New Treatment and Research Strategies for the Improvement of Care of Cleft Lip and Palate Patients in the New Millennium'

S T Lee,* *FAMS, MBBS (Adel), FRCS (Edin)*

Abstract

Surveillance studies have shown that cleft lip and palate (CLP) is one of the commonest craniofacial anomalies (CFA), occurring in approximately 1 in 500 livebirths. Taking into consideration the world population and annual birth rates, it is estimated that there are well over a quarter million babies born each year with CLP. The cost of managing this huge number of clefts is enormous and exceeds the available resources of most developing countries in Asia, Africa and Latin America. Thus, CLP constitutes a major health problem which requires globally-based strategies to deal with the issues of epidemiology, primary prevention and treatment strategies which are evidence-based and cost-effective.

Basic research to unravel the aetiological factors responsible for clefting disorders is occurring on a worldwide scale, especially in the areas of molecular genetics and gene-environment interactions. There are also in place international organisations such as the WHO Task Force on CFA, the International Consortium on Oral Cleft Genetics (ICOCG), Interplast and other international volunteer cleft missions to help in the treatment ofpatients with cleft disorders in developing countries, in data collection, in pooling of genetic material and sharing of information. However, there is an urgent need for more randomised clinical trials (RCTs) to evaluate the outcomes of treatment so that clinical guidelines and treatment protocols are based on strong evidence. Currently, there is a dearth of RCT-based information and multi-centre trials on treatment outcomes should therefore be actively pursued and encouraged.

***Ann Acad Med Singapore 1999;* 28:760-7**

Key words: Aetiogenesis, Literature survey on cleft lip and palate, Craniofacial anomalies, Gene-environment interactions, Genetics of clefts, Incidence patterns worldwide, International collaboration in cleft lip and palate, Multi-centre studies, Randomised clinical trials, Primary prevention strategies

Introduction

I have chosen as the title of my keynote address "New Treatment and Research Strategies for the Improvement of the Care of Cleft Lip and Palate Patients". The reason for this is that despite the tremendous strides we have made over the past 50 years in the management of cleft lip and palate (CLP), there are still wide gulfs in our knowledge and understanding of the embryogenesis of clefts and the causative factors responsible for CLP, especially the role of gene-environment interactions in non-syndromic clefts. We are also striving to find the most cost-effective and evidence-based interventions in cleft care. So, as we stand on the brink of this new century, I thought that it would be appropriate to take a step backwards, carry out a proper SWOT analysis of our Strengths, Weaknesses, Opportunities and work out a Time frame for us to plan our strategies to address the complex issues of the aetiogenesis, prevention and treatment of CLP-so that hopefully we will come up with the right answers and solutions, as we enter the next century.

I would like to dedicate this lecture to all my peers and predecessors, who have made tremendous contributions in the arena of cleft lip and palate, of whom there are too many for me to mention individually, but who have left their imprint in their various disciplines involved in the care of patients with cleft lip and palate. It is on their shoulders that the hope of future generations of CLP healthcare providers will rest, so that we can improve on the standard of care of our patients.

As the Distinguished Nobel Laureate, Dr Joseph Murray,' said in his Keynote Address to the IPRAS Congress in Yokohama 4 years ago,

"We all have drunk from wells we did not dig.
We all have been warmed by fires we did not build."

So with these words, I wish to pay a humble tribute to all those who have preceded me and contributed to cleft craft in the past.

* *Senior Consultant*
Department of Plastic Surgery
Singapore General Hospital
Address for Reprints: Dr ST Lee, Department of Plastic Surgery, Singapore General Hospital, 1 Hospital Drive, Singapore 169608

† *Keynote address delivered at the 12th Congress of the International Confederation of Plastic, Reconstructive and Aesthetic Surgery, San Francisco, California, USA, 26 June to 2 July 1999. Recipient of Lyndon Peer Award for this address.*

International Strategies in CLP-The Global Challenge

CLP is one of the commonest craniofacial anomalies (CFA) occurring in 1 in 500 births to 1 in 1000 births.[2] It is a global problem because of its high prevalence. Hence, the strategies that we adopt should be global in approach, whether it is in epidemiologic surveillance, in molecular genetics or in prevention. Similarly, our intervention programmes should take the form of multicentre trials. Volunteer cleft missions by their very nature are already international in their outreach.

In 1992, we published a case-control study" based on approximately 45,000 livebirths and we found that CLP was the 4th commonest birth defect in Singapore after musculo-skeletal deformities, congenital cardiovascular anomalies and chromosal disorders. The prevalence of CLP in this hospital-based study was 1.72 per 1000 or 1 in 580 live births (Table I).

TABLE I: INCIDENCE DATA FROM THE CLEFT LIP AND PALATE PROGRAMME AT THE DEPARTMENT OF PLASTIC SURGERY, SINGAPORE GENERAL HOSPITAL FROM 1985 TO 1999 (14 YEARS)

Complete unilateral cleft lip and palate (UCLP)	537
Complete bilateral cleft lip and palate (BCLP)	258
Cleft palate (CP)	270
Incomplete cleft lip (CL)	308
Cleft lip and alveolus (CLA)	52
Total	1425

World Population/Births in 1997

The data on World Population and Births are obtained from the United Nations Yearbook on Demographics.[4] The world population in 1997 stood at 5.7 billion and with an annual birthrate of 24 per 1000, the estimated total number of births in the world was approximately 138 million for that year.

The estimate of the cleft population in the world, depending on whether the rate of 1 in 500 or 1 in 1000 births is used, is in the region of 277,000 or 138,000 respectively. This is the magnitude of the global cleft problem-approximately a quarter million new babies with clefts are born each year.

In the USA, the number of live births per year is approximately 4.0 million which translates into 8000 new clefts per year[5] (based on 1 in 500 live births). It is estimated (CF Research, NIH)[2] that it costs approximately US$100,000 to treat a patient with a cleft from infancy to adulthood, based on current rates. Hence, each year, the budget for taking care of these patients in the USA alone is approximately 800 million dollars. This figure exceeds the GNP of some of the smaller nations of the world. How much more would it cost to deal with 1/4 million new cleft patients globally even if we can have the capacity to deal with them. Hence, the cost factor alone, if nothing else, will play a major role in determining our approach and strategy in the overall management of this problem.

New Clefts in Various Continents (Table II)

I will now briefly review the new cleft population in various continents and countries of the world. These data are culled from the 1997 United Nations Demographics Yearbook,[4] the UNICEF State of the World's Children 1999 Statistics[5] and the World Atlas of Birth Defects published by the WHO's Human Genetics Programme in 1998.[6]

(a) *North America:* I have already mentioned the figure for the USA, the next highest number is from Mexico with an estimated 5000 new clefts per year. Canada has approximately 700 new clefts per year.

TABLEII: NEW CLEFT POPULATION IN VARIOUS CONTINENTS AND COUNTRIES OF THE WORLD

Country	No. of births/year	Estimated no. of CLP cases	
		1 in 1000 births	1 in 500 births
North America			
Canada	376,000 (1996)	376	752
Cuba	148,000 (1996)	148	296
Mexico	2,750,000 (1995)	2750	5500
Panama	60,000 (1996)	60	120
USA	3,900,000 (1995)	3900	7800
South America			
Argentina	659,000 (1995)	659	1318
Brazil	3,108,000 (1996)	3108	6216
Chile	280,000 (1995)	280	560
Peru	615,000 (1995)	615	1230
Venezuela	596,000 (1996)	596	1192
Oceania			
Australia	256,000 (1995)	256	512
Fiji	21,000 (1995)	21	42
New Zealand	58,000 (1995)	58	116
Asia			
China	2 1,260,000 (1993)	21,260	42,520
Hong Kong	65,000 (1996)	65	130
Japan	1,203,000 (1996)	1203	2406
South Korea	705,000 (1995)	705	1410
Malaysia	552,000 (1996)	552	1104
Singapore	49,000 (1996)	49	98
Turkey	1,379,000 (1996)	1379	2758
Europe			
Denmark	68,000 (1996)	68	136
France	734,000 (1996)	734	1468
Germany	765,000 (1995)	765	1530
Italy	526,000 (1995)	526	1052
Spain	352,000 (1996)	352	704
Sweden	95,000 (1996)	95	190
United Kingdom	733,000 (1996)	733	1466

(b) *South America:* Brazil has the largest population of clefts, over 6000 cases per year. Last year, I had the opportunity to visit the Centrinho Cleft Centre in Bauru, near Sao Paolo, which receives over 120 new patients per month and sees over 1500 cases per year. It was an amazingly well run centre, affiliated with the University of Sao Paolo. They have 31,000 cases registered with their centre and 23,000 are currently still receiving follow-up treatment.

(c) *Europe*: the cleft cases are more evenly distributed amongst all the countries, with the more populous ones like France, Germany, the UK and Italy all having 1000 to 1500 new cases each year.

(d) *Asia:* where more than half of the world population resides. China with a birth figure exceeding 21 million, has over 42,000 new clefts each year to deal with. India has a higher birth figure of 26 million which translates into 52,000 new clefts per year. Indonesia, the 4th most populous country in the world, has 4.7 million births per year and therefore about 9,400 new cleft cases to contend with. Japan similarly has a high figure of 2400 new clefts per year. Therefore in Asia alone, there is a total of approximately 150,000 new clefts per year to deal with and in most countries, the resources for dealing with this non-life threatening condition are negligible or non-existent.

(e) *Oceania:* for the sake of completeness I will mention the figures for Australasia. There are 500 new cases born in Australia and about 120 new cases in New Zealand annually.

Research Strategies in CLP (Fig. 1)

It is obvious that limited global health resources will not be able to cope with the ever increasing backlog of cleft cases in the world. No amount of international effort and goodwill in terms of volunteer cleft missions will ever significantly impact on the global cleft population. That is not to underestimate the value of these missions, especially for the individual cleft patient fortunate enough to receive such expert volunteer aid and surgery. The magnitude of the problem underscores the importance of having the right strategy so that maximal use can be made of limited resources.

Secondary Prevention

A disturbing trend in some countries which will nonetheless limit the growth of the cleft population is early pre-natal diagnosis and subsequent termination of pregnancy (TOP).

In the most recent issue of the Cleft Palate-Craniofacial journal, Blumenfeld and Bronshtein[7] from Israel reported that cleft lip can be accurately detected by trans-vaginal sonography (TVS) at 13 to 16 weeks of pregnancy i.e. during the 1st trimester. In 23 out of 24 cases detected by TVS, the parents elected to undergo termination of pregnancy.

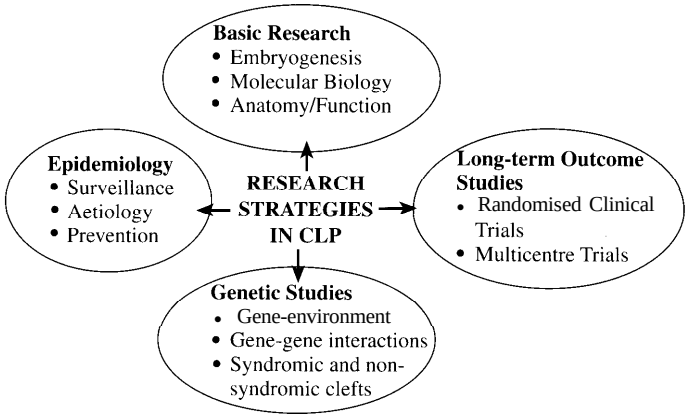

Fig. 1. Global research strategies in cleft lip and palate for a better understanding of aetiognenesis, incidence patterns, molecular genetics of clefts and long-term treatment outcomes.

On the other hand, Marilyn Jones[8] from Southern California reported her experience with prenatal diagnosis but the reactions of the parents were quite different in that all of them decided to continue with their pregnancies and never regretted their decisions. If the trend towards TOP increases, it will of course dramatically reduce the incidence of CLP but it raises a whole host of ethical and moral issues. This form of cleft population control is spoken of as "secondary" prevention.

Primary Prevention

Some primary prevention programmes are taking place globally:[9]

(1) In the Philippines, case control studies have been carried out and they suggest the association of biochemical markers for B6 and folic acid with oro-facial clefting. There is evidence that multi-vitamin usage reduces the occurrence of clefting and at the moment, Ron Munger from the University of Utah is conducting a cleft prevention trial amongst pregnant mothers to determine the specific role of vitamin B6 and folic acid in the prevention of clefts.

(2) In Indonesia, on the island of Timor, there is a high prevalence of CLP which is thought to be due to dietary deficiency as well as low levels Zinc in the water supply and hence, in the maternal blood circulation. Dr A Hidayat of the University of Brawijaya, Malang, Indonesia is supervising this population-based interventional study, supported by the World Bank.

(3) In South America, the programmes for prevention of clefts by folate and vitamin B12 supplementation has been initiated by Maria Tolarova from UCSF. In Argentina, a case control study has shown that indi-

viduals with clefts carry a mutant folate pathway gene which influences gene-environment interactions.

International cleft prevention trials will be a considerable challenge because of the heterogeneity of different populations, cultural/dietary differences, being just two examples. So far, these projects in Asia, Latin America and Europe have taken place independently. There needs to be standardisation of these prevention research protocols and trial designs so that the validity and applicability of these studies can be enhanced. So far, no consistent conclusions regarding dietary supplementation during the peri-conceptual period have emerged for worldwide recommendation.

Genetics of CLP

The era of molecular genetics, especially the development of recombinant DNA technology, has helped us in our understanding of the genetic basis of clefts. The mapping of the human genome and of abnormal mutant genes to explain the myriad of clefts and CFA has been occurring at a rapid pace over the last decade.

It is well to remember that it was over 50 years ago, in 1942 to be exact, that Poul Fogh-Anderson'" expounded his thesis, based on twin studies and 703 CLP cases, that genetic factors play a major role in its aetiology and that the inheritance patterns for CLP versus CP only were quite different. I have to say that the Danish CLP Register which has been in existence since 1936 with complete records of now well over 7000 CLP cases is unique. It has been the source of a multitude of studies looking into gene-gene and gene-environment interactions. Recently, Kaare Christensen,[10] has added a new dimension to the Danish CLP register by enrolling 100,000 pregnant mothers into a prospective cohort study that will hopefully unravel some of the causative factors and gene-environment interactions responsible for clefts.

The incidence studies of the Danish Cleft population make a distinction between the two common phenotypes-CLP and CP only. There were 4989 CLP patients over this period (1936 to 1987) and the prevalence is 1.5/1000 with a preponderance of males over females. For CP only, there is no gender predominance and the prevalence is around 0.8/1000 (about half the rate of CLP) (Table III).

What is interesting is the occurrence of associated anomalies and syndromes. Whilst 6.4% of 4989 CLP cases were associated with syndromes, 15.1% of 2301 CP cases had associated anomalies.

Syndromic vs Non-syndromic Clefts

Clefts which are associated with a constellation of other congenital abnormalities are known as syndromic clefts whilst those that exist in isolation, which forms the vast majority of cases, are known as non-syndromic clefts.

TABLE III: EPIDEMIOLOGY OF CLEFT LIP AND PALATE (CLP)[10]

Danish CLP Register
- 7000 CLP cases from 1936 to 1987
- P. Fogh-Anderson 1942 thesis "Inheritance of Harelip and Cleft Palate"
- Heritability of CL(P) and CP different
- Recurrent rates indicate effect of multiple interacting genes
- 100,000 pregnant women-study cohort for 2 1 st century to unravel aetiology of CLP

There are well over 300 syndromic clefts, the commonest being the Van der Woude Syndrome. About 1% of all cleft patients have the Van der Woude Syndrome. The gene locus for this syndrome has been mapped to chromosome lq.

DNA Technology-Genetics of CLP[11]

Using all the recent advances in recombinant DNA technology such as polymerase chain reaction (PCR), linkage analysis and restriction fragment length polymorphisms (RFLPs), various syndromic clefts have been genetically identified-Stickler Syndrome to chromosome 12, Treacher Collins to chromosome 5, Saethre Chotzen to chromosome 7p and Velocardiofacial Syndrome to chromosome 22. Already over 50 craniofacial syndromes have been mapped in this way.

There are occasions when identical gene mutations produce different syndromes, suggesting the influence of other genes or environmental factors at work i.e. gene to gene or gene to environmental interactions.

Non-syndromic clefts, although phenotypically simple, are aetiologically very complex. The genes for non-sydromic clefts are more elusive and at present, there are international collaborative efforts in the search for the non-syndromic cleft gene. Large population samples are needed and hence the setting up 2 years ago, of the International Consortium on Oral Cleft Genetics (ICOCG).[9]

Strong environmental factors are at work e.g. cigarette smoking, alcoholism, anti-convulsants such as dilatin, retinoic acid, steroids and folic acid deficiency. The gene for CLP may be related to some of these environmental teratogens e.g. the gene for cell receptor that binds retinoic acid or the gene for Transforming Growth Factor a (TGFA) or the homeobox gene MSX1 which controls susceptibility to steroids in induced clefting in animal models.

Computerised "Square-Dance" Study Design[10]

This particular study design is used for evaluating gene-environment interactions. It is known as the Computerised "Square-Dance" Study Design. It is based on the premise that modern life, as in a square dance, often involves more than one partner and one position. Kaare

Christensen found using this study design that the CLP recurrence risk was significantly reduced for women who changed partners, while the risk was ineffective if the change involved only the residency but not of the partner.

Let me conclude my observations on cleft genetics by saying that for non-syndromic CLP, the gene(s) has yet to be identified but the hunt is on. Many centres worldwide, under the auspices of the ICOCG are collaborating on this project, including the California Birth Defect Monitoring Board.[2] Hopefully, in the not too distant future, we may determine the genetic basis of non-syndromic CLP.

Strategies in Treatment and Studies in Treatment Outcomes (Fig. 2)

At the International Task Force Meeting on CFA in Bauru in October 1998, I stated that although there has been great improvement in various therapeutic techniques, both surgical and rehabilitative, there is a paucity of long-term reports in the literature of the results of CLP management. Certainly, randomised trials are almost non-existent. Hence, many of our surgical approaches lack uniformity at the present time and I suspect, many of our interventions may not be evidenced-based and stand up to scrutiny if there were strict clinical practice guidelines on CLP management for us to follow.

Papers in the Lancet and the Cleft Palate Craniofacial (CP-CF) Journal (Table IV & V)

For purpose of my paper in Bauru,[12] I looked at the publications in the Lancet in the year 1997 to see how the general medical literature compares with ours. I was pleasantly surprised to find that 70 out of 180 papers, almost 40%, were randomised clinical trials (RCTs). Looking at our own specialty journal, the CP-CF Journal, I went through 2 years 1996 and 1997, there was a surfeit of case reports and retrospective studies but no randomised clinical trials. Not a single RCT was reported.

TABLE IV: ANALYSIS OF PUBLICATION IN THE LANCET ACCORDING TO EVIDENCE-BASED MEDICINE CRITERIA (1997)

Design type	
Observational studies	
Case report or series	61
Cross-sectional	42
Case-control	21
Follow-up (cohort)	
Prospective	36
Retrospective	3
Experimental studies	
Clinical trials	
Non-randomised	8 (4%)
Randomised	70 (39%)

TABLE V: ANALYSIS OF PUBLICATIONS IN THE CLEFT PALATE CRANIOFACIAL JOURNAL ACCORDING TO EVIDENCE-BASED MEDICINE CRITERIA (1996 AND 1997)

Design type	1996	1997
Observational studies		
Case report or series	18	16
Cross-sectional	10	11
Case-control	10	9
Follow-up (cohort)		
Prospective	4	3
Retrospective	13	11
Experimental studies		
Clinical trials		
Non-randomised	0	0
Randomised	0	0
Basic research	11	15
Review articles	2	3
Others (new techniques in diagnosis and treatment)	10	12
Total	76	80

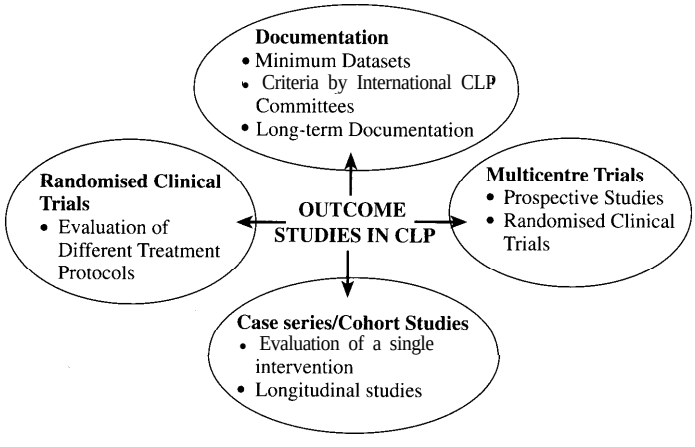

Fig. 2. Treatment outcome studies in cleft lip and palate should include RCTs, long-term care studies and multi-centre trials.

Are there peculiarities within our specialty that prevent us from conducting proper RCTs or do we think that we are "special" and can therefore afford to be out of phase with the rest of medicine?

For this keynote address, I reviewed 3 other relevant journals in plastic surgery in order that I am not accused of bias against the CP-CP journal.

Analysis of all cleft-related papers in Plastic and Reconstructive Surgery (PRS)–from Jan 95 to May 99-a period of $4^1/_2$ years, showed that out of 86 papers on CLP, only one paper was a prospective randomised study. Even this one paper, the study design was suspect according to our Clinical Trials expert. There were very

TABLE VI: ANALYSIS OF CLEFT LIP AND PALATE PAPERS PUBLISHED IN THE PLASTIC AND RECONSTRUCTIVE SURGERY JOURNAL (JANUARY 1995 TO MAY 1999)

Retrospective studies	25
New techniques/ideas and innovations	16
Basic research (anat, fetal, exptl)	15
Letters to editors	11
Case reports	6
Reviews (State-of-the-art)	6
Long-term results	6
Randomised clinical trial	1
Total	86

TABLE VII: ANALYSIS OF CLEFT LIP AND PALATE PAPERS PUBLISHED IN THE BRITISH JOURNAL OF PLASTIC SURGERY (JANUARY 1995 TO MAY 1999)

Retrospective studies	6
Case reports	6
Basic research	7
Cleft rehabilitation	3
Reviews and classic reprint	4
Letters to editors	3
Total	29

few papers reporting long-term results (i.e. >10 years follow-up) (Table VI).

The British Journal of Plastic Surgery (BJPS) had 29 papers over the same period on clefts with no long-term results or RCTs (Table VII).

The Scandinavian Journal of Plastic and Reconstructive Surgery and Hand Surgery was slightly better in having 3 long-term results out of 17 papers but again, there were no randomised clinical trials (Table VIII).

Difficulties in Performing RCTs for CLP

There could be reasons why cleft surgeons and other cleft providers are slow in adopting a more scientific and evidenced based approach to CLP management:-

1. Firstly, there is an uneven distribution of cleft material versus treatment resources in the world. As I have illustrated in the cleft incidence maps of various countries, the vast majority of clefts are to be found in Asia and Latin America where there is a deficiency of medical expertise available, let alone the ability to carry out outcomes research on them.
2. Secondly, the assessment of treatment outcomes requires long-term follow-up extending to almost two decades. This poses a problem in documentation as well as maintenance of records.
   If comparative studies were to be done, then standard documentation and minimum datasets must be agreed upon by the cleft community. That was the reason why in 1993, Harold McComb set up the International Task Forces on Cleft Documentation[13] and Speech Assessment. These were reinforced in the International Cleft Palate Congress in Singapore 2 years ago.
3. Thirdly, surgical skills take a long time to develop and this applies to all the other specialties in CLP management as well. There is a long learning curve and if one is truthful, you never quite stop learning how to manage clefts, even after you have stopped wielding the scalpel.

TABLE VIII: ANALYSIS OF CLEFT LIP AND PALATE PAPERS PUBLISHED IN THE SCANDINAVIAN JOURNAL OF PLASTIC, RECONSTRUCTIVE AND HAND SURGERY (JANUARY 1995 TO MAY 1999)

Retrospective studies	
Techniques/Innovations	3
Long-term longitudinal studies	3
(> 10 years)	3
Basic research	
Rehabilitation	2
Case report	2
Review	1
Total	17

Two papers have addressed to what I have called the "Surgeon Factor" in CLP management which is often played down but which I think is an extremely relevant and important factor.

Ian Jackson[14] and his colleagues at Rochester and Southfield stated that "Fistula occurrence is related most to the experience level of the operating surgeon". Peter Witt[15] and his colleagues in St Louis made similar observations that "the surgeon's cumulative experience" was important in the improvement of the results of palatoplasties.

The Need for RCTs (Fig. 1)

Having stated the possible reasons why we have been reticent in carrying out RCTs, no amount of rationalisation, either on ethical and other grounds, can we allow our specialty to stay on the sidelines.[16] Either our patients or the health authorities will sooner or later catch up with us. Any other discipline of medicine, in evaluating a new modality of treatment, whether it be a drug or other therapeutic interventions, will need to go through the scientific rigour of a proper clinical trial. We may give reasons for not participating in evidence-based medicine (EBM) but in the end, we need to heed the words of someone I quoted before, Dr Joseph E Murray.' He said " It is a DUTY for all physicians to nourish the scientific side of clinical practice". Describing a new technique and carrying out the procedure without a proper clinical trial is not science. It is experimental at the expense of the patient and the practice is certainly not evidence-based medicine.

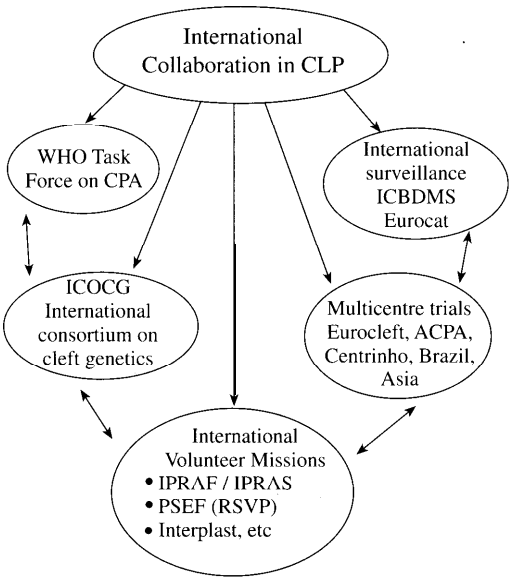

Fig. 3. International collaboration in cleft lip and palate is directed at surveillance studies to establish incidence patterns, genetic studies, multi-centre trials and international volunteer cleft missions.

Global Strategies for a Global Problem

I started my keynote address on the global problem of CLP because of its high prevalence in the world amounting to 250,000 new cleft cases per year.

International Collaboration in CLP (Fig. 3)

I wish to return to the issue of International Collaboration in rounding up my address. There are already in existence various agencies that can help us in this collaboration.

1. **The WHO Task Force on Craniofacial Anomalies** is headed by Professor Bill Shaw[17] and has 4 main subcommittees working on epidemiology, genetics, prevention and outcomes.
2. **The ICOCG or International Consortium on Cleft Genetics**[9] is seeking collaboration from all cleft centres to increase their genetic database in their quest to find the genetic basis of CLP.
3. **The International Volunteer Missions** under various agencies, including IPRAF, Interplast, PSEF etc are trying to co-ordinate their volunteer efforts in developing countries worldwide.
4. **Multicentre Trials** under auspices of Eurocleft, American Cleft Palate/Craniofacial Association and major high volume centres in Latin America and Asia will collaborate in randomised clinical trials to answer some of the outstanding issues in cleft management.

These outcome studies in CLP will require standardised documentation for comparison of results and also minimum datasets. These standard criteria have already been produced by the International Task Forces of the International Confederation of CP and CF anomalies in 1993 and 1997.[13] Thev are available.

For all new interventions in treatment, they should be subjected to rigorous evaluation by RCTs and multicentre trials if possible in order to enhance the level of evidence and the general acceptance of the results. Case series may have a place, provided they are prospective long-term studies using standardised documentation protocols and if they represent a totally new approach with no standard techniques to compare with.

Conclusion

In conclusion, ladies and gentlemen, I wish to provide you with 2 millennium scenarios in CLP.

1. Firstly, to achieve a thorough understanding of the aetiology of CLP, whether they are syndromic or non-syndromic. With the knowledge of the causative factors, we may then proceed into the areas of prevention, to reduce the number of CLP in the world whether by primary intervention or by gene therapy.
2. Secondly, for the babies who are born despite whatever measures we take and there will always be those, I propose to you that we should be scientific in our approach and carry out more randomised clinical trials. Where this is not possible, then properly documented longitudinal studies should be carried out with the reporting of long-term results. In order to improve the evidence and power of these outcome studies, multicentre trials should be conducted in the major high volume cleft centres in the world.

As John Mulliken[11] has said in his article on Molecular Genetics in Cleft Surgery, our ultimate goal should be fewer cases to operate. That should be our dream as cleft providers and hopefully it will come true in the coming millennium.

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