of drug (e.g., name of manufacturer)	Y	N
3·6	Presentation (e.g., tablet, syrup, etc.)	Y	N
3·7	Timing of drug administration in relation to factors affecting absorption (e.g., meals)	Y	N
3·8	Checks that drug was taken	Y	N
3·9	Other therapeutic measures (if drug was not used)	Y	N
	If yes, are they described?	Y	N
3·10	Total duration of treatment	Y	N
4·1	Persons who made the observations	Y	N
4·2	Inpatient/outpatient	Y	N
4·3	Setting (e.g., one or several hospitals/clinics/wards)	Y	N
4·4	Dates when trial began and was completed	Y	N

5. *METHODS AND DESIGN*

5·1	Are the methods of assessing therapeutic effects clearly described?	Y	N
5·2	Were these standardized methods?	Y	N
5·3	Were control measures used to reduce variation that might influence the results?	Y	N

If *yes*, specify:

Concurrent controls	☐	Patient his own control	☐
Stratification or matched subgroups	☐	Identical ancillary treatment	☐
Run-in period	☐	Other	☐

5·4	Were controls used to reduce bias?	Y	N

If *yes*, specify:

"Blind" observers	☐	"Blind" patients	☐
Matching dummies	☐	Random allocation	☐

TABLE II.—*Check List for Assessing a Therapeutic Trial Report*—Side 2

6. *ASSESSMENT OF THE TRIAL*

6·1	Were the subjects suitably selected in relation to aims (see sections 1 and 2)?	Y	N	
6·2	Were the methods of measurement valid in relation to the aim?	Y	N	
6·3	Were they adequately standardized?	Y	N	
6·4	Were they sufficiently sensitive?	Y	N	
6·5	Was the design appropriate?	Y	N	
6·6	Were enough subjects used?	Y	N	
6·7	Was the dosage appropriate?	Y	N	
6·8	Was the duration of treatment adequate?	Y	N	
6·9	Were carry-over effects avoided or allowed for?	Y	N	
6·10(a)	If no controls were used were they unnecessary?	Y	N	
(b)	If controls were used were they adequate?	Y	N	
6·11	Was comparability of treatment groups examined?	Y	N	
6·12	Are the data adequate for assessment?	Y	N	
6·13(a)	If statistical tests were not done were they unnecessary?	Y	N	
(b)	If statistical tests are reported			
	(i) Is it clear how they were done?	Y	N	
	(ii) Were they appropriately used?	Y	N	D

ARE THE CONCLUSIONS JUSTIFIED?

Completely ☐ Partially ☐ No ☐

COMMENTS

Is the trial ACCEPTABLE?

Definitely yes ☐ Probably yes ☐ No ☐

Useful as these methods are, they are too rough-and-ready to permit a full assessment of reports. Very detailed analyses have been made of reports of drug trials in psychiatry (Sandifer, Dunham, and Howard, 1961; Smith, Traganza, and Harrison, 1969), but the systems used are difficult to apply to reports concerning other branches of medicine. What is needed is a practical and flexible approach which combines generality with comprehensiveness. We have tried to provide such a systematic approach, and hope that it will facilitate the assessment of any therapeutic trial in the way in which systematic examination of a patient facilitates good diagnosis.

Check List

The method of assessment we have developed is based on a check list which can be applied to any report of a prospective investigation of a therapeutic effect in patients. The list focuses attention on the various features that may be important. These vary with the disease, the setting, and the authors' methods of assessment. For this reason some items may not be needed in assessing a particular report. They are included in the check list so that they will not be forgotten where they are needed.

The check list is in two main parts, each of which occupies one side of a sheet of foolscap. The first, sections 1 to 5 (Table I), examines the aim, the authors' description of their subjects, the way in which the drugs or other therapeutic measures were used, and the authors' experimental design and methods of assessment. All the questions in these sections can be answered by consulting the report of the therapeutic trial. It is necessary to check that the authors' descriptions are sufficiently clear and complete to enable the reader to interpret their findings.

The second part of the check list (Table II) helps the reader to consider whether the various criteria of a satisfactory therapeutic trial have been met, whether the data are adequately presented, and whether the conclusions are justified. These questions require some critical judgement based on acquaintance with the therapeutic problem under study. The decision whether a report is acceptable or not is best made after such a systematic examination of the relevant points.

Survey of Four Journals

Method

With the help of the check list we have examined all the reports of therapeutic trials published in four non-specialist British journals, two weeklies and two monthlies, between January 1 and June 30 in 1966 and in 1969. We chose these journals because each of them publishes many reports of clinical trials which are widely quoted. Reports described as preliminary or pilot studies were excluded because such trials primarily serve to establish an effective dosage and to reveal unwanted effects; they rarely give much information on efficacy.

Reports were considered *acceptable* where the criteria fulfilled included among others a clear definition of the aim of the trial, an adequate description of the subjects and of the treatment, appropriate methods of assessment, the use of adequate controls where necessary, and the use of appropriate statistical tests where such tests were needed to assess the results. Reports were classed as *not acceptable* if they had one or more of the following defects: poor or inappropriate methods of assessment, absent or inadequate controls, and lack of relevant statistical tests where they were needed. A report was classed as *probably acceptable* when the trial was apparently satisfactory but the report lacked important descriptive information, so that its validity was difficult to assess. The main defects were inadequate description of the subjects or of the authors' methods, or lack of information on the comparability of treatment groups.

Findings

Of the 141 trials examined 51% were definitely acceptable, 16% probably acceptable, and 33% unacceptable. Though over half the reports were acceptable, some of these could have been improved by better description. Information about the race of the patients studied was given in very few reports, though important racial differences are known to exist in the responses to various drugs. In many parts of the world a hospital address is no longer a reliable guide to the racial origins of its patients. Many reports do not state whether any additional therapeutic measures were used apart from the treatment under investigation; or such measures are mentioned only in a throw-away phrase.

Sometimes important details of treatment are omitted. For example, in an interesting and important trial of prednisone in the treatment of cirrhosis of the liver, the daily dose was described as "a minimum of 10 mg." The reader is not told how an individual patient's dose was decided, nor the range within which it varied. Variation in dosage might be expected to have some effect on the results. Another shortcoming in the same trial concerned the allocation of patients to treatments. This was determined by a digit in the patient's date of birth, a method which is less satisfactory than the use of a table of random numbers.

In a trial of azathioprine in rheumatoid arthritis the dosage was 2·5 mg./kg./day, but the report does not state whether this was given as a single dose or in divided doses. Whether the dose is divided or not might influence the therapeutic effect and with many drugs is known to do so. Checks that the patient has taken the treatment he has been given are still incorporated in few studies, though it is now well known that many patients are very unreliable in this respect (Joyce, 1962; Porter, 1969); in some trials as many as 50% defaulted. Undetected failures to take medication may invalidate a trial.

In a few reports the authors' conclusions were not completely justified by the findings reported, but the data appeared sound, and since the reader could reach useful conclusions of his own we considered these reports acceptable.

In the reports which we considered "probably acceptable" the shortcomings were more difficult to overlook. Most frequently the method was inadequately described (Table III).

TABLE III.—*Trials Assessed as "Probably Acceptable"*

Reason*	No. of Trials
Subjects inadequately described	5
Methods inadequately described	15
Comparability of treatment groups not examined	2
Too few subjects	2
Other reasons	2
Total	23*

*Some trials had more than one of these defects.

TABLE IV.—*Trials Assessed as "Not Acceptable"*

Reason*	No. of Trials
Methods inadequate	19
Methods inappropriate	3
Controls not used where required	23
Controls inadequate	16
Statistics not reported where required	32
Total	46*

*Many trials had two or more of these defects.

For example, in a trial of analgesics in acute myocardial infarction patients were classified according to the severity of their pain. But the authors do not say how mild, moderate, and severe pain were distinguished from one another. An example of poor description of the subjects occurred in a report of a trial comparing the value of two corticosteroids injected into arthritic joints. The patients and their joints were described in these words: "Patients attending a special clinic for intra-articular injections volunteered to take part in the trial. Thirty joints were investigated of which 15 were hips, 13 knees, and 2 thumbs. The diagnosis in 27 was osteoarthrosis, in 1 rheumatoid arthritis, and in two mixed osteoarthrosis and rheumatoid arthritis." Important information that is missing includes the severity and chronicity of the arthritis.

TABLE V.—*Assessments of Reports of Trials Published in Four Journals in the First Six Months of* 1966 *and* 1969

Category (see Text)	Two Weeklies		Two Monthlies	
	1966	1969	1966	1969
Acceptable	25	33	4	10
Probably acceptable	5	5	8	5
Not acceptable	10	4	16	16
Total	40	42	28	31

Reasons for finding reports unacceptable were more serious than merely inadequate description (Table IV). Controls were absent or inadequate in 39 out of 46 unacceptable trials, but inadequate or inappropriate methods also contributed significantly. An example was a trial of an antihypertensive drug carried out by 38 general practitioners. The report described the method used in one sentence: "Blood pressure readings were taken before and after a period of treatment not less than 12 weeks and not exceeding 16 weeks." Such use of casual and unstandardized measurements is inadequate for assessing drug effects on blood pressure. Lack of statistics was also common, but always occurred together with some other major defect; no report was classed as unacceptable solely because statistics were absent.

Differences Between Journals

There was a striking difference between the weeklies and the monthlies; the reports in the weeklies were predominantly acceptable, whereas those in the monthlies were not. This difference was similar in 1966 and 1969 (Table V); in the weeklies, however, the number of unacceptable reports decreased, whereas in the monthlies it remained unchanged. The total number of reports published by the individual journals was very similar in the two six-month periods; for the two weeklies the means were 26 and 15 reports respectively, for the monthlies 19 and 10.

Differences Between Observers

Each of us independently assessed all the reports using the check list. Differences on individual items occurred in about one-third of the assessments. They mostly concerned minor items of description; for example, one observer would regard age as having been specified by the mention of "women in the reproductive age group," while the other would not accept this as sufficiently clear. Other differences arose when one observer spotted a difficulty that had been overlooked by the other. In all these instances the differences were resolved by re-examining the report and discussing the particular point. This is, of course, analogous to the occurrence and resolution of observer variation in clinical medicine. A more detailed study of observer variation in the use of the check list is now under way.

Discussion

The use of controls, double-blind evaluation of therapy, and statistical analysis of results are now recognized as important

features of drug trials whose presence or absence has been used to assess reports of trials (Ross, 1951; Mahon and Daniel, 1964; Reiffenstein *et al.*, 1968). Such a method of assessing reports may, however, give the impression that if these requirements are met then the therapeutic trial must be reliable and valid. It overlooks the fact that many other points—for example, the selection of patients, the dose, mode of administration of the drug, and method used to assess the response to treatment—can be equally important in determining the validity of a trial. Use of the check list ensures that features which may be important in assessing the report of a particular therapeutic trial will not be forgotten.

The lack of important items of description in some apparently well-designed and well-executed trials is not necessarily the fault of the authors, but may at times be due to editorial insistence that papers be short. The check list can help not only authors writing up reports, but also the editors to whom they are submitted, to ensure that all the essential information needed to assess the reports is included. It can also help the individual doctor to reach a soundly based conclusion on the validity of a report in the same way as a thorough clinical examination of a patient helps him towards a correct diagnosis.

The check list, however, should not be regarded as an automatic device for assessing the quality of a report. Its proper use requires some familiarity with the various factors that may influence the results in a particular therapeutic situation.

The use of check lists can be extended to reports of investigations other than therapeutic trials—for example, case reports of unwanted effects of drugs, reports of retrospective studies, and reports of pharmacological investigations performed without therapeutic intent. These different classes of report require different check lists, which would, however, be similar in arrangement to the check list described in this paper.

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How Old is Leprosy?

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One by one the myths and legends surrounding leprosy are being exploded. Leprosy is incurable, said the world's leading experts gathered at the first Leprosy Congress, held in Berlin in 1897—that was the only thing they agreed about. The myth of incurability was destroyed when the sulphones came into use. Later the bacteriostatic activity against *Mycobacterium leprae* of dapsone and sulphormethoxine and more recently of clofazimine and rifampicin,[1] was demonstrated experimentally in the mouse foot-pad. Again, far from being very catching, as used to be thought, leprosy is now known to be one of the least contagious of transmissible diseases.

In the same way, the antiquity of leprosy—for years almost an article of faith among doctors and laity alike—is being questioned and denied. The age of doubt began when a Danish general practitioner, V. Møller-Christensen, started on the second phase of a distinguished career that has taken him via the ossuaries of a mediaeval churchyard in Denmark and the osteological collections in many museums to the chair of the history of medicine in the University of Copenhagen. Blessed with the flair of a sleuth-hound and the patience of Job, and encouraged by fortune's unexpected smile, Moller-Christensen lighted on the cemetery attached to a mediaeval monastery near Næstved in Denmark. Here were buried (from about A.D. 1175 to 1544) some hundreds of persons whose bony extremities exhibited the well-recognized changes noted in leprosy. Not content with recording with scrupulous care and accuracy these changes, described in the living by D. E. Paterson,[2] S. Karat and his colleagues,[3] and others, Møller-Christensen[4 5] noted two departures from the normal that were consistently present in skeletons showing advanced destruction of the phalanges—namely, erosion of the anterior nasal spine and of the alveolar process of the maxilla. He called this condition facies leprosa, or the Bergen syndrome. The previously unnoticed changes were subsequently seen radiographically in living patients suffering from severe lepromatous leprosy, and are now generally recognized as pathognomonic of leprosy.

FIG. 1.—A senile female skeleton excavated in 1951, with flexion contractures in the hip joints, facies leprosa, and leprosy changes in hands and feet.

Ritual Defilement

One of his disciples, J. G. Andersen,[6] has recently published a doctoral thesis embodying the results of his own linguistic, osteo-archaeological, and clinical researches into the history of leprosy. He demolishes without difficulty the flimsy deductions that certain swellings referred to in the Ebers papyrus (*c.* 1552-1350 B.C.) were manifestations of leprosy. He goes on to confirm the view rapidly gaining acceptance that the word translated "leprosy" in the Old Testament (*tsara'ath*) does not refer to true leprosy at all, but rather to a