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Report of a WHO Scientific Group

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WHO SCIENTIFIC GROUP ON PAEDIATRIC RESEARCH

Geneva, 28 November - 4 December 1967

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PAEDIATRIC RESEARCH

Report of a WHO Scientific Group

A WHO Scientific Group on Paediatric Research met in Geneva from 28 November to 4 December 1967 to advise the Director-General on present trends and future opportunities. The Group described some notable achievements in the wide field of paediatric research, identified certain important gaps in knowledge, and made proposals for future research programmes.

The meeting was opened by Dr J. Karefa-Smart, Assistant Director-General, who welcomed the participants on behalf of the Director-General. Professor N. Kretchmer was elected Chairman and Professor P. M. Udani Vice-Chairman. Professor E. Rossi and Professor H. Barnett acted as Rapporteurs.

1. INTRODUCTION

The Group agreed to consider as paediatric research any scientifically conducted studies that add to existing knowledge of child health. Paediatric research has made many important contributions to medicine and human biology. It is concerned with the period from conception, through foetal life, infancy, and childhood to the end of adolescence; it includes, therefore, the health of the mother as well as that of the infant and child.

One of the main functions of paediatric research is to elucidate factors responsible for both normal and aberrant human development. Such factors may be inherent in the organism or present in the environment. This research, which utilizes methods ranging from those of the molecular biologist to those of the social scientist, may be pursued in the laboratory, at the bedside of the sick child, in the outpatient department, in the health centre, or in the community. Many other disciplines, such as biochemistry, physiology, and the social sciences, including

psychology and social anthropology, contribute to such research. Some of the recent achievements in paediatric research, from which the directions of future investigations may be predicted, are responsible in part for the marked decrease in the infant mortality rate, which in one developed country has now reached the very low level of 12.6 per 1 000, although in some of the developing countries it is still over 200.¹ Other medical disciplines, such as public health and obstetrics, as well as improvements in the general standards of living, have contributed to the decline in infant mortality.

Examples of outstanding achievements in paediatric research include :

- (a) prevention of certain infectious diseases through immunization;
- (b) elucidation of the etiology of many nutritional disturbances, the prevention and treatment of which in many areas of the world now depend upon the development of methods of applying existing knowledge;
- (c) greatly increased knowledge of physiological factors controlling volume and composition of body fluids applied to the treatment and prevention of water and electrolyte disturbances in infants and children;
- (d) increased understanding of the pathogenesis, diagnosis and, in some cases, etiology of many important medical problems of infants and children, such as iso-immunization, various inborn errors of metabolism, and congenital heart disease.

Paediatric research has also made many contributions to our knowledge of biochemical, physical, psychological and social development.

During recent years one of the major concerns of paediatric research has been the newborn infant and its problems. It is likely that future research will be focused increasingly on (1) problems affecting the foetus and on the genetic and intra-uterine environmental factors that influence foetal development; and (2) the problems of adolescence. There is an especially urgent need for research into means of applying available knowledge as quickly as possible to improve the health of all children.

The wide scope of paediatric research made it impossible for the Group to survey the whole field. The subjects selected for discussion were determined in part by epidemiological data available concerning the five leading causes of death during childhood throughout the world, and in part by the specialized knowledge of the participants.

¹ It has become customary to describe countries as "developing" or "developed". These descriptive terms are useful as long as it is remembered that in most "developed" countries poverty and other adverse social conditions still exist, with all their well-recognized ill effects on child health, and that the provision of health services to at least some sections of their communities is far from satisfactory. Conversely, in many "developing" countries there are sections of the community whose living conditions and health standards are relatively high.

2. PRESENT STATUS AND TRENDS OF PAEDIATRIC RESEARCH IN SELECTED SUBJECTS

2.1 Growth and development

Studies concerned with the biology of the developing organism from conception through adolescence constitute the very core of paediatric research. Such investigations relate directly to maternal and child health and contribute to an understanding of normal and abnormal growth and development, including congenital malformations. Although there are various views on the scope of research on growth and development, the Group has taken it to include physiology and biochemistry as well as anthropometry and psychology. Consequently, such research could encompass studies of: (1) intra-uterine environment and its effect on the foetus; (2) changes in enzymatic activity and regulation of protein synthesis during development; (3) physiological development of the lung relative to pathogenesis of the respiratory distress syndrome; (4) biochemical and physiological development of the nervous system and its response to environmental stimuli; (5) nutritional requirements of infants of low birthweight; (6) long-term effects of disease and malnutrition on the subsequent mental and psychological development of the individual; and (7) environmental influences on the timing of the physiological and psychological changes accompanying puberty and adolescence.

The Group was also concerned about the necessity for a central source of data on growth and development. These data could be helpful to studies of maternal and infant interaction as well as to the investigation of the effects of nutrition, infection, and social and physical environments on the developing organism. There is also a lack of standardization of data-gathering. Although a more systematic approach is being adopted to the collection of anthropometric data, there is a need for correlation of these data with functional and biological information. The Group recommends that an international reference centre on growth and development be established for the storage of information concerning physical, physiological and psychological aspects of growth and development. Specific international groups selected for their ability to adhere to the rigorous requirements for standardization should be invited to participate in the work of the centre.

There is also a need to establish international banks for the storage of cross-referenced fetuses and placentae obtained from abortions; these would make such material available for study by more investigators and also permit the co-ordination and correlation of the work of individual investigators. The many problems concerned with the storage

and preservation of these biological materials would require intensive investigation.

From the vast field of study concerned with growth and development, the Group selected for more extensive discussion the following two aspects (sections 2.1.1 and 2.1.2) that are considered of particular international importance.

2.1.1 *Neonatal and perinatal research*

Despite much activity in perinatal research,¹ many questions remain unanswered concerning the biochemical, physiological, physical and psychological development of infants of low birth weight. The investigation of these problems is of great importance in terms of preventive paediatrics, especially in regard to the relationship of low birth weight to mental retardation. Investigation of infants of low birth weight² should, in general, have a different focus in developing and in developed countries; for example, the highly specialized techniques necessary for extensive research in pulmonary adaptation, which is being investigated so extensively in the more affluent countries, should probably not receive so much emphasis in the developing countries. On the other hand, the large number of infants of low birth weight in the developing countries provides excellent opportunities for studying the effect of such factors as maternal nutrition on the incidence of low birth weight and its relationship to survival and subsequent development.

Knowledge of the regulation of metabolism during development is imperative for adequate care of the infant. The major regulators of metabolism in the mammal are the neurological and endocrine systems, which mediate their effects through cellular and molecular metabolism. These systems are particularly important during prenatal and postnatal development in determining the physiological stability of the infant.

In addition to the important problems of the respiratory distress syndrome, congenital malformations, and neonatal infections in the newborn infant, all of which require additional research, neonatal jaundice with kernicterus is a problem of widespread occurrence throughout the world. This condition provides one example of the type of study urgently requiring international co-operation.

The prevalence and virulence of neonatal jaundice in the developing nations give it a position of high priority for detailed and extensive

¹ Some of this research was reviewed in 1964 by the WHO Scientific Group on the Effects of Labour on the Foetus and the Newborn (*Wld Hlth Org. techn. Rep. Ser.*, 1965, No. 300).

² See the third report of the WHO Expert Committee on Maternal and Child Health: *Public health aspects of low birth weight* (*Wld Hlth Org. techn. Rep. Ser.*, 1961, No. 217).

study. The etiology of more than 50% of the cases encountered is unknown.

Because of the complexity of the mechanisms involved in neonatal jaundice, it is recommended that various aspects of the problem be examined by a meeting of experts, with the aim of evolving a co-operative and co-ordinated study, and that certain specific aspects of neonatal jaundice be investigated, including :

(a) the role of specific steroids of breast milk in the pathogenesis of neonatal jaundice in various populations;

(b) the relationship between the erythrocyte enzyme deficiencies (particularly of G6PD and its variants) and the occurrence of neonatal jaundice;

(c) the relationship between concentration of serum albumin, bilirubin binding and eventual kernicterus;

(d) the effect of drugs on the production of jaundice and haemolytic anaemia (including a study of drugs used in traditional medicine);

(e) the relationship, on a population-wide basis, between particular infections, such as cytomegalic inclusion disease or toxoplasmosis, and the occurrence of jaundice;

(f) additional studies of the problems of iso-immunization and the distribution of minor blood groups.

These problems should be studied epidemiologically, clinically and biochemically. International co-ordination would be essential for some of the most important.

2.1.2 *Congenital malformations and genetic disease*

The term "congenital malformations" is used in this report to include not only anatomical defects but also molecular and cellular abnormalities present at birth. This definition implies that a congenital malformation may be obvious to the observer or it may be hidden. The obvious congenital malformations are those of gross anatomical nature, whereas hidden malformations may involve the tissue, the cell, or the molecule and their detection requires special techniques. It is apparent that this definition is more extensive than that usually employed, and includes the inborn errors of metabolism.

Congenital malformations occur throughout the world, the greatest morbidity and mortality being reported by the most highly developed nations. In the developing countries, malformations are overshadowed by numerically more important causes of death in childhood, especially widespread malnutrition and infectious diseases. Although studies of the incidence of congenital malformations in consecutive births have

already been conducted under the auspices of WHO,¹ it is apparent that more detailed epidemiological studies are necessary. A central registry for such data is being recommended.

A better understanding of the mechanisms responsible for the development of congenital malformations is needed and the task of achieving this challenges the imagination and efforts of all those concerned with developmental biology. Although there is considerable information concerning the transcription of genetic information and its translation into a protein molecule, the phenomenon of differentiation is still unexplained. The development of a congenital malformation can be studied with a variety of techniques from different disciplines, e.g., molecular biology, as has been done in the case of sickle-cell anaemia; cytogenetics, as in Down's syndrome; or embryology, as in the development of a cleft palate. It can also be studied in relation to maternal factors, as exemplified by teratogenic agents, such as methotrexate and thalidomide. Paediatricians have participated extensively in all these studies and have made major contributions to the identification of specific inborn errors of metabolism as well as to studies of normal changes in metabolism during development. However, much more research into these questions is still needed.

There is no doubt that the age of the mother at the time of conception is directly related to the frequency of Down's syndrome, and paternal age has been incriminated as a possible factor in the development of achondroplasia. More information is required concerning the age of the individual in relation to spermatogenesis and oogenesis.

The relationship of maternal environment to the development of malformations in the foetus has been of concern to WHO, and the principles for the testing of drugs for teratogenicity were the subject of a recent report.² Some maternal infections, such as rubella, have been identified as the cause of malformations. However, a considerable amount of information is still required concerning other viral infections.

The high incidence and wide distribution of congenital malformations present a variety of problems of major concern — in the population, in the community, and in the family. An important community problem is the most appropriate care of the malformed or handicapped child. Although the paediatrician must play the major role in studies related to these problems, the participation of specialists in many other disciplines will be required. The purpose of these studies would be to design the best possible programme to maintain the child with malformation in his home, community and school environment, so that he may attain as normal an adult life as possible.

¹ Stevenson, A. C. et al. (1966) *Congenital malformations : a report of a study of series of consecutive births in 24 centres*, Geneva (*Bull. Wld Hlth Org.*, 34, Suppl.).

² *Wld Hlth Org. techn. Rep. Ser.*, 1967, No. 364.

Knowledge of the incidence of congenital malformations is needed for both the developing and developed countries. However, many of the problems referred to above would need to be studied within the more affluent nations, although with the co-operation of the developing countries. It may be anticipated that the information gathered from biology, medicine and public health will lead to prevention as well as to improved treatment.

2.2 Nutrition

On a world-wide basis, nutritional disorders and their consequences constitute the most serious single threat to the health of children. Over the past fifty years, a vast amount of research on nutritional requirements and disturbances has been conducted by investigators from many disciplines, including paediatrics.

One of the major advances made during this period, to which paediatric investigators have in large part contributed, has been the elucidation of the etiology of many nutritional disturbances, especially those involving vitamins, proteins and calories. The prevention and treatment of malnutrition in many areas of the world now depend upon the development, through research, of methods of applying existing knowledge.

The complexity of the problems involved in nutritional research demands a comprehensive multidisciplinary approach. The degree to which the physician participates in the various aspects of nutritional research is shown in the Annex¹ on page 26. If, through such research, successful methods of applying existing knowledge were utilized in the prenatal and postnatal care of infants and children throughout the world, one of the major health problems would be solved.

Paediatric studies have also made a major contribution to the understanding of factors regulating the volume and composition of body fluids and to the application of the underlying physiological principles to the development of methods for treating water and electrolyte disturbances.

Although many questions concerning the etiology and pathogenesis of nutritional disorders remain unanswered, the most urgent need as regards nutrition is for paediatric research on the following questions :

- (a) methods of improving the utilization of existing nutritional knowledge for preventing and treating malnutrition;
- (b) the consequences of malnutrition; and
- (c) optimal and minimal nutritional requirements.

¹ Modified from a diagram prepared by Professor J. Meneghello.

The underlying principles upon which the recommendations for future research in the field of nutrition should be based are as follows :

It is essential that there be some means of identifying the role of malnutrition as a cause of death in order to permit proper assessment of its importance. Amongst the published mortality data on causes of death in infants and children malnutrition does not appear specifically, despite the fact that in many deaths attributed to other causes, such as gastroenteritis or pulmonary infection, the underlying cause is malnutrition. The WHO "International Classification of Diseases"¹ does permit the identification of malnutrition as both an underlying and a contributory cause of death, and efforts should be made to obtain more complete reporting of causes of death so that this information can be included in mortality statistics.

It has long been recognized or suspected that malnutrition during childhood, and especially during early infancy, has a persistent and perhaps permanent unfavourable effect on physical growth and development. However, the most significant consequences of malnutrition would now appear to be on mental development and the underlying biochemical development of the nervous system. The urgency of research into this relationship stems from at least two considerations : first, the very great concern that it may be one of the mechanisms whereby both ignorance and poverty are perpetuated; secondly, investigations into the effects of malnutrition on behavioural and neurological development may provide insights into the normal development of these two functions.

Another aspect of paediatric research in the field of nutrition concerns the question of nutritional adaptation. Evidence gained over many years from animal experiments has indicated that the nutritional experiences of early life may permanently affect the nutritional status of the organism, suggesting a process of nutritional adaptation. Through the use of modern methods of biochemistry and physiology it should now be possible to investigate the mechanisms underlying this intriguing and potentially important process.

Other fruitful areas for research are :

(a) The problems of the weaning period should be given a high priority as the health of the child is particularly vulnerable during this period. A major health hazard is diarrhoea, and research on this problem should include investigations of infections of the gastrointestinal tract and of the effect of malnutrition on the development of intestinal enzymes.

¹ World Health Organization (1967) *Manual of the International Statistical Classification of Diseases, Injuries and Causes of Death*, 1965 revision, Geneva.

(b) The relationship between maternal nutrition and maternal and infant mortality and morbidity needs more study.

(c) Possible relationships between social and cultural factors, nutritional status, and mortality and morbidity in mothers and infants also require study.

(d) Although many of the problems of kwashiorkor have been elucidated, the mechanisms responsible for some of the physiological abnormalities, such as hypothermia and hypoglycaemia, are still not understood and require paediatric research.

(e) The composition of human milk in different ethnic groups, social conditions, and geographic regions should be examined by modern methods; for example, the question of whether proteins of human milk could be used as genetic markers should be investigated.

(f) The increasing problem of overnutrition in the developed countries is an important subject for investigation.

(g) In spite of a number of studies, the optimum food intake for babies of low birth weight remains unsettled. Research is needed on the effects of various levels of calories, proteins, fats, and carbohydrates on the metabolism and the physical and mental development of such babies.

One of the most important recommendations of the Group is that a co-operative long-term study be organized using rigorous epidemiological methods (see section 3.1). Such a study would be essential for the investigation of the most important questions in the field of nutrition.

2.3 Infectious diseases

Impressive progress has been made in understanding the etiology of infectious diseases, many of which can not only be treated effectively but, even more important, can be prevented by safe methods of immunization. For these diseases the great need now in the developing countries is for improved hygienic conditions and for operational research into ways of applying available knowledge for their prevention and treatment.

However, important gaps remain in knowledge of many other infectious diseases. For example, diarrhoeal disorders continue to constitute a major health problem and are a frequent cause of mortality and morbidity in children in developing countries. Here, too, research must be directed not only to applying existing knowledge, but also to specific problems of etiology and treatment, including rehydration, the answers to which may be different in various parts of the world.

For many of the problems listed below, especially sections 2.3.1, 2.3.2 and 2.3.3, a long-term prospective study (see section 3.1) is necessary.

2.3.1 *Immunizations*

(a) Because of the major public health problem of ensuring a wide coverage in the immunization of infants and children and because of the high risk of infection in many of the developing countries, combined administration of immunizing agents as early as possible after birth would be desirable. Therefore, research into the immunological response to combined administration of immunizing agents in infants and children is needed.

(b) Other aspects of immunization, such as methods of administration and the various immunization schedules, require further study. For example, there are many important unanswered questions concerning the prevention of congenital rubella by the use of rubella vaccine, including determination of the optimal time for immunization, depending on the presence or absence of antibodies during the preconceptional period.

2.3.2 *Cytomegalic inclusion disease*

Research is needed to determine the frequency with which this infection, transmitted from the mother to the foetus, causes congenital abnormality.

2.3.3 *Chronic infection and growth*

Studies should be made to determine the effect of chronic infection on both physical and psychological growth.

2.3.4 *Other infectious disease problems*

There are a number of other problems related to infectious diseases, some of which are important in all parts of the world, others in specific regions only. Research is especially needed on the following :

1. The rate of postnatal development of immunoglobulins in infants, possible differences in the rate between developed and developing countries, and factors influencing the rate.
2. Tuberculosis continues to be a major health problem for children in many developing countries. A specific question requiring investigation is the degree of immunity (as distinguished from allergy) induced by BCG vaccine given in the first days of life, compared with that obtained when it is given later. This question is also important in relation to the need for revaccination with BCG. In the treatment of tuberculosis in children, as in so many diseases in developing countries, operational research is required to develop methods for increasing the acceptance of chemoprophylaxis with isoniazid.

3. Research is needed on many aspects of acute respiratory diseases, especially those of viral origin, since they constitute a major cause of mortality, especially in infants, in both developed and developing countries.

4. There is an increasing number of children in residential institutions and day-care centres in many countries and the problem of cross-infection under such circumstances needs further investigation.

5. Certain specific infectious diseases constitute special problems in various parts of the world, e.g.,

- (a) dengue fever and haemorrhagic fever;
- (b) encephalitis, which, although a world-wide problem and usually of unexplained etiology, appears to occur more frequently in the developing countries;
- (c) schistosomiasis;
- (d) cancrum oris, which has a high incidence in many of the developing countries and which might be related to social, cultural or nutritional factors.

2.4 Diseases of specific systems

Among the diseases of specific systems that are important in paediatric research, the following were discussed :

2.4.1 *Cardiovascular system*

In most developed countries heart disease constitutes one of the five leading causes of death in children over the age of five years; with control of other health problems through improved nutrition and better control of infections, a similar situation may be anticipated in the developing countries.

(a) *Congenital heart disease*

The diagnosis and treatment of congenital heart disease in children is the subject of intensive research in the developed countries. Although attempts are also being made to tackle this difficult and expensive form of research in many developing countries, other types of cardiovascular research may be more appropriate at present. For example, the apparently higher incidence of patent ductus arteriosus at high altitudes needs to be documented and better methods of determining the prevalence of congenital heart disease as diagnosed by clinical

methods are needed. Any comprehensive investigation into the relationships between prenatal factors and the occurrence of congenital heart disease would require a long-term prospective study (see section 3.1).

Research into congenital heart disease has probably passed the stage where it is concentrated on description of new anomalies, and in future should be concerned with both the etiology and the physiological and biochemical consequences of known anomalies.

(b) *Cardiomyopathies*

Unexplained cardiomyopathies, including sub-endocardial fibro-elastosis, occur in many parts of the world, particularly in the developing countries.¹ Further research is indicated, particularly concerning the primary and contributing roles of viral infections and malnutrition.

(c) *Rheumatic heart disease*

For reasons that are not fully understood but probably include better social conditions and better control of streptococcal infections, the incidence of rheumatic fever and rheumatic heart disease in the developed countries has decreased; in the developing countries, however, rheumatic heart disease is still an important and an increasing cause of morbidity and mortality. The natural history of the disease in these countries differs from that previously encountered in the developed countries in that mitral stenosis develops much sooner after the initial attack. Further investigations are needed into the biology of the streptococcus, into its relationship to the initial infection, into the fundamental immunological mechanisms involved, and into the efficacy of primary prophylaxis. Other investigations of rheumatic fever that should be carried out in the developing countries include its epidemiology, the correlations between streptococcal infections and rheumatic fever, and the effect of environmental influences on susceptibility to rheumatic fever and rheumatic heart disease.

(d) *Ischaemic heart disease*

Paediatric research could make an important contribution to knowledge of ischaemic heart disease through a long-term study, starting in infancy, of serum lipids in relation to nutrition. Ischaemic heart disease is one of the main causes of death in adults in the developed countries and the elevation of certain serum lipids plays a role in the complex etiology of the condition. It is likely that paediatric research

¹ *Bull. Wld Hlth Org.*, 1965, 33, 257.

will help to elucidate the etiology of other conditions that do not usually manifest themselves until adult life but that have their origin in childhood.

2.4.2 *The kidneys and urinary tract*

In the developed countries, renal disease constitutes one of the five leading causes of death in children over the age of ten years; in the developing countries it is also an important cause of death. Morbidity from these disorders far exceeds mortality.

(a) *Infections of the urinary tract*

A study of the natural history of these conditions should constitute one aspect of a long-term prospective study (see section 3.1) and would include examination of the urine of the mothers during pregnancy and of the infants during the neonatal period, using standardized cytological and bacteriological methods.

(b) *Congenital malformations of the urinary tract*

The incidence and etiology of these conditions would constitute another aspect of such a long-term study.

(c) *The nephrotic syndrome*

An international study group concerned with an evaluation of the use of immunosuppressive agents in the treatment of this condition already exists and work on its etiology is being carried out in many centres. The relationship of the condition to quartan malaria is being studied intensively in Africa. Congenital nephrosis, rare in most communities, has a high incidence in Finland; investigations into the causes of this unique geographical distribution may throw light on the etiology of this syndrome.

(d) *Renal tubular disturbances and developmental renal physiology*

Many disturbances of specific tubular functions have been described during the past decade and it is likely that others still await description. Investigations are required to define the enzymatic mechanisms involved and the importance of genetic and developmental factors in the etiology of these tubular disturbances. While some of them may be the result of developmental arrest others may merely represent the lower part of the normal range of distribution of development of tubular function. Much more research is necessary into these developmental aspects of renal physiology.

2.5 Psychological problems

Several disciplines, including child psychiatry, psychology, sociology, and paediatrics, are concerned with the etiology, treatment and prevention of psychological disorders in children. Unfortunately, there is a world-wide shortage of personnel working in these disciplines. At the same time, it is realised increasingly that it is not possible to consider the etiology, pathology, complications, and management of organic disease without an understanding of possible psychological co-determinants and consequences. There is a growing need, therefore, for personnel from the above-mentioned disciplines to take part in research, which in this field will usually have to be pursued by a team of investigators. During recent years many important investigations have been carried out on the psychological development of children. Only a few well-designed studies have, however, been conducted in an attempt to clarify causative factors affecting the evolution of psychological problems in children. Further studies of this sort are needed in the hope that they might lead to methods of prevention and treatment of these problems. More rigorous research in this area is particularly indicated because these disorders present one of the most frequent health problems of children and adolescents in the developed countries. Reports from developing countries indicate that similar situations exist there, though the importance of these disorders has been overshadowed by the magnitude of other and even more urgent paediatric problems.

It was not possible for this Group to review all the aspects of child psychiatry and psychology requiring further research. However, observations in many countries indicate that there are four problems that have been increasing in frequency and now constitute a great hazard in children and adolescents. In the investigation of three of these — suicide, drug addiction and delinquency, particularly during adolescence — the paediatrician should be one of the participants in research into their cause, treatment and prevention, though the main responsibility will probably fall on scientists from other disciplines. In the investigation of the fourth problem, that of the "battered" child who has been physically or emotionally abused, the paediatrician must play a leading role, though a team approach will again be necessary. Some studies have already been made in which paediatricians, with the help of psychologists and social workers, have analysed the psychological characteristics of the families of battered children. Research in this area is dependent on detection of cases and it is therefore important that physicians caring for children should become more aware of the possibility that unexplained injuries may have been inflicted by parents or other adults.

2.6 Accidents and poisoning

Mortality statistics show accidents to be one of the major causes of death after the first year of life. Though few reliable statistics relating to morbidity are available, there can be no doubt that morbidity from accidents is far greater than mortality.

Research is being carried out in many countries into the prevention of all varieties of accidents. The paediatrician's role in these investigations is necessarily limited but it is important and in some ways unique, especially in terms of prevention. In this connexion, the recommendations made in 1956 by a WHO Advisory Group on Accidents in Childhood¹ are still valid.

2.7 Social and cultural factors

There has been a great deal of interest recently in the effect of social and cultural factors on health and disease, including the use of traditional medicines. For example, in communities in which the availability of dietary protein is barely sufficient, attempts have been made to discover why kwashiorkor occurs in the children of some families in a community and not in others. Observations have suggested that the reason resides in such social and cultural factors as poverty, family breakdown, ignorance, and parental irresponsibility in the families of children in whom protein malnutrition occurs. Although these observations do not constitute research in the classical sense, they do provide important background material and suggest interrelated co-determinants of disease conditions. It is then possible to construct hypotheses which can be tested by well-designed clinical investigations.

Scientific investigations of traditional medicines have in some instances confirmed their value. For example, the anti-ascaris activity of certain extracts from the bark of *Polyadoa umbellata*, one of the plants commonly used in the preparation of brews for the treatment of intestinal worms, was shown to be equal to that of piperazine. However, traditional medicines may also be harmful, as suggested by the demonstration that a mixture prepared from cow's urine, widely used in Western Nigeria to prevent convulsions, produces severe hypoglycaemia in experimental animals.

Though it is difficult to design well-controlled research studies on the effects of many social and cultural factors, it is important that serious attempts continue to be made and that preceding observations be as accurate and objective as possible.

¹ *Wld Hlth Org. techn. Rep. Ser.*, 1957, No. 118.

The co-operative long-term prospective study proposed in section 3.1 would offer a unique opportunity for the investigation of several important questions concerning the effect of social and cultural environments on the health of children. Some additional examples of questions requiring investigation are :

(a) The effect of a changing pattern of family structure on the physical, mental and psychological development of children. The rapidity with which such changes are occurring in many countries may be of special importance.

(b) The effect on the health of children of environmental hazards resulting from socio-economic changes. The effect of air pollution on the health of adults has been studied in some detail, but only few investigations deal with its effect on the health of children and adolescents. It has been suggested that "smog" in Mexico City and Santiago may be responsible for an increased incidence of rickets and respiratory infections.

2.8 Delivery of health services

An urgent problem in many countries, and particularly in those where there is a scarcity of technical staff, facilities and financial resources, is to determine the most effective method of providing health services to large numbers of children.

Paediatric investigators have so far played little part in operational research of this type, for which scientists from other disciplines are, by training and experience, better equipped. Technical aspects of child health care, such as the selection of the most vulnerable groups of children and of the measures to be applied, the assessment of the quality and effectiveness of the health care, and the recognition of changing problems in child health in a given community, are, however, in the domain of the paediatrician and his participation in such studies is therefore essential.

There is also a need for properly designed comparative studies to determine which methods of therapy are most suitable for application under primitive conditions such as obtain, for instance, in many rural health centres in the developing countries. An example is the need for more suitable methods for the rehydration of children suffering from diarrhoea.

In research of this kind it is essential for the paediatric member of the team to be aware of the principles of public health practice.

2.9 Paediatric education

The Group decided to devote time to a brief discussion of medical and, in particular, paediatric education.

One of the functions of medical education is to stimulate the student to develop a critical and enquiring attitude of mind. This is just as necessary for the discriminating clinician who spends little or no time in research as it is for the investigator. The major problems here are by no means unique to paediatric education.

There is a great need for research into medical education. Although many experiments have been attempted during recent years, their evaluation is difficult and reliable methods have not yet been developed to compare the effectiveness of different types of undergraduate medical education. Further studies should be undertaken by educationists, psychologists and other social scientists in co-operation with medical educators.

Though much useful research into the effectiveness of various teaching methods has been undertaken by other educationists, medical educators have been slow to make use of the results of these investigations. In countries with a shortage of teaching personnel it is particularly important that the most effective teaching methods should be employed.

Some of the problems relating more specifically to paediatric education are as follows :

2.9.1 *Undergraduate paediatric education*

In the developing countries the child population under the age of fifteen constitutes more than 40% of the total population, and children under the age of five years account for roughly 50% of the crude death rate, as compared with less than 5% in certain of the developed countries. Despite these facts, in some medical schools a total of less than 300 hours are devoted to the teaching of paediatrics and the subject does not invariably constitute an independent part of the qualifying examination.

Answers to the following questions are urgently needed :

(a) How much of the medical curriculum should be devoted to the teaching of paediatrics and should the proportion vary according to the needs of the community ?

(b) How should the time devoted to paediatric teaching be distributed between study on the ward, in the outpatient department, in health centres, and in the community ?

(c) What specific contributions should paediatrics make to medical education ?

(d) Which of the pre-clinical and clinical subjects have particular relevance to paediatrics and how can better co-operation and integration be achieved between these various disciplines with respect to their contributions to paediatrics ?

2.9.2 *Postgraduate paediatric education*

Only brief reference was made to possibilities for research into postgraduate paediatric education. Two questions were raised :

(a) How many highly qualified paediatricians does a given community need and what opportunities does it offer them ?

(b) What training should a paediatrician receive in order to equip him to give effective service to his community ? For instance, how much teaching of public health and sociology should be included in his training ?

2.9.3 *Training of paediatric investigators*

The Group emphasized the importance of international co-operation in the training of paediatric investigators and considered it desirable that more fellowships and training grants should be provided for this purpose.

2.10 **Unique opportunities for paediatric research**

In recent years, some of the most striking advances in understanding diseases of childhood have come from the investigation of certain genetic disorders that are unique to certain population groups. In addition, a number of other diseases are highly localized in their geographical distribution. Extensive investigation of such diseases by modern methods of physiology, biochemistry and genetics has yielded important new knowledge. Many of these unique opportunities for research occur, however, in regions of the world where at present there are few if any facilities for detailed laboratory and epidemiological investigations.

The following are some examples of diseases that are confined to certain areas or population groups and demand future study :

endemic nephropathy of South-Eastern Europe

congenital nephrosis in Finland

kuru

dengue fever

alactasia

acatalasia

Indian childhood liver cirrhosis

bladder calculi in South-East Asia

infantile tremor syndrome in India
porphyria variegata
carbohydrate deprivation syndrome

Most of these conditions have their onset during childhood, although often they may become apparent and lead to serious illness and death only in adult life.

In the investigation of these diseases it would be especially advantageous to organize international co-operative studies that would bring together the facilities and personnel for fundamental research available in the more affluent countries and the paediatric clinical investigators in the countries where the diseases occur. In some instances, it has proved a fruitful arrangement for paediatric research workers from one country to provide facilities and send trained personnel to work in conjunction with the laboratories of the developing country. Such arrangements require true co-operation based on mutual understanding between the two groups.

It is important that paediatricians throughout the world be aware of the potential value of recognizing and investigating diseases such as those listed above and that opportunities be provided for their investigation on a co-operative basis.

3. RECOMMENDATIONS

In the foregoing sections, a large number of programmes have been described that the Group considered to be both highly important and also appropriate for future paediatric research. The research programmes recommended below have been selected as holding the greatest promise of contributing to the solution of important problems in clinical paediatrics and in maternal and child health.

3.1 Investigations requiring a co-operative long-term prospective study

For many programmes a co-operative long-term prospective study is required and it is recommended that such a study be organized using rigorous epidemiological methods. Although the main subjects of the investigation will be newborn infants, it is suggested that initially studies should be made on adolescent girls who should be followed up through marriage and before and during pregnancy. Their infants would then be followed through childhood to the end of adolescence. Despite the difficulties and expense of prospective investigations, sufficient experience has now been gained in their design to warrant the recommendation

that such a study be organized, because the answers to many important questions related to child health can probably not be obtained in any other way. It is recommended that long-term prospective studies be made on the following problems :

(a) The effect of maternal and infant nutrition on physical and mental development.

(b) The correlation of events prior to conception and during pregnancy with the incidence of congenital malformations, the distribution of birthweight, and subsequent physical and psychological development.

(c) The effect of anaemia and hypoxia during pregnancy on the incidence of birth defects and on the development of the child.

(d) The correlation of events prior to conception and during pregnancy with the incidence of jaundice in infancy.

(e) The effectiveness of various combinations of vaccines given at different ages and by different techniques.

(f) The effect of nutrition during childhood on serum lipids in relation to the incidence of ischaemic heart disease in adults.

3.2 Central registry of congenital malformations

A central registry should be established for the collection, through international co-operative studies, of data on congenital malformations, including inborn errors of metabolism.

3.3 Specific paediatric problems

(a) A study of specific proteins in breast milk.

(b) Investigations into the etiology of idiopathic cardiomyopathies.

(c) Investigations into the etiology and pathogenesis of childhood hepatic cirrhosis in India.

(d) Research concerning the delivery of health services to children.

(e) Studies of the causes and prevention of physical or psychological abuse of the child.

3.4 Research problems requiring initial study by meetings of experts

(a) Biochemical and physiological adaptation to nutrition during development.

(b) Regulation of metabolism during development.

(c) The establishment of banks for the storage of fetuses and placentae.

(d) The causes of unexplained jaundice in infancy.

3.5 Reference centre

A reference centre for the storage of physiological and anthropometric data on growth and development should be established.

3.6 Future meetings

Finally, it is suggested that after an interval of about five years another meeting of experts should be convened to survey progress made in paediatric research during the intervening period and to advise the Director-General on future opportunities.

Annex

**EXTENT OF MEDICAL RESPONSIBILITY
IN MULTIDISCIPLINARY NUTRITIONAL RESEARCH**

TOTAL MEDICAL RESPONSIBILITY	}	Assessment of nutritional problems	{	morbidity sequelae mortality
		Provision of medical care	{	prevention diagnosis treatment
PARTIAL MEDICAL RESPONSIBILITY	}	Study of etiological factors	{	social economic cultural health
		Development, provision and utilization of supplementary feeding	{	increased food production new foods (proteins)
LIMITED MEDICAL RESPONSIBILITY	}	Interdisciplinary co-ordination (integrated approach)		
		Determination of national policy		