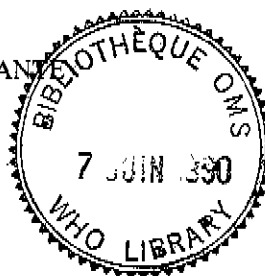




HEREDITARY DISEASES PROGRAMME
 DIVISION OF NONCOMMUNICABLE DISEASES



London, 12-14 June 1989

REPORT OF A JOINT WHO/ICF(M)A MEETING
 ON THE FEASIBILITY STUDY ON
 HEREDITARY DISEASE COMMUNITY CONTROL PROGRAMMES (CYSTIC FIBROSIS)

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1. INTRODUCTION

Since the last joint WHO/ICF(M)A meeting on prevention and control of cystic fibrosis (CF) in Oslo, June 1987, contacts between the two organizations have been maintained. Over the last few years it has become increasingly clear that CF is a common genetic disorder with worldwide occurrence. In developed countries, it appears that CF is rapidly transforming from a fatal childhood disease to a chronic disorder persisting to adult life. Also, comprehensive medical care leads to improved diagnosis. The overall outcome is still fatal and CF represents one of the most serious chronic life-threatening conditions.

The average life expectancy in western Europe and North America is now somewhere in the region of 25 years but is unknown, and much lower in the developing world. Whether early treatment will improve the prognosis considerably remains to be ascertained. Regarding the distribution of CF in various countries of the world, there are considerable differences among various parts and among various ethnic groups. High frequencies among Caucasians with the exception of the Finnish population (1:40,000) contrast with lack of knowledge of the true incidence in countries in Asia, Latin America and elsewhere. Case finding efforts have established the occurrence in Egypt, India, Jordan, Kuwait, Cyprus, and there is recent anecdotal evidence that CF occurs also in China. The marked variability of the incidence of disease among different ethnic groups could be due to variable awareness and also to several mutations.

Sweat testing still represents the most reliable test for establishing the diagnosis of CF. In developed countries, neonatal screening techniques are used either in the form of the meconium albumin test or increasingly in the form of measurement of trypsinogen in blood spots. Progress in molecular biology for the diagnosis of hereditary disease makes analysis of the gene structure possible. DNA probes seem to be the most promising tool and may have further applications for studying the gene frequency in populations. Presently, they are reserved for the detection of heterozygous people and the affected fetuses in families with previously affected individuals.

Control programmes for CF must include treatment and prevention of the disease. Such programmes have to be defined now and in the future for both developed and developing countries. The model of haemoglobinopathies was used as a working instrument, which, by prenatal detection, led to the identification of the need for care and to the prevention of the birth of affected fetuses. Models for the future, including individual national requirements, have to be outlined carefully to comply with underlying national health structures.

Promotion of professional education and carrier testing and quality controls as well as counselling for all couples at risk have to be stressed. The final aim would be incorporation of screening and counselling at primary health care.

2. APPROACHES FOR ESTABLISHING PROGRAMMES FOR THE CONTROL OF CF

2.1 Screening

2.1.1 Neonatal screening

Meconium assays for increased albumin and lactase contents have been used extensively. Despite the ease of performance and decentralized evaluation, results have been disappointing as interpretations were unreliable. Even under ideal conditions and with experienced hands, false negative rates up to 40% have been reported. There is also an appreciable rate of false positives. Under present knowledge, the test cannot be recommended any longer for case finding for developed countries. Should expensive equipment for other test methods not be available, it might be considered a cheap alternative for setting up CF clinics in developing countries.

Immuno-reactive trypsin (trypsinogen) assays (IRT) have been widely used since the first description in 1979 by Crossley et al. Presently, at least six commercial kits are

available, of which five are radioimmunoassays using a polyclonal antibody. Only two of these kits have had extensive usage. The other available kit is a monoclonal antibody based sandwich assay. Experience with this is still rather limited.

Screening strategies for the evaluation of dried blood spot screening are as follows: a two-tier system, in which elevated IRT levels lead to repeat IRT testing, has been used in at least 14 laboratories carrying out large-scale screening programmes, and over two million babies have been screened this way. The mean recall rate was 0.73% range 0.29-4.66. The positive predictive value after the first test averaged 4.7%, and after the second, 55%. The false negative rate averaged 6.4%, so that early diagnosis was achieved in 93.6% of babies. A second strategy involves sweat testing all babies who have an initial elevated IRT level. This approach has been used in a large scale programme in Wisconsin, USA. The Verona (Italy) laboratory uses meconium lactase assays in babies where elevated blood spot IRT levels are found. In this way, they achieve a very low recall rate of 0.16%. The rationale behind newborn screening was the possibility that pre-symptomatic detection and early treatment would improve the outcome. The Wisconsin programme is a prospective randomized clinical trial designed to test this hypothesis.

The experience of screening 642,000 newborn infants in New South Wales (Australia) up to February 1989, revealed 239 known cases with CF. 6.3% were missed by screening. The apparent incidence was 1:2,680. Use of an ELISA (enzyme-linked assay) gave different results compared to the radioimmunoassay. The former method seemed to miss more patients. The reasons for these differences are not known. Altogether, the false negative rates for 14 CF programmes was found to be 6.1% which is comparable to figures for screening for hypothyroidism (around 5%). Well over two million newborns have now been screened using the IRT methods and a total of more than 730 CF cases has been found.

Difficulties as regards specificity and sensitivity have still not been overcome. False negative results pose a special problem and in most programmes data are not available for demonstration of completeness of ascertainment. The three methods employed showed little systematic difference in the results; however, the efficiency of case finding was quite variable from laboratory to laboratory. Screening for assessment of incidence in various ethnic groups among 400,000 "Australian" babies, the mother's ethnic background gave an apparent incidence among Caucasians from the UK, northern Europe, North America, South Africa and New Zealand, of 1:2,200. Mothers from southern Europe, the Mediterranean, Greece, Yugoslavia, Italy and Malta, appear to have affected CF children with a frequency of 1:3,500, while in Scandinavia, the frequency still appears to be lower. Mothers from elsewhere, including the Middle East and Vietnam had an overall frequency of CF offspring of 1:12,000. Regarding the effects of early diagnosis, it was understood that there were no results from randomized control studies, however, short-term cost-effectiveness for the first two years due to the reduced number of hospitalizations could be established for New South Wales. The benefit of the established diagnosis to the family is unquestionable. DNA analysis for confirmation of suspect cases was considered not yet practicable, and would depend on exact knowledge of the mutations in given populations according to the ethnic background.

2.1.2 Prenatal diagnosis

Progress in prenatal diagnosis of CF was reported after the development of amniotic fluid microvillar intestinal enzymes (MIE), localization of the CF gene and finally isolation of DNA probes tightly linked to the CF locus. Among 321 families, 421 diagnoses were made. 90% of 1:4 risk families are fully informative using the DNA analysis and full information can be given in 50% by using only the KM19 probe. In semi-informative families, 50% could be confidently classified as healthy, but the rest had to be complemented by amniotic fluid analysis.

In couples with a deceased affected child, it is now possible to combine the results of amniotic fluid MIE analysis and the probabilities calculated from the linkage disequilibrium data, especially when the DNA analysis showed that parents are heterozygotes with KM19 probes allowing the use of PCR amplification technique on amniotic fluid cells. These calculations are improved when there is DNA from a living normal child. These

equilibrium studies have to take into account different ethnic backgrounds as haplotypes are quite variable.

Linkage disequilibrium data can be applied for counselling of couples with less than 1:4 risk of CF. This would apply to CF affected pregnant women, the remarried parent of a CF child, thus an obligatory carrier, and the brothers and sisters of an affected child. The calculated risk could be more correct if the disequilibrium data were combined with the theoretical risk, the latter being very close to what could be found with the amniotic fluid examination. Studies on couples with a 1:4 risk with a referral for a second prenatal diagnosis showed that acceptance of further prenatal diagnosis was limited. Out of 75 couples, 44 had had a first affected fetus and 31 had had a normal fetus. In the former group, 44% wanted further prenatal diagnosis, while in the latter only 16.7%. For families with an affected child, prenatal diagnosis affords the possibility to constitute families with normal children. For these families, prenatal diagnosis based on the analysis of the segregation of DNA markers linked to the CF gene is a reliable technique. It was mentioned that the CVS risk (chorionic villus sampling) is around 2% which may be lower than the spontaneous abortion risk. Combination of CVS and DNA may become necessary. Stored dry blood spot tests (Guthrie tests) could be used for the DNA analysis of deceased children.

Reviewing carrier detection, it was said that only 10-15% of CF cases were born into families where CF was already known, and most will therefore be born into families not known to be at risk. This would definitely underline the need for population screening. In the future, non-invasive methods such as buccal washing for PCR analysis might be valuable especially when the exact locus has been determined. The CF locus can now be established within an area of 200 KB between the D9 and G2 locus. There is some evidence that a second mutation independent from the major one has occurred. In this less common haplotype there were more cases with pancreatic sufficiency. Differences in clinical expression might be related to different haplotypes. This might be especially pertinent for liver disease.

The question of whether heterogeneous haplotypes could have implications for the neonatal screening programmes was raised. Screening depending on pancreatic abnormality may miss patients with pancreatic sufficiency. However, it appears that 37% of all children under the age of 1-2 years found by high IRT at screening in Australia had adequate pancreatic function, yet had raised IRT levels. It was predicted that the precise locus for CF might be established within the next year. (Please see attached addendum).

2.2 Treatment

Several important points concern use of antibiotics (continuous versus intermittent, prophylactic treatment), immunizations, parental smoking and new respiratory pathogens (Ps. cepacia). There is no universal agreement among centres as to the duration of antibiotic treatment. Recent aspects of nebulized medication including bronchodilators were reviewed, as were physiotherapy, heart/lung transplantation, gastrointestinal problems, diabetes and sclerotherapy for liver disease in CF.

Reviewing the role of physiotherapy it was agreed that very few investigations concerning long-term effects have been documented. Some studies are available on the long-term effects of the different techniques, but not comparative ones. Treatment must be individualized and no single treatment modality is clearly superior to other methods practiced. The International Physiotherapy Committee for Cystic Fibrosis will stimulate studies of this kind in the near future in order to provide better information and educational materials.

New directions emphasized in treatment were regionalization of CF care, nutritional support, use of advanced new anti-microbial agents, use of inflammation modifiers (steroids), enhancement of the pulmonary defences in CF patients, clarification of the role of other agents, psychosocial maintenance and rehabilitation and organ transplantation. The need for specific therapy directed against the underlying basic CF defect will appear when that defect is characterized. Prolongation of life, improvement of quality of life and support of those around the CF patients are of over-riding importance. Achievement of a survival plateau might imply that maximum improvement of longevity has been achieved.

2.3 Cost-benefit

Cost-benefit calculations of the prevention of CF must be viewed in financial, social and physical terms. Financial aspects are the ones which can be measured most easily. There may be other psychosocial costs of stigmatization and early labelling. The current cost of treatment for a patient per year was estimated at between US\$7,500-15,000. If the life-expectancy of a patient today would be calculated to be 25 years, prevention by prenatal diagnosis and termination of pregnancies with an affected fetus would save 25 x US\$7,500-15,000 giving a minimum of US\$187,500. Since the cost of the test is about US\$25, at an incidence of 1:3,000 and assuming a 50% uptake of abortion, the savings per case would be at least US\$65,000. Combination of neonatal screening for CF with testing for PKU when a DNA-based test is available might be feasible and could reduce costs. It would also identify carriers, enabling appropriate genetic counselling to be given to their parents and establishing a database for the the next generation.

2.4 Research needs

Over the last few years, major progress in the field of understanding of the CF basic defect has been achieved. This might lead to improved control of the disease by (a) establishing a true cure, (b) carrier detection with prenatal diagnosis or (c) improvement of genetic counselling. While the correction of the molecular defect is not possible so far, treatment of the symptoms has made stupendous progress. Support of CF research is essential and future trends have to concentrate on joint programmes, exchange of materials and recruitment of top experts. The control of the symptoms needs considerable efforts in clinical research into a variety of topics such as anti-bacterial treatment, surgical interventions (transplantation), overcoming colonization and infection and evaluation of the effectiveness of the early clinical management of the CF patient diagnosed by neonatal screening. Suggestions for the use of animal models for study of the genetic abnormality must not be expected to meet with universal approval. In addition, different animals could have different physiologies which make interpretation of the results difficult.

2.5 Educational aids and training

The organization of the ongoing WHO programme on haemoglobinopathies can serve as a model approach. Experience was accumulated for solving similar problems. Knowledge of what the patients want will help towards reduction of the incidence. Preparation for such a CF preventive programme may take years. Generally speaking, poor countries have a greater desire for information whereas developed countries were less interested in prenatal diagnosis. Results of future studies would be dependent on which country was studied owing to the importance of social and socio-economic factors. Availability of technology was not enough as there should also be national monitoring programmes which had been used for the haemoglobinopathy study. Link-up with established associations and the role of parents' associations were considered vital.

In reviewing the services needed, and the organization of services, it was underlined that prevention and treatment are complementary and best achieved by a patient registry monitoring system. Counselling should be done by health care givers such as nurses, midwives or district nurses. Reaching populations with a message was much more difficult in more densely populated countries. Availability of adequate technology was not enough for fighting CF and should also be accompanied by a monitoring programmes. For developing countries, prevention is of far greater importance than treatment. Both modalities must be considered complementary. It was however questioned whether pre-symptomatic treatment was of any known value. Similarly, it is unclear whether presymptomatic treatment has risks. Concerns include the possibility that early treatment could accelerate colonization with pseudomonas or other resistant organisms; a possible increase in unnecessary hospitalizations; and, stigmatization affecting the parent-child relationship and/or the child's self-esteem. Finally, there was concern that routine presymptomatic screening might constitute a misallocation of limited health resources.

2.6 Ethical issues

Concerning ethical issues, it was mentioned that lessons learned from the PKU story were worth remembering. Once a screening programme had become mandatory, it was difficult to stop and it was felt that zeal could obscure critical thinking. Clearly screening was not for everyone, but careful weighing of benefits and risks such as experience in sickle cell disease might make decisions more easy. This was particularly true in view of the fact that screeners might have conflicting interests. In PKU, it took about 10 years before screening was successful and minor and major tragedies at the high rate of false positive cases and of difficulties in getting diet right had to be dealt with. Screening certainly was not for everyone and required consent. As long as there was no proper controlled study, it was felt that screening might have to remain a research tool for the time being. It was however felt by the majority of participants that screening was of value.

In a prospective screening study in Wisconsin, USA, all patients were screened although only half of the cases were decodified. Access to data was always possible. As it was considered that this was the only way to have an established benefit of early diagnosis, the only way how to actually randomize newborn infants, and since it was felt that no harm arose for control children, this study was planned to continue for at least four years and possibly followed-up to 10 years. Factors in favour of screening procedures were that there was an existing treatment network and that there would be no ethnic overtones.

3. STRATEGIES TO BE FOLLOWED IN THE ORGANIZATION OF CONTROL PROGRAMMES

3.1 Strategies in developing countries with an unknown cystic fibrosis burden

Knowledge of CF is low in 4.2,000,000,000 people, i.e., in the population of the world minus those in developed countries. Even leaving out China with an approximate population of 1,000,000,000, based on an uncertain and probably low incidence of CF, there still remain 3,200,000,000 people in 132 countries where the diagnosis of CF is grossly underestimated. 95% of the developed countries are members of ICF(M)A. These have a total of about 548,000,000 people with 38,000 reported CF patients leading to an incidence of 7:100,000. Of these, 20% are over the age of 18. In contrast, only 0.19% of CF cases in 100,000 are known in developing countries. 9% of these are over the age of 18 years. The figure of 0.19:100,000 increases to 0.4, if Pakistan and India were excluded as they have very few known cases.

In developing countries, society is usually heterogeneous with different economic, religious and other background factors. The experience in managing CF in developed countries must be applied to developing countries. Strategies used in countries without knowledge of CF compared to those with some knowledge but no regular centres for CF will be different. Activities must therefore be different according to the starting age, consultation age, and finally confirmatory units where sweat testing could be performed.

Establishment of diagnosis and research centres should be instituted. Whether or not diagnosis and research centres should be instituted depends on many variables including the competing demands for limited health care resources, and the availability of follow-up treatment. The cost of providing developing countries with possibilities of diagnosis and treatment in centres are small in comparison to funds spent by different major CF foundations throughout the world. Local sponsors should be found for the people who thereby could start to find their own way. An overall calculation as to the worth of spending money on CF in developing countries rests on improvement of basic health care. Only when elementary health care can be improved, CF may be surfacing as a major problem. In addition, if there is nothing to offer after the diagnosis, the whole effort may be questionable.

However, it was concluded that one centre per country might be a sensible starting point for diagnosis and treatment. This would apply especially to South America. Once the knowledge of the epidemiology of the disease was established, other centres could follow. There was however an overall consensus that establishment of the diagnosis should be attempted as cases could be reduced as has been experienced in the haemoglobinopathy study.

In view of other major problems involving infant mortality and infectious diseases in developing countries, it was assumed to be difficult to interest local health authorities to consider a search for CF worthwhile. However, even in developed countries such as Italy, similar problems had occurred 10 years ago when centralized care became established in northern Italian centres. With guidance from northern Italian centres, services similar in scope and quality were established and taken over.

The introduction of guidelines for people starting to develop knowledge in each country was considered to be of prime importance. ICF(M)A should recognize these problems and together with WHO offer support to institute regional CF health centres. Black Africa and China should presently not be included in the list of countries where it was felt that establishment of CF care was of importance. In contrast, in India, the frequency of CF might be similar to the occurrence in Europe. At present, the question whether unearthing the problem may in fact be a Pandora's box could not be answered. However, due to the possibility of genetic counselling, the number of affected must be eventually reduced. Ignoring the problem cannot be the answer.

Prevention must be considered the key to success in overcoming CF. Providing expertise through WHO and ICF(M)A and inclusion of CF into the curriculum for medical students was considered an inexpensive and effective way of spreading knowledge of CF. In addition, the situation in the USSR was outlined. It can be assumed that in the European part of the USSR, the frequency is the same as in Europe. Thus 2-3,000 newborn infants with CF can be expected every year. Presently, the mean life expectancy is low and only 2-300 per year reach the age of adolescence. No knowledge as to the frequency of CF in the Asian part is available. Up to now, one centre in Moscow and affiliated health resorts by the Black Sea have cared for CF. In Leningrad, two centres have been established, one for treatment and one for diagnosis.

3.2 Strategies in developed countries with a known CF burden

WHO firmly believes that every child born has a right to live with a quality of life as good as possible. This would certainly also be applicable to patients with CF. Prevention and control of CF should be attempted to decrease human suffering, to satisfy human rights, and to eliminate the high cost of care. Two categories of CF prevention programmes are feasible for developed countries:

- (a) Programmes without use of effective CF heterozygote detection methods.
- (b) Programmes using effective CF heterozygote detection methods in whole populations.

In programmes without CF heterozygote detection, education of physicians and other health professionals is of prime importance. All paediatric centres should have a CF centre. The availability of well-trained health professionals able to diagnose CF currently appears the most powerful means of prevention and controlling CF that developed countries possess. Availability of prenatal diagnosis for CF must be ready for high risk families in practically every developed country. In addition, public education on CF should be pursued however difficult.

National CF associations are of importance to influence the general public and governments for contributing to diagnosis, care, delivery and improvement of quality of life. These associations should also make funds available for improvement of care and for furthering research.

Prediction of effectiveness of a programme of prevention and control in a given country is difficult and may not be possible. Neonatal diagnostic programmes using various tests should be available in developed countries. They have been introduced on the assumption that early diagnosis leads to better prognosis and more effective prevention and control. Final conclusions of argumentation for or against the implementation and use of methods of neonatal screening in developed countries have not been reached. The goals should be to provide more effective treatment to affected individuals, and to offer more informed reproductive choices on a voluntary basis.

In programmes with CF heterozygote detection (please see attached addendum), involvement of appropriate government agencies must be developed. Governments need to consider whether establishment of CF programmes should take priority, to make funds available and separate these from other health care needs of the country. Development of an evaluation plan of the effectiveness of the programme in a prospective fashion and with methods guaranteeing objectivity of the evaluation process must be established. Present evidence points to the fact that a plateau of success in treating CF may have been reached and further progress in this field might be slow.

On a warning note, it might be necessary to consider that gene detection may stigmatize at an early age and that in fact the elimination of the CF gene may have unpredictable effects. However, as the Cyprus haemoglobinopathy studies have shown, prenatal information was not used for marital but for reproductive decisions. Should establishment of the gene locus be achieved in the foreseeable future, this may well open up new pharmacological interventions regarding the basic aspects of the disease.

4. PROPOSALS AND RECOMMENDATIONS

Since the joint WHO/ICF(M)A meetings in Vienna and Oslo, considerable progress has been made in prenatal diagnosis. However, it has not become clear which sort of programme to recommend and what kind of information should be given preceding neonatal detection. Identification of needs was the base for all programmes at all kinds of levels in developing countries where the incidence of CF has to be determined. The goals to be tackled were reaching a decision on neonatal screening programmes, establishing the gene frequency in different populations, implement pilot programmes for prenatal diagnosis and termination of affected pregnancies, assessment of cost and educational programmes. The latter were considered to be of paramount importance on the basis of recommendations of the ICF(M)A to WHO.

It was felt that there was not enough educational material available on a worldwide basis and that national materials should be developed concurrently. Clinical diagnostic, preventive and educational needs should be established according to the individual developing or developed countries. Recommendations as to tests and qualifications of centres should be developed and the question of screening for developing countries should be resolved. The setting up of a clinic even in view of loss of cases must be considered an educational exercise. Comprehensive treatment should spread from these centres. Supported programmes should concern themselves with prevention, control and education of CF.

The following major proposals were reached:

- (a) The programme as outlined in WHO document WHO/HDP/CONS/88.2 should be pursued and should also include Bahrain. The programme in Costa Rica has in fact started. Methods employed are open at this time and although the radioimmunoassay appears the most reliable, the ease of performance remains questionable. Quality controls have to be introduced in view of lack of reference standards, a control committee has to be established under the auspices of WHO; it was suggested that Dr Mastella from Verona be named head of this committee.
- (b) Educational programmes must be instituted. These should work in conjunction with experts in the fields of haemoglobinopathies and genetics. Educational material should go to national organizations. Vice-versa, presently available national materials should be sent to educational strategy experts who would include not only medical specialists but also health educators, teachers and others. Data and materials accumulated should be considered during a future meeting.
- (c) A manual for the comprehensive management of CF might be worth undertaking under the auspices of WHO/ICF(M)A. This would be available to the public and centres worldwide. Collection of data of DNA analyses should be undertaken and could be processed by the ICF(M)A Scientific Medical Advisory Committee.

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A D D E N D U M

Identification of the CF Gene

The isolation, sequence and major mutation of the gene at the cystic fibrosis locus was described early in September 1989^{1,2}. The gene itself is large and has the structure of a trans-membrane "Conductance Regulator" (CFTR). It is similar to a previously known gene family encoding the P-glycoproteins alternatively known as multiple drug resistance (MDR) proteins. It is not clear whether the protein itself transports chloride ions or whether it regulates the activity of a protein which does. The major mutation discovered consists of a deletion of a 3 base pair sequence encoding a phenylalanine residue, which is absent from the protein in CF cells. 68% of chromosomes carrying CF had this deletion; work is in progress to determine the nature of the other mutations. It is of interest that CF patients with pancreatic sufficiency (PS) tend to have one chromosome with the three base pair deletion and one chromosome with another, as yet unknown, mutation, i.e., they are compound heterozygotes. Patients with pancreatic insufficiency (PI) on the other hand are usually homozygous for the 3 base pair deletion, suggesting that either this mutation alters protein function more severely than the others or that the phenylalanine residue is particularly important for functional regulation in the pancreas.

At the clinical level the immediate benefits of this advance once all the mutations are characterized, are antenatal diagnosis with a theoretical accuracy of 100% and carrier detection for random members of the population. In the same way it will be possible to confirm a diagnosis of CF in doubtful cases. However, diagnostic difficulty is more likely to occur in milder forms of the disease for which the mutation has not yet been determined. With the availability of the polymerase chain reaction (PCR) it is now possible to detect the major CF mutation using minute quantities of blood. Should this procedure become automated a method of neonatal screening/heterozygote detection would be feasible using the blood on a Guthrie card. With the necessary political will and financial resources, it may be possible as well as desirable to offer total population screening for the CF mutation(s). Such action would perhaps not only improve family planning services but potentially ameliorate the course of the disease in affected individuals. Current estimates are that there may be more than 30 mutations, with differing frequencies in different populations. It is likely to be some time before these have all been characterized.

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