Cystic Fibrosis—Assessing the Effects of Treatment

A report by Dr. M. Mearns (1972) (p. 5) gives the 5-year follow-up findings in 76 cases of cystic fibrosis diagnosed in the first year of life, divided into two groups: group A, pre-1957, 30 cases; group B, 1957–1964, 46 cases.

Of the whole series—and there was little difference (86% and 75%) between the two groups in this respect—80% had Staph. aureus in cough swabs at the time of diagnosis. Lower respiratory tract pathogen recovery in such observations is less than 100% complete, and it can be assumed that nearly all these babies had experienced staphylococcal lung infection before diagnosis. The staphylococcus was repeatedly cultured from cough swabs between the ages of 1 and 5, in between one-quarter and one-third of the cases, despite antibiotic therapy; and staphylococci were cultured from the lungs in all the four cases in which there was necropsy. Entry to this reported series ceased in 1964. Penicillinase-resistant penicillins were therefore not available at all to group A, and were not available in the first year of life to group B.

The results reported here are a remarkable tribute to the work of the clinical service led and inspired by the late Dr. Winifred Young, and I do not think that they can be matched in the literature of the period. In group A (pre-1957) there was a 10% mortality (3 cases) between diagnosis and age 1 year. Between ages 1 and 5, 7% moved from category I to category II, and one further child died. In group B (1957–1964) there was a 4% mortality (2 cases) between diagnosis and age 1 year. Between ages 2 and 5, 2% moved from category I to category II, and one further child died.

This report on the results of meticulous clinical care over a period of nearly 20 years nevertheless leaves a number of questions unanswered. Some of these children undoubtedly had irreversible lung damage at diagnosis. How far could this be avoided by even earlier diagnosis, and the use of antibacterial agents which were not then available? Were all the category I children actually free of irreversible secondary lung damage? Clinical and radiological appraisal are more likely to under-diagnose than to overdiagnose, and it may well be that its incidence is closer to the incidence of staphylococcal infection, than to the incidence of radiologically observable change.

These children probably had the earliest possible clinical diagnosis. They had regular professional and supervised parental physiotherapy. They had substantial antibiotic treatment, mainly on the basis of treating established and bacteriologically proved infection, except that antistaphylococcal therapy was given routinely in the first year of life in group B. They did not all have continuous antistaphylococcal therapy as a routine. They had appropriate replacement and supportive nutritional therapy. They did not have mist tents: and the very success of this series in the most threatened period of life suggests that very hard evidence is now needed if the routine use of nocturnal mist tent therapy is to be justified.

Where do we go from here?

The question of overriding importance to be asked now, from our vantage point of steadily increasing therapeutic success over 3 decades, is this: how much is the course of the disease as shown in its natural history when untreated (rare survival beyond the second year) an inevitable peripheral result of the genetic defect? And how much is this due to the interaction of controllable environmental factors with these biochemical or structural remote effects of the gene? We know that the lungs are histologically normal at birth. All agree that bacterial infection plays a large part in the progression of lung damage. Some say that this damage is the specific result of the staphylococcus (Lawson, 1970). If this were so, it is unlikely that lung damage could be prevented unless a permanently effective antistaphylococcal agent were given regularly from birth. This became a question of serious practical importance with the advent of such therapeutic agents nearly 10 years ago.

Which of the components of treatment are responsible for the measure of success so far achieved? We all use more than one treatment, and many of us hold firm but unproven views on this matter.
David Lawson

The known history of the disease before it was generally recognized was such that few cases survived infancy and early childhood. In 30 years the 50% survival time has increased substantially, probably by about 7 years in each decade; which means that lung damage has at least been delayed if not yet entirely avoided.

The life tables of Warwick and Pogue (1969) for cystics in North America have indicated a 50% survival time of about 12 years from diagnosis irrespective of the age at diagnosis, for children diagnosed at varying stages of the disease progress, and treated by widely varying methods. This, as is pointed out, is the pattern of an acquired disease superimposed upon one which is known to be genetic in origin. This large-scale statistical observation strongly supports clinical evidence that chance environmental factors play an important part in the 'normally' observed progression of lung damage, which is of overriding importance as the cause of death.

The difficulty in establishing the relative value of the different components of treatment arises from several causes:

1. Clinicians with increasing case experience develop strong subjective judgments which add ethical problems to the already great technical problems of long-term clinical trials.

2. There is no accepted language or nomenclature in which to define the clinical state of the child at diagnosis and at subsequent points of analysis.

3. The exact content of multiple treatment programmes is seldom accurately defined, even if it is consistent over a number of years.

A realization of these problems (and particularly a developing anxiety in North America about the basis for the long-accepted use of routine 'prophylactic' nocturnal mist tent therapy) led, following a discussion in the Fifth International Cystic Fibrosis Conference (Lawson, 1969), to the formation of the Anglo/North American Co-ordinating Committee. This Committee agreed that large-scale inraservice control trials were not ethically feasible, and directed its attention to defining criteria of assessment of clinical status, and to trying to persuade clinicians to define the content of their treatment programmes.

More recently the European Working Group for Cystic Fibrosis devoted their annual meeting in London in June 1971 (Lawson, 1971) to the two topics of screening and assessment.

If treatment programmes have any effects at all, and there is good historical evidence that they do; and if there are environmental causes that initiate or accelerate lung damage; then it is presumably desirable to start treatment at the earliest possible stage, and before irreversible lung damage has been caused. If cases are allowed to present clinically, the cause of such presentation will frequently be lung infection itself, which will often have already caused irreversible damage. This seems sufficient justification in itself for preclinical diagnosis, i.e. whole population infant screening, if this can be achieved. Though the value of preclinical diagnosis can be reasonably assumed, its precise effect can only be measured if the progress of cases diagnosed preclinically on the one hand, and clinically on the other, can be precisely compared under circumstances in which both populations are treated by definably identical treatment programmes. The requirements for screening and for assessment are thus indissolubly linked.

The European Working Group at their June meeting accepted the case for screening on both service and research grounds, and reviewed carefully all the possibly available methods for mass population infant screening under the age of 4 months. Dr. P. T. Bray, of the Welsh National School of Medicine, was appointed Chairman of a Standing Screening Sub-Committee to pursue the Group's intentions in this field. The Group expressed interim views on the following tests which they deemed worthy of further evaluation, and the estimated costs are indicated per case diagnosed, expressed in dollars (June 1971), and assuming a case incidence of 1 in 2500 live births.

1. **Protein in meconium.** Available on first day of life. Requires further evaluation and development, but looks promising. (Cost $600.)

2. **Sodium in nails measured by neutron activation analysis.** Probably unreliable before about the sixth week and requires further evaluation. (Cost $6000 (but this might be reduced by very large-scale operation.).)

3. **Skin chloride direct-reading electrode, and measurement of the conductivity of sweat.** These methods are still of doubtful reliability in the first weeks of life. Both require stimulation of sweating and in neither case is the volume of sweat measured: this carries a danger of underdiagnosis at low sweat rates. (Cost $1500.)

4. **Direct reading of sodium content of unstimulated saliva with sodium-sensitive electrode.** Not available before the fourth month of life. Has been used in a large scale pilot trial in two London Boroughs. 3%-4% false posi-
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Different methods of assessment were discussed in detail, a division of their Health and Social Services. All current methods would immediately become obsolete if a method became available which required only the postal transmission of a drop of dried blood on the first day of life.

Preliminary work on a computer input form for clinical assessment was discussed in detail, a first draft having been precirculated. Professor K. F. Kerrebijn of the Sophia Children's Hospital, Rotterdam, was appointed Chairman of a Standing Sub-Committee on Standardization, to pursue the development of the form with a view to its introduction. This form will include agreed coding techniques for symptoms, signs, growth, bacteriology, and chest x-rays. There will be supplementary forms for pulmonary function tests and other criteria where these are available. The purpose of the form is to enable statements to be coded about the clinical status of each case, at each point of analysis, which are strictly comparable with the data fed in for every other case, and which are more precise than the distinction between life and death, which is all we can agree on at the moment. The main problem, in fact, is to ensure that the data asked for are not too complex and demanding for large-scale use.

If co-operative trials are to be carried out and effectively assessed, the following conditions need to be met:

1. Separation of cases into (a) those diagnosed without respiratory signs or symptoms, and therefore probably without acquired lung damage (i.e. output of mass infant population screening, preclinical diagnosis of new sibs of known cases, and cases presenting neonatally with meconium ileus); and (b) those diagnosed following presentation with clinical signs and symptoms.

2. Standardization of diagnostic techniques. As the purpose of early treatment is to avoid the development of secondary lung damage and as the pancreatic lesion is incompletely developed at birth, and does not occur at all in up to 10% of cases, diagnosis must rely entirely on biochemical techniques. Currently all screening and other diagnostic operations should be confirmed by the classical sweat test, carried out by the method of Gibson and Cook (1959), and readings should only be accepted on the basis of adequate sweat volumes, and after repeated confirmation.

3. Precise definition of treatment principles in all fields: antibiotics, physiotherapy, nutritional therapy, mist tents, other.

4. Bacteriological monitoring of respiratory tract flora in sputum productive cases.

5. Serological study. Serial specific serum precipitins against respiratory tract pathogens and quasi-pathogens, correlated with bacteriological monitoring. It should be possible by this means to clarify the relative roles of the staphylococcus, pseudomonas, and other bacteria in causing lung damage and in subsequently colonizing the lung.

6. Precise definition of clinical status by agreed criteria, including symptoms, activity, growth, pulmonary radiology, minimal pulmonary function criteria, (a) at diagnosis, (b) at all subsequent points of analysis.

7. Some estimate of the extent to which therapeutic and prophylactic advice is actually carried out. This must inevitably be a subjective measurement, but can probably be accurate enough to have value.

The most useful material for evaluation will be the output of screening programmes. About 300 cases are born per annum in the United Kingdom, and about 2500 in Europe as a whole. There should be excellent opportunities for comparing the results of one whole treatment programme against another, and for intragroup control studies of specific treatment components where this is ethically acceptable.

The Young/Mears series shows what excellent results were being achieved in cases diagnosed in the first year of life, between 7 and 20 years ago, before the advent of the newer antistaphylococcal agents. It is, however, clear that in this series acquired lung damage was not entirely avoided, and it is not possible to define the exact contribution of each component of treatment, one of the most important of which was undoubtedly a dedicated devotion to clinical, social, and bacteriological detail.

As clinicians looking after patients with cystic fibrosis we must continue to emulate Dr. Winifred Young's high standards of individual care. But for future case-finding and treatment evaluation this will not be enough. Cases must be diagnosed before they come, in trouble, to a clinician: and sophisticated co-operative recording and analysis of...
prospective studies are necessary if future treatment is to be based upon emerging fact, rather than upon disparate opinion.

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REFERENCES