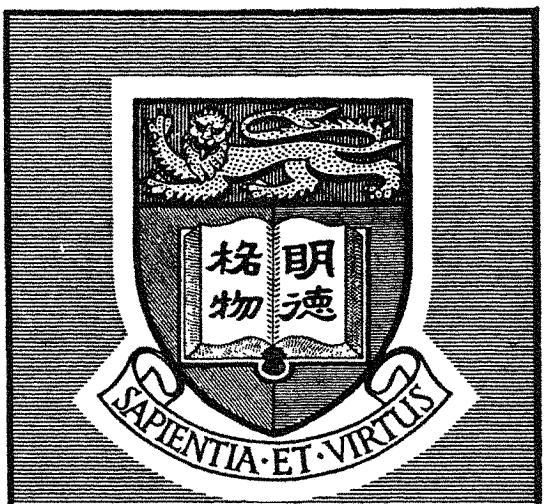
CHILD HEALTH BEYOND 1990

Queen Mary Hospital

Department of Paediatrics

University of Hong Kong

1990



Department of Paediatrics

University of Hong Kong

1990

香港大學兒科部

Queen Mary Hospital, Pokfulam, Hong Kong

Forward

The Department of Paediatrics has always been well-known for its patience; having to wait and persevere before achieving her objectives. She waited 75 years before paediatrics became a recognised and autonomous discipline in the medical faculty of our University. A further 18 years past before resources became available to organise subspecialty programmes such as neonatal medicine, intensive care, cardiology, and developmental paediatrics. Again we have waited nearly 10 years for the commissioning of the new children's wards of Queen Mary Hospital K-Block.

Distinct from the old hospital, the new children's wards have play areas, isolation facilities, mother-and-infant rooms and provision of 'micro-laboratory services' on-site to the ICU. The five children's wards opened in September this year marked the first phase of the expansion of paediatric facilities in Queen Mary Hospital. The Infectious Diseases Unit, the Adolescent Unit, the short-stay ward and the extension of the paediatric and neonatal ICU as well as the paediatric out-patient clinic will be opened in the later phases of the QMH extension programme.

Upon completion, the improved paediatric facilities in QMH, together with the Cardiac Unit in Grantham Hospital, the Neonatal Intensive Care Unit in Tsan Yuk Hospital, the Child Assessment Unit in the Duchess of Kent Hospital, will provide a comprehensive paediatric service in nearly all sub-specialties in Hong Kong.

To commemorate the occasion, we held a 3-day scientific conference in April this year. Although we were disappointed with the unexpected postponement of the commissioning of the new paediatric wards to September, we were most delighted with the turn-out and response at the conference. Speakers and participants were drawn from Australia, Canada, China, Philippines, Macau, Taiwan, U.S.A. and Hong Kong. Lively academic and social exchanges were fostered among the participants, especially among the delegates from Taiwan, China and Hong Kong. Everyone who attended the meeting had thoroughly enjoyed the programme.

The K-Block project could only come to fruition with significant contributions and efforts of many people. The list of all to acknowledge is simply too long to enumerate but I would like to mention especially a few: my predecessor, the late Prof. J.H. Hutchison, for creating the appropriate political climate by arousing the public's awareness of the need to improve the poor hospital facilities for sick children in the public sector; Dr. K.L. Thong, the former Director of Medical and Health Department and Dr. S.H. Lee, the former Deputy Director, for accepting a proposal which I put forth a couple of months after returning to Hong Kong 10 years ago; my medical and nursing colleagues who helped in many different ways to improve the project; the staff of the Commissioning Unit especially Mr. H.C. Hui, for his unfailing effort to assist in all aspects; Dr. T.Y. Chau, the Director of Hospital Services, for his sympathy and support. We are looking forward to even stronger support from the newly appointed Chief Executive of the future Hospital Authority. We are also grateful to Lady Ford for officiating the commissioning of the new paediatric wards on 28th September 1990.

To document these events, we are publishing this bulletin which contains the proceedings of the scientific meeting and some photographs. We hope that it will not only be of historical interest but also of scientific value to our readers.

C.Y. Yeung
Professor and Chairman
Department of Paediatrics
University of Hong Kong
September 1990

Organizing Committee for the Scientific Meeting

on

Child Health Beyond 1990

7 - 9 April 1990.

Chairman	:	Prof. Chap-Yung Yeung
Scientific Sub-committee	:	Dr. Kai-Chiu Lau Dr. Anita Ming-Cheng Li Dr. Roxy Ngok-Sing Lo
General Management Sub-committee	:	Dr. Maurice Ping Leung Dr. Alfred Yat-Cheung Tam
Editorial Sub-committee	:	Dr. Louis Chung-Kai Low Dr. Yu-Lung Lau
Finance Sub-committee	:	Dr. Barbara Cheung-Cheung Lam Ms Lenny Kun Cheng

Content

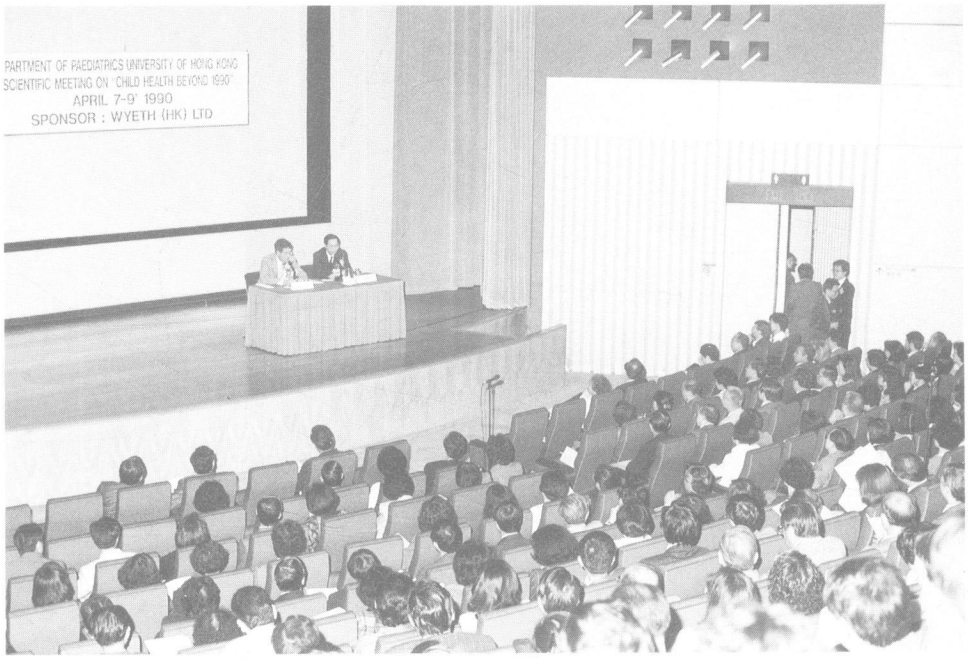
Photographs

of

The Scientific Meeting

and

Commissioning of the New Paediatric Wards



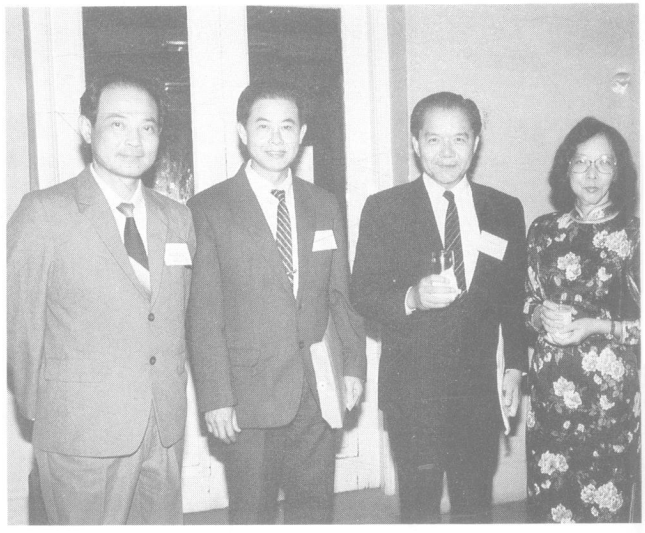
Scientific meeting at the Hong Kong Convention Centre celebrating the commissioning of the Paediatric Wards in Block K of Queen Mary Hospital

Participants at the Scientific Meeting at the Convention Centre

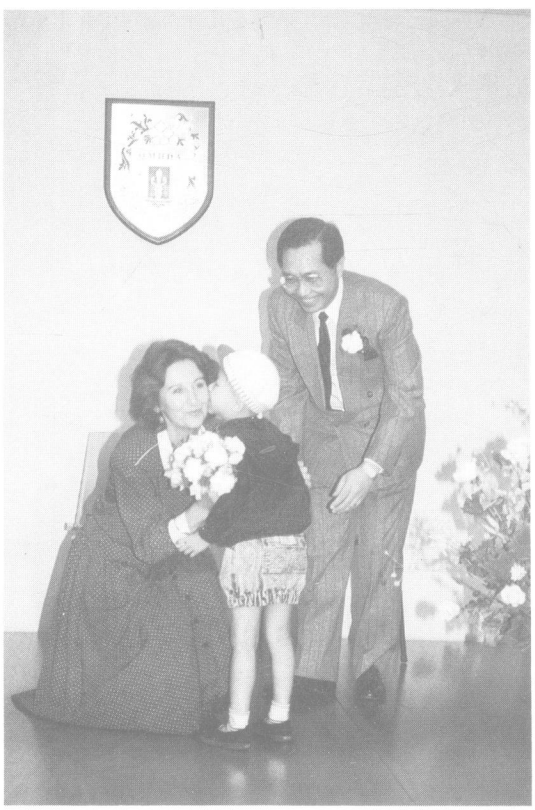
Conference banquet at the Convention Centre

Seminar in session at Queen Mary Hospital

Dinner for overseas participants and the staff of the Department of Paediatrics at the Convocation Room in the University of Hong Kong

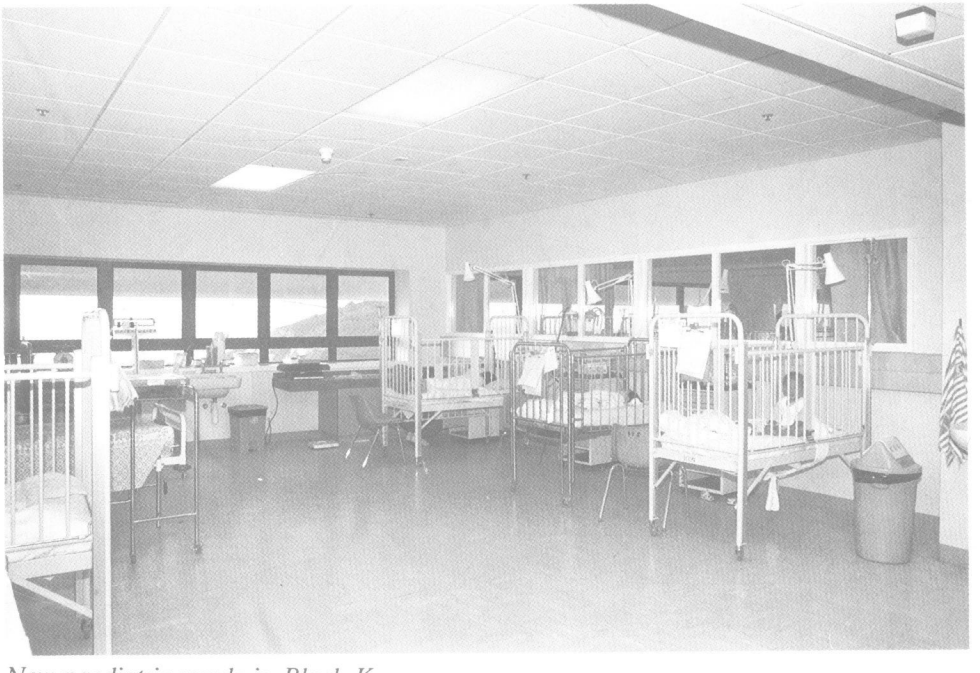


Participants from the People's Republic of China (Beijing, Shanghai, Guangzhou) and Taiwan (Taipei)

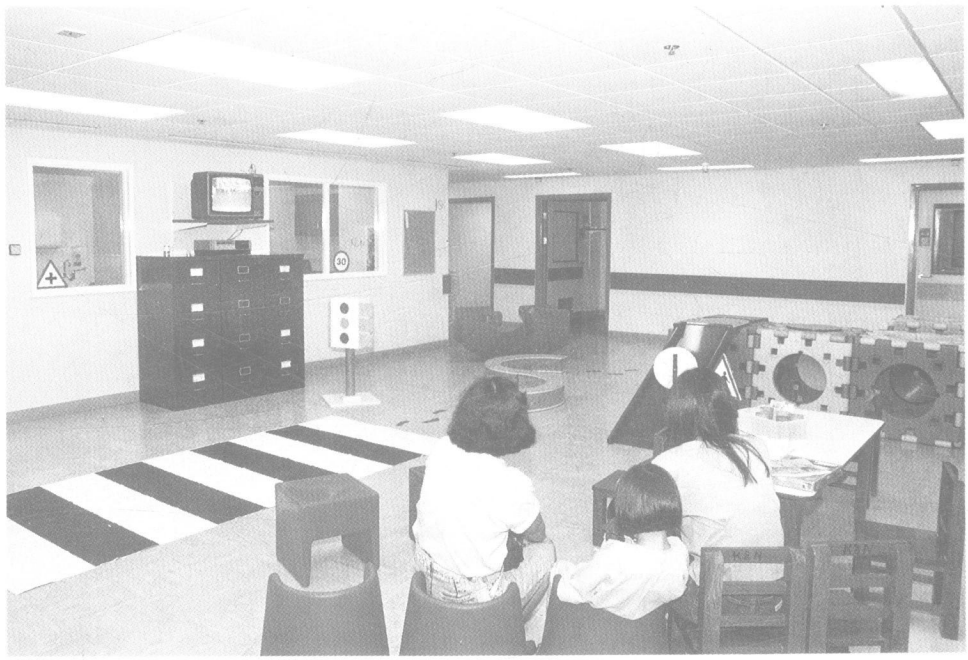


Lady Ford officiating the commissioning of the paediatric wards of Block K of Queen Mary Hospital

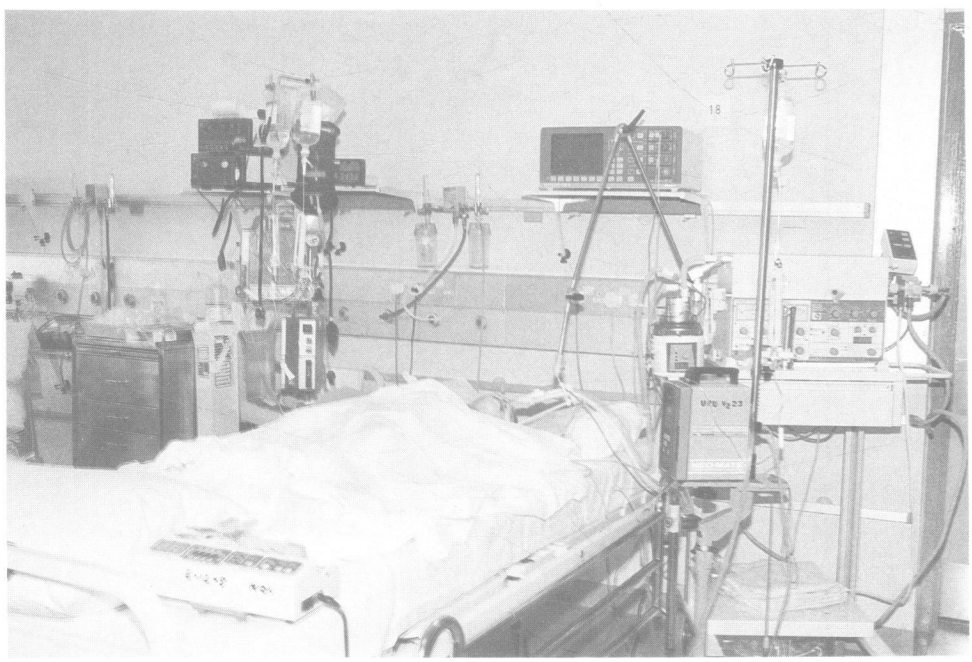
Old paediatric wards in Queen Mary Hospital



New paediatric wards in Block K



The play area in a new paediatric ward in Block K



The new Intensive Care Unit in Block K

First academic activity in Block K : Examination for the membership of the Royal College of Physicians of the United Kingdom. Examiners from the three Colleges and the staff of the Department of Paediatrics

PROCEEDINGS OF THE SCIENTIFIC MEETING

Programme

Saturday, April 7, 1990

Convention Centre, Causeway Bay

OPENING LECTURE

Chairperson : Dr. Chap-Yung Yeung

19.30 Lecture (Theatre II)

Recent Advances in the Therapy of Childhood Asthma
- Dr. Victor Chernick (Winnipeg)

Sunday, April 8, 1990

Rayson Huang Theatre, University of Hong Kong

08.30 - 09.00 **Fosters viewing**

PLENARY LECTURES

Chairperson : Dr. Chap-Yung Yeung

09.00 - 09.40 I. Surfactant replacement therapy for hyaline membrane disease
- Dr. Victor Chernick (Winnipeg)

09.40 - 10.20 II. Adolescent Medicine - Paediatrics preparing for the 21st Century
- Dr. Richard G. MacKenzie (Los Angeles)

10.50 - 11.30 III. The aetiology of pneumonia in children
- Dr. Frank Shann (Melbourne)

Sunday, April 8, 1990

Rayson Huang Theatre, University of Hong Kong

SYMPOSIUM I : Regional Paediatric Experience

Chairperson : Dr. Anita Ming-Cheng Li

11.30 - 11.50 Resurgence of acute rheumatic fever in children
- Dr. Hung-Chi Lue (Taipei)

11.50 - 12.10 Is symptom free bronchial hyperresponsiveness an indication of potential asthma ?
- Dr. Nan-Shan Zhong (Guangzhou)

12.10 - 12.30 Lactose malabsorption in Chinese children
- Dr. Chap-Yung Yeung (Hong Kong)

12.30 Lunch

SYMPOSIUM II : Infectious Diseases

Chairpersons : Dr. Louis Chung-Kai Low
Dr. Nai-Kong Leung

14.00 - 14.30 New antibiotics in children
- Dr. Frank Shann (Melbourne)

14.30 - 14.45 Lymphokines and infection
- Dr. Allan Lau (Toronto)

14.45 - 15.00 Infection in primary immunodeficiency diseases
- Dr. Yu-Lung Lau (Hong Kong)

15.00 - 15.15 Hepatitis B vaccine - Longterm follow-up
- Dr. Shu-cheng Duan (Shanghai)

15.15 - 15.30 Hepatitis B - Efficacies of vaccinations
- Dr. Tsee-Chung Wu (Taipei)

Sunday, April 8, 1990

Rayson Huang Theatre, University of Hong Kong

SYMPOSIUM III : Cardio-respiratory Disorders

Chairpersons : Dr. Alfred Yat-Cheung Tam
Dr. Shoubao Ning

16.30 - 16.45	Changing pattern of childhood asthma in Taiwan - Dr. Kue-Hsiung Hsieh (Taipei)
16.45 - 17.00	A 10-year nation-wide survey of hospitalized children with wheeze in China - Dr. Yu-Zhi Chen (Beijing)
17.00 - 17.15	Surfactant replacement therapy in animal experiment - Dr. Sheng-Huan Dong (Beijing)
17.15 - 17.30	The incidence and epidemiology of congenital heart disease. - Dr. Shoubao Ning (Shanghai)
17.30 - 17.45	Paediatric valvuloplasty and angioplasty in Hong Kong. - Dr. Roxy Ngok-Sing Lo (Hong Kong)
17.45 - 18.00	"Oriental" ventricular septal defect - Dr. Kai-Chiu Lau (Hong Kong)
18.00 - 18.15	Critical aortic stenosis in early infancy - surgical and echocardiographic substrate for successful pen valvotomy - Dr. Maurice Ping Leung (Hong Kong)
18.15 - 18.30	General Discussion

Sunday, April 8, 1990

Rayson Huang Theatre, University of Hong Kong

15.30 - 16.30 **Posters Discussion**

Runme Shaw Building

Posters 1 - 6
(Room 101)

Chairpersons : Dr. Victor Chernick
Dr. Lily Chiu

Posters 7 - 12
(Room 102)

Chairpersons : Dr. Richard G. MacKenzie
Dr. Maurice Ping Leung

Posters 13 - 18
(Room 103)

Chairpersons : Dr. Frank Shann
Dr. Kai-Chiu Lau

Monday, April 9, 1990

Underground Lecture Theatre I, Queen Mary Hospital

SYMPOSIUM IV : General Paediatrics Update

Morning Session

Chairpersons :	Dr. Roxy Ngok-Sing Lo Dr. Alice Chau
09.00 - 09.40	Apnoea in infancy and childhood - Dr. Victor Chernick (Winnipeg)
09.40 - 10.20	Infection in intensive care - Dr. Frank Shann (Melbourne)
10.45 - 11.25	Developmental dynamics of the teenager - Dr. Richard G. MacKenzie (Los Angeles)
11.25 - 11.40	Unsustained sexual precocity - Dr. Louis Chung-Kai Low (Hong Kong)
11.40 - 11.55	Depression in Hong Kong children suffering from thalassaemia major - Dr. Anita Ming-Cheng Li (Hong Kong)
11.55 - 12.10	Physical fitness in Hong Kong children - Dr. Henrietta Man-Hing Ip (Hong Kong)
12.10 - 12.30	General Discussion
12.30 - 14.00	**Lunch hour Departmental meeting** :- Seminar on Clinical Research to Paediatric Residents Guest Speaker : Dr. Victor Chernick (Winnipeg)

Afternoon Session

Chairpersons :	Dr. Alfred Yat-Cheung Tam Dr. Man-Chun Chiu
14.00 - 14.40	Congenital nephrotic syndrome - Dr. Robert L. Vernier (Minnesota)
14.40 - 15.20	Acid-base disorders in renal diseases - Dr. James Chan (Richmond)
15.20 - 15.50	Two decades' of bone marrow transplantation - Review of published results - Dr. Man-Yung Cheng (Hong Kong)

PROCEEDINGS OF THE SCIENTIFIC MEETING

Opening Lecture

Recent Advances in the Therapy of Childhood Asthma

Victor Chernick

RECENT ADVANCES IN THE THERAPY OF CHILDHOOD ASTHMA

Victor Chernick
Pediatric Respirology
Department of Paediatrics and Child Health
The University of Manitoba
Manitoba, Canada

The rate of hospitalization in children with acute asthma has increased substantially worldwide since the mid 1960's (figure 1)[1]. This has occurred despite perceived improvements in medical management and the introduction of drugs thought to be more efficacious in the treatment of asthma. The reason(s) for this observation are unclear but it does suggest that either the frequency or severity, or both, of asthma has increased. Despite this the mortality rate remains low and death from asthma in the hospitalized child is a rare event.

Figure 1 Hospital admission rate for asthma (ages 0-14 years) Mid 1960's to 1980*

	Fold increase
Canada	4
USA	3
England & Wales	6
New Zealand	10
Tasmania	3
Queensland, Australia	8

* adapted from Mitchell, E.A. Arch Dis Child 1985; 60:376.

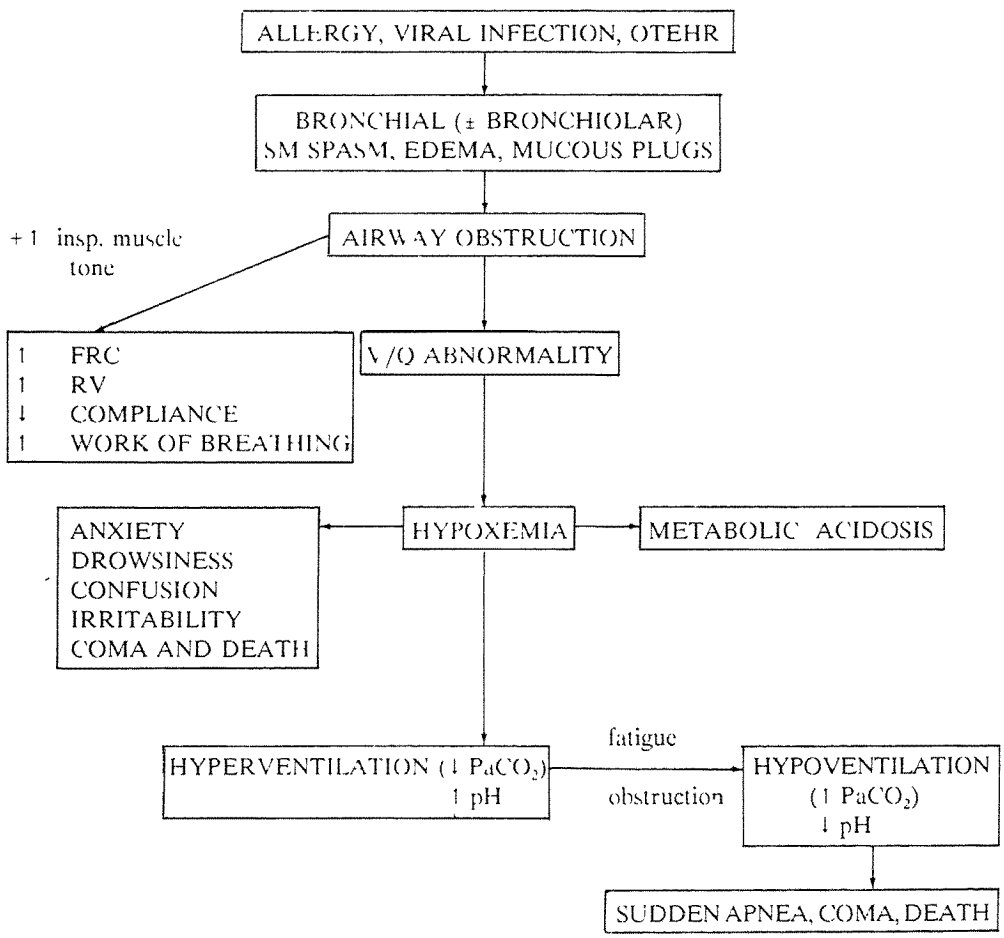
PATHOPHYSIOLOGY OF STATUS ASTHMATICUS

Status asthmaticus is a term which refers to the patient with severe acute asthma who does not respond to bronchodilator therapy. The term has no precise definition and the diagnosis depends on clinical assessment and the precise bronchodilator therapy which is administered.

Figure 2 illustrates a pathophysiologic scheme of severe acute asthma. The acute attack may be triggered by an allergic response, viral infection or other factors. This leads to bronchial smooth muscle spasm, mucosal edema and mucous plugs. The latter are responsible for the so-called Curschmann's spirals, which are expectorated mucous casts of the airways, and probably more accurately should be called Robertson's spirals[2]. It is the presence of mucous plugs which is the hallmark of severe status asthmaticus and the primary reason for failure to respond to bronchodilator therapy. These plugs are of critical importance in determining the course of patients with acute respiratory failure, as will be discussed later. Airway obstruction plus an increase in inspiratory muscle tone lead to hyperinflation with increased functional residual capacity, residual volume and decreased compliance of the lung. Inspiratory obstruction

capacity, residual volume and decreased compliance of the lung. Inspiratory obstruction is also present but is usually less severe than the expiratory obstruction which leads to a prolonged expiratory time. Since the airway obstruction is not homogeneous, ventilation-perfusion abnormalities result in hypoxemia (at sea level a PaO_2 of < 90 mm Hg) of varying degrees. In the absence of respiratory failure the patient usually hyperventilates with resultant respiratory alkalosis and hypocapnia. With severe obstruction and/or fatigue of the ventilatory pump hypoventilation occurs with respiratory acidosis and hypercapnia ($PaCO_2$ usually > 50 mm Hg). Worsening of hypoxemia (PaO_2 < 60 mm Hg) results in metabolic acidosis secondary to the accumulation of lactic acid. Worsening of the disease process may lead to sudden apnea, coma and death, as indicated earlier, a rare event[3].

Figure 2 Pathophysiology of severe acute asthma



THERAPY OF THE HOSPITALIZED PATIENT

First let us consider what not to do! Irritability and anxiety are classical side effects of hypoxemia even in children. Any attempt at sedation or the use of tranquilizers to treat these symptoms is absolutely contraindicated unless ventilator therapy is indicated since respiratory failure can be precipitated. Similarly antihistamines which have both a sedative effect and cause additional thickening of secretions should not be prescribed. Cromolyn, a mast cell stabilizer is ineffective during status asthmaticus and therefore not indicated. Chest physiotherapy should be delayed until mucous plugs loosen and are being expectorated. Early institution of chest physiotherapy may worsen obstruction instead of offering relief. In the vast majority of cases antibiotics are also unnecessary since bacterial infection as a precipitating cause is rare[4].

What therapy is indicated? The current management of the patient hospitalized with status asthmaticus has in some instances been scientifically studied and in others has depended on the inherent bias of a particular clinician. The following is a combination of my own bias and carefully controlled clinical trials[5-8] (figure 3).

Figure 3 Management of Status Asthmaticus

THERAPY CONTRAINDICATED IN STATUS ASTHMATICUS
SEDATIVES OR TRANQUILIZERS
ANTIHISTAMINES
CROMOLYN
CHEST PHYSIOTHERAPY
ANTIBIOTICS
THERAPY INDICATED IN STATUS ASTHMATICUS
OXYGEN
HYDRATION IV
AMINOPHYLLINE IV
STEROIDS
β ADRENERGIC AGENTS
VENTILATOR

Additional oxygen is essential in the management of status asthmaticus. The aim should be to keep arterial PO_2 > 60 mm Hg and in general 25-30% humidified oxygen by facemask is adequate. I have not seen hypoventilation on the basis of oxygen therapy in children with asthma. However, higher concentrations of oxygen may contribute to atelectasis in areas of the lung which are poorly ventilated yet perfused. IV fluids must be given in adequate quantity since these patients are frequently dehydrated and have increased water loss. I prefer to use 1.5 times maintenance requirements and aim to keep urine specific gravity below 1.010. At this infusion rate pulmonary edema, a potential complication, has not occurred.

Aminophylline IV in adequate doses to maintain a serum level of 10-20 ugm/ml appears to be a reasonable approach and a double blind study supports the efficacy of this drug[9]. However, a review of all controlled trails of the use of aminophylline in severe acute asthma failed to find conclusive evidence of efficacy[10].

Most clinicians still use intravenous steroid therapy but recognize that their major effect may not be seen until 24 to 48 hours coincident with the mobilization of mucous plugs[10]. A double blind study did not find a significant effect of steroid on pulmonary function at 24 hours following hospitalization but did find a beneficial effect on PaO_2 as early as 3 hours after initiating treatment[11]. One Canadian study did not find that steroids were beneficial in patients who were not steroid dependent prior to hospitalization[12].

Selective β-adrenergic agents such as salbutamol should be given by inhalation aerosol as an adjunct to aminophylline bronchodilator therapy. IV isoproterenol or salbutamol has been used to treat patients with status asthmaticus with severe hypercapnia and appears to be effective in lowering $PaCO_2$ and obviating the necessity for artificial ventilation in a high percentage of patients[13,14]. Such therapy should be reserved for the intensive care situation where a skilled team can monitor the effect of the drug and is prepared for the institution of artificial ventilation if necessary.

MECHANICAL VENTILATION

Clinical and laboratory criteria for the institution of mechanical ventilation are shown in figure 4. The clinician must be astute enough to diagnose impending respiratory failure in the patient who, despite therapy, has increasing restlessness, decreasing or absent breath sounds and increasing respiratory effort. Both impending respiratory failure and frank respiratory failure with elevation in $PaCO_2$ > 55 mm Hg require that mechanical ventilation be instituted without delay. Intubation, sedation, neuromuscular blockade and ventilation with a volume ventilator are rarely required for more than 48 hours. By 24-36 hours inspissated mucus begins to be mobilized and is associated with clinical improvement. Endotracheal suction prior to this time is usually not worthwhile since the plugs are located in more peripheral airways. Complications of ventilator therapy include lung rupture with consequent pneumomediastinum, pneumothorax or subcutaneous emphysema, accidental extubation and post intubation laryngeal edema. Ventilator therapy requires an intensive care setting with a skilled team including physicians, nurses and respiratory therapists in order to provide the appropriate level of expertise and avoid long term sequelae.

Figure 4 Selection criteria for mechanical ventilation

CLINICAL

RESPIRATORY	:	APNEA, decreasing BREATH SOUNDS, WEAKENING EFFORT
CARDIAC	:	ASYSTOLE, SHOCK, SEVERE BRADY OR TACHYCARDIA
CEREBRAL	:	COMA, RESTLESSNESS, ANXIETY, decreasing RESPONSIVENESS

LABORATORY

$PaCO_2$	:	> 55 mm Hg OR > 5 mm Hg/HOUR RISE
PaO_2 (FiO_2=1.00)	:	< 50 - 60 mm Hg

THERAPY OF THE AMBULATORY PATIENT

The increasing rate of hospitalization for asthma is very disturbing. We need to analyze the phenomenon further to assess possible reasons. Optimal therapy of asthma for the ambulatory patient obviously requires further study in an attempt to prevent status asthmaticus.

Approaches to the therapy of asthma involve both environmental considerations and drug therapy. Environmental control is difficult but dust collections such as stuffed animals, shag carpets should be removed. Regular vacuuming of the home including bedroom and mattress and avoidance of feather pillows and wool blankets are important. Any known allergens should be eliminated. Pets are a problem. Get rid of the cat immediately and change the pet dog from a shedding to a non-shedding variety.

Drug therapy is the mainstay of the current approach to asthma. About 75% of pediatric patients are well controlled on intermittent or regular inhalation of salbutamol, a selective β_2-agonist. Salbutamol is administered by a metered dose inhaler, spinhaler or with young infants via compressor, nebulizer and face mask. Side effects of this drug are minimal and there is no evidence of tachyphylaxis.

In the past, theophylline was widely used for asthmatic children. However, side effects such as behaviourial disturbance, insomnia, and poor school performance have made this drug less appealing. My view is to avoid the use of theophyllines if at all possible. If they are used then serum levels must be monitored to ensure a therapeutic level of 10-20 ugm/ml[15].

Cromolyn is a mast cell stabilizer which is administered by inhalation. It is particularly useful for seasonal allergic asthma and for the prevention of exercise induced asthma.

Inhaled steroids should be started in asthmatic patients who require regular or increasing amounts of β-agonist drug. Sufficient time (4-6 weeks) is required to observe a beneficial effect. Side effects are infrequent and the use of inhalation devices (spacers) and mouth-washing after each dose eliminates oral candidiasis. Oral steroids can be given to control moderate to severe breakthrough symptoms. One approach is to give a high dose (1 mg/kg) for 3-4 days and then to taper the steroid slowly over a 7 day period. In the very severe asthmatic child (<5% of asthmatics in my experience) oral steroid given every other day may be necessary.

Finally the role of inhaled ipratropium bromide (Atrovent) in asthma is not yet clear. The drug may be useful in controlling cough if that is a major symptom. There are some data which suggest that a combination of Atrovent and salbutamol results in a greater improvement in pulmonary function in those patients treated in the emergency room with a severe attack.

Drugs being developed now and not yet available include theophyllines with less CNS side effects, longer acting β-agonist drugs (e.g. formoterol) and more effective mast cell stabilizers.

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PROCEEDINGS OF THE SCIENTIFIC MEETING

Plenary Lectures

I. Surfactant replacement therapy for hyaline membrane disease
- Dr. Victor Chernick (Winnipeg)

II. Adolescent Medicine - Paediatrics preparing for the 21st Century
- Dr. Richard G. MacKenzie (Los Angeles)

III. The aetiology of pneumonia in children
- Dr. Frank Shann (Melbourne)

PL1

SURFACTANT REPLACEMENT THERAPY FOR RDS

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Respiratory distress syndrome (RDS), also termed hyaline membrane disease (HMD), is the leading cause of death and disability among premature infants[1]. Among 230,000 - 250,000 infants born prematurely each year[1] in the United States, 40,000 - 50,000 develop RDS[2], and of those who develop RDS, 5,000 to 8,000 die[1]. After 34 weeks gestation, risk for RDS is negligible except in a few situations such as familial RDS or maternal diabetes. Prior to 34 weeks gestation, risk for RDS increases as gestational age decreases. RDS occurs in up to 75% of infants born at less than 30 weeks gestation (< 1250 grams). Prior to the advent of modern neonatal intensive care, the great majority of infants with RDS died; now death from RDS in developed countries is not common except in extremely premature infants. In less developed countries, however, RDS survivors often pay a significant price in both acute and chronic morbidity, since current therapy for moderate to severe RDS requires mechanical ventilation. There are a number of significant complications which occur during positive pressure mechanical ventilation for RDS, including pneumothorax[3], pneumopericardium[3], pulmonary interstitial emphysema[3], bronchopulmonary dysplasia[4], patent ductus arteriosus[5], necrotizing enterocolitis[6], and intraventricular hemorrhage[7].

It is well accepted that surfactant deficiency is primarily responsible for RDS. Thus, surfactant replacement early in the course of RDS should greatly ameliorate the disease and improve symptoms.

TYPES OF SURFACTANT

Several types of surfactant have been used or proposed for the treatment of RDS:

1. Natural Surfactant - recovered from alveolar lavage or amniotic fluid. Species homologous or heterologous.

2. Modified Natural Surfactant - reconstituted after extraction by addition and/or removal of components. Retains hydrophobic surfactant specific proteins.

3. Artificial Surfactant -

   a. dipalmitoyl phosphatidylcholine (DPPC) plus phosphatidylglycerol (PG)

   b. DPPC plus hexadecanol plus tyloxapol (13.5:1.5:1) or Exosurf Pediatric

4. Synthetic Natural surfactant - phospholipids etc found in natural surfactant plus in vitro synthesized surfactant specific proteins - not available yet.

TYPES OF CLINICAL TRIALS

Since the initial report of Fujiwara in 1980[8] who used a modified natural surfactant obtained from cow lung, a number of clinical trials of surfactant in preterm infants have been undertaken

(Table 1). These trials have been of two types:

A. Prophylactic - surfactant was administered at birth to infants usually < 1250 gm (some trials < 1000 gm) birth weight in order to prevent RDS.

B. Rescue - surfactant administered to infants who already have the diagnosis of RDS established by clinical and radiologic criteria.

TABLE 1. Some Recent Clinical Trials of Surfactant in Infants

Surfactant Source or Type	Approximate Dose/Kg (mg)	Infants Treated (n)	Results	References
Treatment of RDS				
Fortified lipid extract of cow lung	100	10	Effective	Fujiwara et al[8]
DPPC 70%:PG 30%	25	12*	No effect	Wilkinson et al[9]
Human amniotic fluid	60	22*	Effective	Hallman et al[10]
Fortified lipid extract of cow lung	100	18*	Effective	Gitlin et al[11]
Fortified lipid extract of cow lung	100	17*	Effective	Raju et al[12]
Prophylaxis of RDS				
DPPC 70%:PG 30%	25	22	No Effect	Morley et al[13]
DPPC 70%:PG 30%	25	10*	No Effect	Milner et al[14]
DPPC + high density lipoproteins	20-30	49*	No Effect	Halliday et al[15]
Extract of calf lung lavage	75-100	39*	Effective	Enhorning et al[16]
Extract of calf lung lavage	100	14*	Effective	Kwong et al[17]
Extract of calf lung lavage	100	16*	Effective	Shapiro et al[18]
Human amniotic acid	60	31*	Effective	Merritt et al[19]

* Randomized, controlled trials

In general, natural and modified natural surfactant have been found to be effective in that treatment allowed a reduction in FIO_2 and mean airway pressure.

In most studies, surfactant treatment has been associated with a decreased incidence of lung rupture, patent ductus arteriosus and mortality and a suggestive decrease in the occurrence of BPD. The number of subjects in these trials has been too small for a definitive conclusion in many circumstances[20].

PROBLEMS WITH NATURAL SURFACTANT

Universal availability of natural or modified natural surfactant has been limited. A number of difficulties have been encountered:

1. Small amounts of foreign protein are present but have not been considered dangerous to date.

2. Techniques of ensuring a sterile product are cumbersome and limit large scale manufacturing of the product at a reasonable cost.

3. The lyophilized product is difficult to reconstitute.

RECENT CLINICAL TRIALS OF EXOSURF PEDIATRIC (ARTIFICIAL SURFACTANT)

Recent multi-centered blinded clinical trials of Exosurf Pediatric conducted in North America have demonstrated that:

1. A single prophylactic dose of Exosurf at birth in 700-1100 gm infants is associated with reduced mortality and morbidity (Table 2). Multiple doses were not used but presumably might be even more efficacious.

2. Two doses of Exosurf (12 hours apart) to infants with RDS who were > 700 gm birth weight (rescue studies) was associated with a marked improvement in morbidity and mortality (Tables 3, 4).

TABLE 2. Effects of Single Prophylactic Dose of Exosurf Pediatric at Birth in 700-1100 Gram Infants

Outcome	Air (n=222)	Exosurf Ped. (n=224)	P Value
Pneumothorax	43	24	0.010
PIE	57	44	0.120
Grade III IVH and/or PVED	29	31	0.949
PDA	110	112	0.288
Days on IMV	18.8 ± 0.7	17.6 ± 0.7	0.263
Apnea	123	146	0.112
BPD	36	43	0.671
Death			
from air leak	5	2	0.251
from RDS	23	12	0.051
Death <10 days	36	22	0.044
Death ≤28 days	47	34	0.091
Death ≤ 28 or survival with BPD	75	70	0.543
All deaths	66	44	0.010

TABLE 3. Effects of Two Rescue Doses of Exosurf Pediatric in 700-1350 Gram Infants with RDS

Outcome	Air (n=213)	Exosurf Ped. (n=206)	P Value
Pneumothorax	62	40	0.022
PIE	102	51	0.001
Grade III IVH and/or PVED	26	18	0.168
PDA	141	118	0.067
Days on IMV	17.9 ± 0.7	15.6 ± 0.7	0.004
Apnea	102	134	0.001
BPD	39	31	0.141
Death			
from air leak	14	6	0.064
from RDS	21	7	0.007
Death <10 days	38	15	0.001
Death ≤28 days	50	23	0.001
Death ≤ 28 or survival with BPD	80	48	0.002
All deaths	58	30	0.002

TABLE 4. Effects of Two Rescue Doses of Exosurf Pediatric in Infants > 1250 Grams Birth Weight with RDS

Outcome	Air (n=619)	Exosurf Ped. (n=613)	P Value
Pneumothorax	123	60	0.001
PIE	150	79	0.001
Grade III IVH and/or PVED	28	24	0.714
PDA	333	227	0.004
Days on IMV	9.2 ± 0.7	6.8 ± 0.7	0.001
Apnea	225	260	0.033
BPD	35	17	0.009
Death			
from air leak	3	6	0.312
from RDS	19	6	0.010
Death <10 days	34	22	0.110
Death ≤28 days	43	26	0.039
Death ≤ 28 or survival with BPD	73	41	0.002
All deaths	53	36	0.067

CONCLUSION

Artificial surfactant either given prophylactically or as rescue therapy will markedly reduce morbidity and mortality of RDS in North America when it is released for general use. This will probably occur in 1990. It is still not clear how many doses of drug should be given and in some cases more than 2 doses probably are required.

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PL2

ADOLESCENT MEDICINE-PEDIATRICS PREPARING FOR THE 21st CENTURY

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No single age group has reflected the new morbidities of pediatrics than the adolescent. The socialization of the child from family to community, the increased technology within the world of work, distortion of the family unit through 'working parents' or divorce, and values popularized through the media which are incongruent with the fundamental teachings of conventional society, have changed the nature of the adolescent experience. The adolescent in his struggle for a place in Society, is confronted with a prolonged educational experience during which rewards are remote and yet the immediate need for identification and acceptance real. The new morbidities result as teenagers struggle with these pressures for adaptation and change.

New risks to health now exist for the teenager. Adolescence in most cultures is characterized by a testing out of new ways of being, the exploration of new experiences, and the trying out of perceived adult behaviors. Each exploration carries with it an inherent risk, the degree being determined by the behavior itself, the personality characteristics of the individual, and the environment. Closer examination of these issues leads to a better understanding of the new challenges to pediatrics specifically, and to organized medicine, in general.

PL3

THE AETIOLOGY OF PNEUMONIA IN CHILDREN

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About 4 million children die from pneumonia every year, and 97% of these deaths occur in developing countries. If we are to reduce the number of children dying from pneumonia, we need to know what causes it.

In children, the aetiology of pneumonia can be determined accurately only by culture of tissue obtained by needle aspiration of the lung. Tracheal aspirates are unreliable because of contamination by upper respiratory flora (false positives), and blood cultures will detect only encapsulated organisms that survive in the bloodstream (false negatives). Studies performed in hospitals where antibiotics are freely available in the community will be biased because, first, many children with bacterial pneumonia will be cured by antibiotic therapy and so never present to hospital and, second, those children who do present will often have antibiotic activity in the serum which will inhibit growth of bacteria.

There are at least 13 studies in developing countries where lung aspiration has been used to determine the aetiology of severe pneumonia in children with no recent history of antibiotic therapy. Bacteria were isolated from the lungs of 62% of the 1029 children studied; these were usually S. pneumoniae or H. influenzae. The two studies that serotyped the isolates of H. influenzae found that many strains were nonserotypable (unencapsulated) organisms, or were serotypes other than type b. In studies that looked for evidence of viral infection, this was found in about 30% of patients. Many patients with viral infection also had bacterial pneumonia. Chlamydia and mycoplasma may also be important causes of pneumonia in children in developing countries.

In developing countries, a very high proportion of children carry S. pneumoniae and H. influenzae in their nasopharynx. Pneumonia is probably caused by aspiration of these organisms into the lung : the radiological appearance is a patchy perihilar bronchopneumonia typical of aspiration, it is common to find more than one organism in the lung, and the organisms found in the lung are almost always those present in that child's nasopharynx. It is possible that viral infection may predispose to aspiration of nasopharyngeal secretions and bacterial infection of the lung.

There are no good studies of the aetiology of pneumonia in developed countries. Lung aspiration is associated with a low but definite mortality, so it cannot ethically be performed routinely in developed countries where the mortality from pneumonia is very low. Most studies have sought evidence of bacterial infection with a combination of blood culture (which has very low sensitivity) and antigen detection (which reliably detects only H. influenzae type b). Typical findings have been evidence of viral infection in about 30% of patients (as in developing countries), and bacterial infection in a very small proportion of patients. However, the techniques used to detect bacteria have been insensitive, and most children have been studied without being tested for the presence of antibiotic activity in their serum.

Most deaths from pneumonia in children are caused by bacterial infection. In the short term, we could reduce mortality by simple, cheap antibiotic regimens that could be used in developing countries. In the medium term, we need to develop vaccines that protect young children against S. pneumoniae and H. influenzae (not just type b, but nonserotypable strains as well as a, c, d, e and f). In the long term, mortality could be reduced by improved housing with less crowding and less pollution by smoke.

PROCEEDINGS OF THE SCIENTIFIC MEETING

Symposia

SYMPOSIUM I

S.I.1

RESURGENCE OF RHEUMATIC FEVER IN CHILDREN

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ABSTRACT

Rheumatic fever and rheumatic heart disease, which are the most important sequelae to Group A streptococcal infection, have once again become the focus of concerns because of the resurgence of rheumatic fever occurring in the United States and Chile. An outbreak of rheumatic fever, though not large, has also occurred in Taiwan during 1987 to 1988. The age at the first attack of rheumatic fever has increased. The percentage frequency of carditis in Taiwan remained high, leading to congestive heart failure in about half of the cases. The percentage frequency of rheumatic fever recurrence became less common (22.1%) than before (46.8%), reflecting the effectiveness of benzathine penicillin G secondary prevention programs. It is emphasized that rheumatic fever is a cyclic disease. The physicians, especially the pediatricians, should be kept alerted.

Key words: Rheumatic fever, rheumatic heart disease, Group A streptococcus, benzathine penicillin G, epidemiology

INTRODUCTION

Rheumatic fever and rheumatic heart disease, the most important acquired cardiac problems affecting children and young adults, have once again become the focus of conerns since 1986, when an unexpected resurgence of acute rheumatic fever occurred in the United States[1-7]. An outbreak of rheumatic fever has also occurred most recently in Santiago, Chile[8] and Taiwan. It is quite timely that Professor C.Y. Yeung asked me to review this important topic at the Conference on "Child Health Beyond 1990".

RHEUMATIC HEART DISEASE AMONG CHILDREN IN TAIWAN

Serial school surveys carried out in Taiwan during the past 20 years from 1970 to 1989 showed that the prevalence rate of rheumatic heart disease among school children was the highest, 1.4 per thousand in 1970, and gradually declined thereafter reaching the lowest rate of 0.4 per thousand in 1987 (Table 1). It went up to 0.7 per thousand in 1988, and again dropped to the previous lowest level of 0.4 per thousand in 1989.

This study was supported, in part, by the research grants from the Department of Health, Executive Yuan (DOH 75-0202-13, 76-0202-24,77-08,78-07), and the Cardiac Children's Foundation, R.O.C.. Reprint requests: Dr. Lue, Dept. of Pediatrics, National Taiwan University Hospital, 1 Chang-Teh Street, Taipei, Taiwan 10016, Republic of China.

TABLE 1. Results of serial surveys on the prevalence of rheumatic heart disease among school children in Taiwan

Year	No. of Students	Age(Yrs)	RHD(‰)
1970	19,782	6-13	1.4
1971	10,321	6-16	1.3
1983	12,370	6-15	0.7
1985	380,886	6-18	0.6
1986	53,302	6-18	0.5
1987	59,143	6-18	0.5
1988	52,580	6-18	0.7
1989	65,843	6-18	0.4

The number of rheumatic fever and rheumatic heart disease among pediatric admissions to the National Taiwan University Hospital has significantly varied with the times (Figure 1). It was only 8 to 10 per thousand admissions in 1950s, and started to rise in the early 1960s, reaching its peak, 18 per thousand in 1976. It showed a decline since 1979, reaching to its nadir in 1983, and stayed low until 1986. Following the resurgence of rheumatic fever in the United States[2-7], the number of rheumatic fever patients admitted to the Hospital, again increased in 1987, reaching 13 per thousand in 1988. Based on the hospital statistics and the serial school surveys described above, we regarded that a significant outbreak of rheumatic fever, though not large, occurred in Taiwan during the two years period of 1987 - 1988.

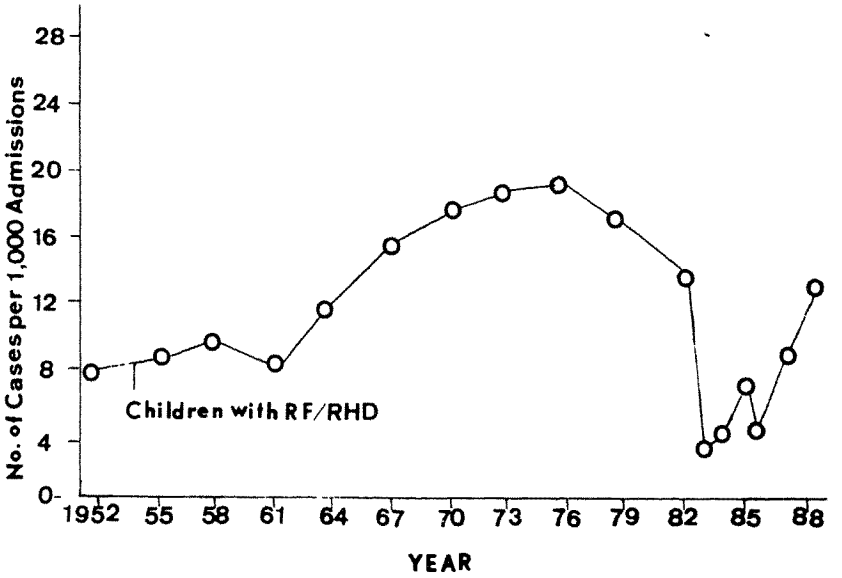

Figure 1

The number of children with rheumatic fever and rheumatic heart disease (RF/RHD) encountered each year at the National Taiwan University Hospital during the years 1952 to 1988.

CHANGING PATTERNS OF RHEUMATIC FEVER MANIFESTATIONS

The age at the first attack of rheumatic fever varied with countries and also with times. The more rampant was the disease such as in India, Egypt and some other developing countries, the higher was the proportion of very young children affected[9,10]. It was observed that approximately 60% of the patients encountered in Taiwan during 1984 to 1988, were aged 11 or more, indicating that the age of rheumatic fever attacks has increased than before (Table 2). The percentage occurrence of each major manifestation of rheumatic fever varied also with the times. In Taiwan, carditis was most common occurring in 67% to 93% of the patients, and chorea minor occurred in 4% to 18%, and subcutneous nodules 0% to 10% (Table 3).

TABLE 2. Age at first attack of rheumatic fever in Taiwan

Years (No. Cases)	Age (Years)		
	3-5	6-10	11-15
1946-60 (90)	11.1	50.0	38.9
1961-75 (344)	5.2	55.5	39.3
1976-83 (150)	7.4	51.3	41.3*
1984-89 (46)	2.1	37.0	60.9*

* $p<0.01$

TABLE 3. Percentage frequency of each major manifestation of rheumatic fever in past four decades in Taiwan

	1946-60 (N=90)	1961-75 (N=310)	1976-83 (N=143)	1984-89 (N=59)
Carditis	66.7	89.0	93.0	83.1
Without failure	(36.7)	(24.5)	(36.3)	(50.0)
With failure	(30.0)	(64.5)	(56.7)	(50.0)
Polyarthritis	52.2	27.4	36.4	49.2
Chorea minor	12.2	3.9	7.7	18.4*
Erythema marg.	3.3	6.8	8.4	11.9*
Subcut. nodule	0.0	2.9	7.7	10.2

* $p<0.05$

CHANGING INCIDENCE OF RHEUMATIC FEVER AND RHEUMATIC HEART DISEASE

During the early 20th century, rheumatic fever and rheumatic heart disease were highly prevalant in the United Kingdom, United States and other temperate regions of the world, being found in 45 to 212 of every 10,000 school children (Table 4).[10-12] On the contrary, rheumatic fever was rare in the tropics. A report in India described that, among 150,000 inpatients seen over 33 years, no single case of rheumatic fever was found, documenting that rheumatic fever and rheumatic heart disease were rare in India at the time[12]. The number of rheumatic heart disease in India dramatically increased, however, during the subsequent years between 1950 to 1970s, reaching a high prevalence of 15-396 per 10,000 school children[11]. The prevalence of rheumatic heart disease in the western countries steadly declined and reached a low value of 1-16 per 10,000 school children in 1950 to 1970s. Rheumatic fever is thus a cyclic disease. The World Health Organization has estimated that 20,000,000 new cases of rheumatic fever occur every year in the world, more frequently in socially less privileged developing countries[11]. In the industrialized countries, the yearly incidence of rheumatic fever could be less than 5/100,000 population, with few scattered outbreaks, such as recent resurgences in the United States[1-7,11]. In developing countries, the yearly incidence of rheumatic fever has, however, significantly increased during the past decades, approaching to 27-116/100,000 school children[10 11]. The prevalence of rheumatic fever and rheumatic heart disease may vary with different ethnic groups and degrees of urbanization in the same country (Table 5).[9-13]

TABLE 4. Prevalence of rheumatic heart disease among school children (per 10,000)

	1920s	1930s	1950-70s	1980s
UK	212	120	1	<1
US	45	72	7-16	<1*
Japan	--	--	18-46	<1
India	none	--	15-396	60-110
Thailand	?	--	12-130	--
Guang Dong	?	--	15	--
Taiwan	?	--	13-14	6-7

* Resurgence of acute rheumatic fever in 1985-1986.

TABLE 5. Prevalence of rheumatic fever and rheumatic heart disease among different ethnic groups

Area	Prevalence		
	High	Average	Low
Israel	Arabs	-	Jews
Singapore	Malaysian	Indian	Chinese
New Zealand	Maoris	-	Whites
South Africa	Bantus	Asians	Whites
Any country	Urban	-	Rural

GROUP A STREPTOCOCCAL INFECTIONS

Group A streptococci are ubiquitous causing many clinical as well as subclinical infections. In Taiwan, the throat carrier rates of Group A streptococcus among students and the children with upper respiratory tract infection have varied from 2.7% to 30% and 2.2% to 13.8%, respectively (Table 6). Monitoring of the streptococcal infections and of the M-type of streptococci, particularly of the so-called rheumatogenic strain is of utmost importance. The predominent M-types and the T-types found in Taiwan during the past years were M-19, 19/57, 24, 59, and T-12, T-4 and T-3. Regretably, the pathogenesis of rheumatic fever remains not clear and the development of vaccines for Group A streptococcal infections has not been successful. Some particular M-types, 1, 3, 5, 6, 14, 18, 19, 24, 27 and 29 are believed to be rheumatogenic strains, of which strain-specific biological properties are under investigation[1,8].

RECURRENT ATTACKS OF RHEUMATIC FEVER

The recurrence of rheumatic fever and rheumatic heart disease may be prevented by administering benzathine penicillin G injections every 3 or 4 weeks intervals[11,14]. The percentage frequency of recurrent rheumatic fever attacks was the lowest, 22.1% in the latest series of patients, reflecting, in part, the effectiveness of secondary preventive measures being implemented among school children in Taiwan (Table 7).[14,15]

TABLE 6. Throat carrier rates of group A streptococcus among students and children with URI in Taiwan

	Students		URI children	
	Culture GAS		Culture GAS	
	No.	%	No.	%
1972-73	966	16	-	-
1973-74	530	20	117	3
1974-75	1,616	30	577	11
1977-83	2,352	6	2,801	11
1985-86	876	5	259	4
1987	660	4.7	-	-
1988	711	4.8	133	2.2
1989	704	2.7	275	13.8

GAS: Group A streptococcus

TABLE 7. Percentage frequency of primary and recurrent attacks of rheumatic fever in Taiwan

RF Attacks	1961-75 (N=310)	1976-83 (N=140)	1984-89 (N=59)
Primary	53.2%	57.1%	77.9%
Recurrent	46.8%*	42.9	22.1*

* $p<0.01$

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S.I.2

IS ASYMPTOMATIC BRONCHIAL HYPERRESPONSIVENESS AN INDICATION OF POTENTIAL ASTHMA?

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INTRODUCTION

Asthma can be considered on two levels: apparent attack and the intercritical state. The attack is the final expression of a whole series of reactions and events. Attention must now center on the latent anomalies, the underlying causes and mechanisms which allow an attack to occur[1]. Bronchial hyperresponsiveness (BHR) is recognised as a characteristic feature of asthma[2] and it has been suggested that the prevalence of BHR in a community could be used as an objective marker of the prevalence of asthma[3]. However, the relation between asthma and BHR is incomplete, so that subjects with BHR do not necessarily have asthma and vice versa[4,5]. In the natural history of asthma, it is still unclear how far BHR is a risk factor for the development of bronchial asthma and how far the control of either symptoms or BHR may affect the final outcome of the condition.

In a survey of bronchial responsiveness in a young student population, 4.1% of the students were found to have BHR[5]. More than half of them were asymptomatic with normal spirometry. We have conducted a two year follow up study to investigate if these asymptomatic subjects with BHR develop asthma and if certain associated factors contribute to the development of asthma.

METHOD

Subjects

From a survey of bronchial responsiveness in a young student population (3067 aged 11-17 years) in Hua-Chiao Middle School and Cong Hua Middle School in January 1988, 125 subjects (M 60, F 65 aged 14.6 ± 1.9 years) were found to have BHR[5]. BHR was defined as a 20% fall in FEV_1 at a provoking dose of histamine (less than 7.8 μmol) on two occasions four weeks apart. A follow up study of these BHR subjects was conducted from January 1988 to January 1990. 126 randomly selected students (M 58, F 68 aged 14.6 ± 1.7 years) in the same schools served as control.

Study design

Daily symptom cards (wheeze, chest tightness, nocturnal cough, exertional wheeze etc.) were recorded by the students and were reviewed by the doctors every two weeks. Peak expiratory flow rate (PEF) was measured four hourly for 24 hours in those subjects when symptoms occurred. Histamine inhalation tests were performed at the end of 12th month and 24th month of the study, using the method of Yan et al[6]. Four stock solutions (10.3%, 0.6%, 2.5% and 5%) of histamine were used to give an incremental cumulative does from 0.03 μmol to 7.8 μmol of histamine. The challenge was stopped when the FEV_1 fell by 20% or more, or when the highest dose of histamine had been administered. A dose response curve for each test was obtained by plotting the percentage change in FEV_1 against the dose of histamine administered on a log scale. The dose of histamine which caused a 20% fall in FEV_1 (PD_{20} FEV_1) was obtained by linear interpolation of the points on the dose response curve.

Atopy was assessed using the skin prick test as described by Pepys[7]. Atopic index as described by Peat[8] was used to relate the extent of atopy to the severity of BHR.

Data Analyses

Subjects were grouped according to the severity of their BHR, determined by PD_{20} FEV_1 values[9]:

Severe BHR	PD_{20} < 0.1 μmol
Moderate BHR	PD_{20} 0.1 to 0.8 μmol
Mild BHR	PD_{20} 0.9 to 3.2 μmol
Slight BHR	PD_{20} 3.3 to 7.8 μmol
Normal BR	No PD_{20} FEV_1 obtained

Asthma was defined as: those with symptoms such as wheeze, chest tightness or nocturnal cough; 24 hour PEF variation ≥ 20% when symptoms occurred and symptoms relieved after bronchodilator administration. Symptoms caused by upper respiratory tract infection (associated with fever, sore throat) were excluded.

Chi square analyses were used to determine the association between various variables. Students' T tests were used to compare the values of PD_{20} FEV_1 within groups.

RESULTS

Among 126 students with BHR (136 with non-BHR), 116 (126) completed the first year and 81(88) completed the second year study. Table 1 showed the incidence of bronchial asthma in two groups, 42% and 40% of the subjects with BHR had asthma in the following 12 months and 24 months. Only two subjects in the non-BHR group developed asthma in the following 24 months. They also developed BHR (PD_{20} FEV_1 4.84 μmol and 7.20 μmol) at the same time. The incidence of BHR in two groups was shown in Table 2. 27% and 31% of the subjects with BHR became normal bronchial responsiveness at 1 year and 2 years respectively. However, five subjects (5.7%) developed BHR in the non-BHR group.

TABLE 1. BHR in relation to asthma

	BHR group			Non-BHR group		
	0 mon	12th mon	24th mon	0 mon	12th mon	24th mon
No	125	116	81	136	126	88
Asthma	59	49	32	0	0	0
%	47.20	42.20	39.50	0	0	2.30

TABLE 2. Incidence of BHR in two groups in two years follow up

	BHR group			Non-BHR group		
	0 mon	12th mon	24th mon	0 mon	12th mon	24th mon
No	125	116	81	126	126	88
Asthma	125	84	56	0	0	5
%	100	72.4	69.1	0	0	5.7

Table 3 showed that 14 out of 66 subjects and 9 out of 37 subjects with asymptomatic BHR developed symptomatic asthma in the following 12 and 24 months. PD_{20} FEV_1 in those subjects were significantly higher than those without symptoms, (Tab 3) but remained unchanged as compared with their own initial PD_{20} FEV_1 (3.81 ± 2.45 μm VS 3.18 ± 2.07 μm $P > 0.10$; 4.27 ± 2.30 um VS 4.10 ± 2.33 um $P > 0.10$).

TABLE 3. Development of Asthma in Asymptomatic BHR subjects

	No	Symptoms free		Asthmatic	
		No	$PD_{20}FEV_1$(um)	No	$PD_{20}FEV_1$(um)
0 mon.	67	67	6.11 ± 2.33	0	
12th mon.	66	52	6.28 ± 2.80	14	3.18 ± 2.07*
24th mon.	49	37	6.12 ± 2.01	9	4.10 ± 2.33*

*$P \leq 0.05$ compared with symptom free group.

The incidence of the newly diagnosed asthmatic in relating to the severity of BHR was shown in Table 4. The severer the BHR, the higher incidence the newly diagnosed asthma.

TABLE 4. Development of asthma in relation to the severity of BHR at 12th month and 24th Month

Severity of BHR	No	No of asthma	%
Moderate or Severe	2 (2)	2 (2)	100 (100)
Mild	14 (10)	4 (3)	28 (30)
Slight	50 (37)	8 (4)	16 (11)

*Figures in blackets are numbers of subjects at the end of 24th month.

Among 50 (32) initially diagnosed asthmatics, 15 (9) became symptom free in the following one (two) year. Three (first year) and five (second year) symptom free subjects had no $PD_{20}FEV_1$ obtained. $PD_{20}FEV_1$ in other subjects were 7.65 ± 2.30 umol and 6.14 ± 2.50 umol respectively, significantly higher than their initial $PD_{20}FEV_1$(4.72 ± 2.82 umol and 4.41 ± 2.82 umol, both $P \leq 0.05$).

In relating the development of asthma to atopy, early respiratory illness (ERI) and parental asthma in subjects with BHR (Table 5), the frequency of ERI was significantly higher in the newly developed asthmatics than in asymptomatic subjects ($P < 0.05$).

TABLE 5. Newly developed asthma in relation to atopic index, ERI and parental asthma

	No	A I	ERI	Parental asthma
Asthmatic	15	2.7 ± 1.6	10 (67%)	2 (13.3%)
Asymptomatic BHR	1	2.1 ± 1.4	16 (31%)	4 (7.8%)
P		> 0.05	< 0.05	> 0.05

ERI - Early respiratory illness.
AI - Atopic Index (Peat JK : Clin Allergy 1987; 17:291),

DISCUSSION

Bramen[10] had found that three out of 16 rhinitis patients with BHR developed asthma in the following one to five years. In the present study, about 20% of the asymptomatic subjects with BHR developed asthma in the following 24 months, significantly higher than 2.3% of the non-BHR subjects. The severer the BHR, the higher risk in developing asthma. On the other hand, being free of symptom in asthmatic was closely related to the severity of BHR. The less severe the BHR, the more asthmatics became symptom free in the following two years. Although $PD_{20}FEV_1$ showed no change when asymptomatic subjects with BHR developed asthma, $PD_{20}FEV_1$ increased significantly or even became unmeasurable (under the histamine dose of 7.8 μm) when asthmatics became asymptomatic. This clearly shows that asymptomatic individuals with BHR, in particular with mild (or above i.e., $PD_{20}FEV_1 \leq 3.2$ μm) BHR, are at high risk in developing asthma.

Two students without BHR developed asthma in the following two years. However, they also developed bronchial hyperresponsiveness at the time they developed asthma. Once again this showed a close association between BHR and the development of asthma.

It is shown that more subjects with newly diagnosed asthma have a history of early respiratory illness.

We conclude that mild (or above) BHR with a history of ERI (or other unknown factors) may be an indication of potential asthma. Further study is needed to ascertain if early control of potential asthma may prevent those subjects from developing symptomatic asthma.

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S.I.3

LACTOSE MALABSORPTION IN CHINESE CHILDREN

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Lactose malabsorption is a common occurrence in adults especially among the Orientals[1]. Weaning from lactose-containing food after infancy probably induces progressive involution of intestinal lactase activities resulting in increasing lactose malabsorption as the infants mature through childhood to adult life.

We adopted the breath H_2 test which is a non-invasive means of detecting sugar malabsorption to study the local Chinese children. The end-expiratory portion of a tidal volume is usually preferred to ensure constancy of the gaseous composition to obtain more reproducible results[2]. To overcome the technical difficulties of end-expiratory sampling from small infants and children, we have developed an electronic automatic end-expiratory air sampling device for infants[3] and a simple T-adaptor to 'entrap' the end-expiratory air for older children[4].

MATERIALS AND METHODS

Chinese newborn infants admitted to the nurseries of Queen Mary Hospital and school children between 3 - 12 years from a primary school and a kindergarten were selected for this study. Informed consent was obtained from the parents for all tests.

End-expiratory breath samples were collected for gases analysis with the Shimadzu (GC8 APT) Gas Chromatrograph. For newborn infants, the automatic electronic sampling device[3] was used. For older children the T-adaptor 'end-expiratory sample trapping device[4] was used. The gas-analysis was by thermal conductivity detector, molecular sieve chromatograph[5] as reported elsewhere[6].

84 Chinese neonates between 25 to 43 weeks gestation and 1.17 to 3.95 Kg weight were studied. 280 older Chinese children of 3 - 12 years old were also investigated. Breath-H_2 production following a standard lactose load of 1 gm/Kg was studied by ½ hourly interval sampling for 3 - 4 hours and the profile charted.

RESULTS

Table I shows the degree of end-tidalness (or approximation to alveolar concentration) of the breath samples as obtained in the newborn and older children. The infant automatic electronic sampler was highly efficient in obtaining 87% end-tidalness[3] as judged by the arterial $paCO_2$ which was used as an alveolar air reference. The T-adaptor was obtaining 78% (72 - 86%) end-tidalness from older children[4].

TABLE 1. Efficacy of the end-expiratory sampling devices

Device	CO_2 Concentration	Percentage End-tidalness
Infant automatic Sampler[2]	4.35 % (3.9 - 5.1)	87 % (78 - 100)
T-adaptor for children[3]	4.08 % (3.8 - 4.75)	78 % (72 - 86)

Figure 1 shows the 84 lactose-breath-H_2 tests results obtained in the newborn infants[7]. It can be seen that there appears two overlapping populations with dividing point near 20 ppm corresponding to the conventional cut-off point[8] for diagnosing lactose-malabsorption. One population with normal distribution of breath H_2 response below 20 ppm and the other population more widely dispersed above 20 ppm. The latter is apparently the group of malabsorbers. Similar findings are also obtained for the older children[4] who also showed an increasing frequency of high H_2 response with advancing age (Figure 2).

Fig. 1 Breath H_2 Response in 84 Newborn Infants (NRBH) ppm)

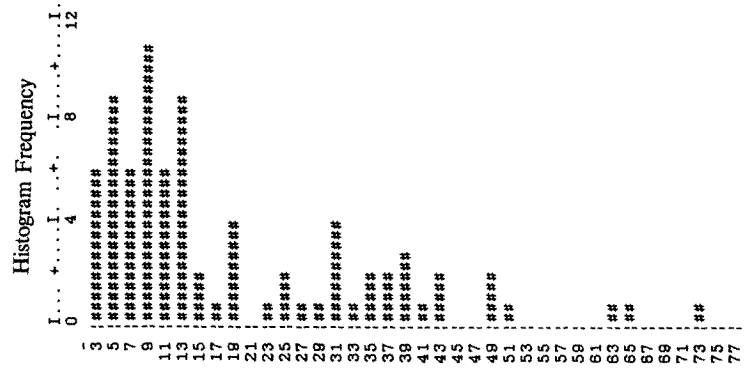


Fig. 2 Breath H_2 Response to Lactose in 280 children

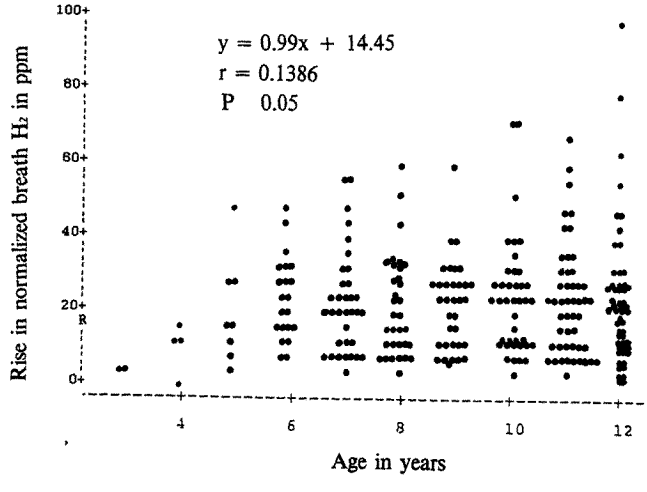


Figure 3 shows a typical study result of breath-H_2 response to lactose and simultaneous blood glucose profile in a lactose malabsorber and Figure 4 that of a lactose absorber. Such findings confirm the efficacy of the breath H_2 test.

Fig. 3 Lactose Malabsorber

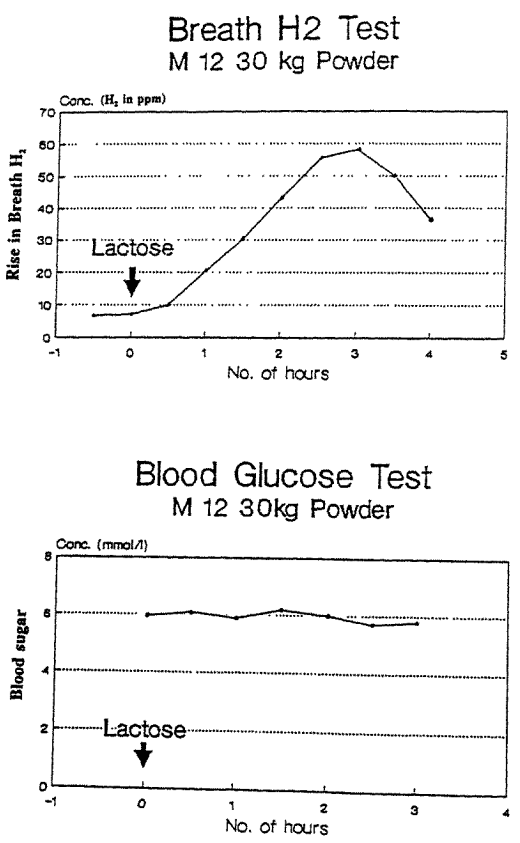
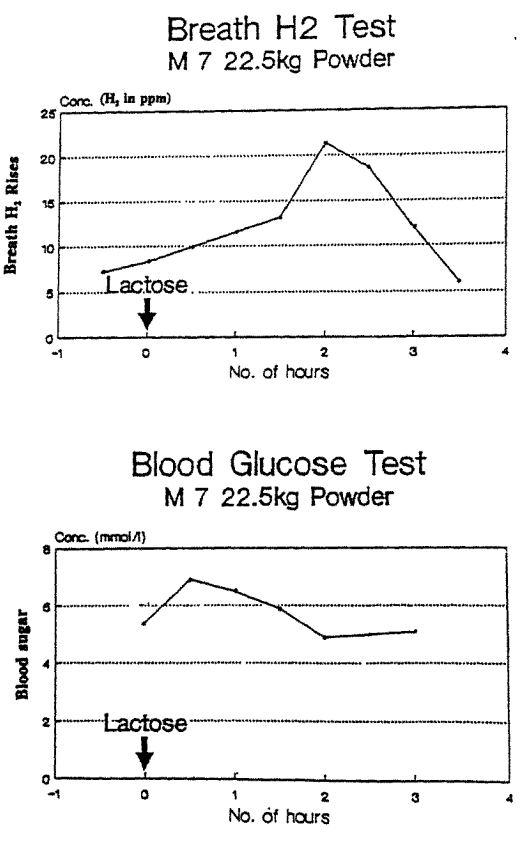


Fig. 4 Lactose Absorber



DISCUSSION

We have confirmed earlier reports[9,10,11] that the breath-H_2 response to lactose is a useful test for lactose malabsorption. It has the distinct advantage of being non-invasive and apparently equally diagnostic as the standard lactose tolerance test.

We have also overcome some of the technical difficulties in obtaining end-expiratory or alveolar samples for tests from small infants. Our newly developed electronic device can collect cumulative end-expiratory samples from rapidly breathing small infants for gases analysis[3]. A mean of 87% and range from 72 - 100% of end-tidalness were attainable[3]. The equipment depends on a sensor to pick-up expiratory signals from the infant and to automatically collect a sample of the expired air for test. To-date, the device is the first of its kind to perform such a function automatically with such a high degree of efficiency.

The T-adaptor we developed is a very simple equipment[4] which can be used readily in field studies and many clinical situations. It is extremely simple and easy to operate. A big breath is all that is needed from the child. Little intelligence or teaching is required, and absolutely no discomfort would be elicited.

We have shown in our survey that many Chinese newborn infants demonstrate lactose malabsorption. This is particularly prevalent in the low birth weight and the prematurely-born. In another study[7], we have shown that pure lactose solution produces significantly more breath H_2 response than the same amount of lactose given as milk to the infants. In the older children, we have shown that there is an increasing trend of excessive breath-H_2 production with advancing ages from 3 - 5 years to 12 years old. (Figure 2). Our findings differ significantly from those in Japan[12], Finland[13], or other Caucasian countries. Our data[3,4,7] may be a useful reference for future studies on Chinese children or in other anthropological studies.

ACKNOWLEDGEMENT

This work was accomplished by the joint effort of two other departments of the University of Hong Kong, viz the Department of Chemistry (Dr. K.W. Fung) and the Electronic Services Unit (Mr. Y.P. Ma, Mr. H.C. Kwan and Mr. E.S.H. Ng).

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Editor's Note

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SYMPOSIUM II

S.II.1

NEW ANTIBIOTICS FOR USE IN CHILDREN

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Important new antibacterial agents are being produced by modification of existing classes of antibiotics (penicillins, cephalosporins and quinolones), but the major developments are development of much less toxic antifungal and antiviral agents. Antiviral therapy is now in an interesting stage of development that is similar to the beginning of antibacterial therapy 50 years ago.

However, we must not underestimate the problems of antibiotic therapy. Most antibiotics are substances (or modification of substances) produced by one micro-organism to give it a survival advantage over other micro-organisms. This chemical warfare has been going on for a very long time, and micro-organisms are adept at developing resistance to the weapons used by their enemies. It is important that we use our antibiotic weapons carefully -using them only when we really need to, using our older, less powerful ones when they will do the job, and keeping our new secret weapons in reserve until we are forced to use them.

The acylaminopenicillins (mezlocillin, azlocillin and piperacillin) have increased activity against pseudomonas and other gram negative bacteria. Imipenem is a carbapenem that is active against a very wide range of gram positive and gram negative aerobic and anaerobic bacteria; it is given with cilastatin, which inhibits an enzyme in the renal tubule that inactivates imipenem. Aztreonam is a monobactam antibiotic that is active only against gram negative bacteria.

The third generation cephalosporins (cefotaxime, moxalactam, cefoperazone, ceftriaxone, ceftazidime, etc) are active against most enterobacteriaceae, but they are not active against S. faecalis or MRSA and they have variable activity against Pseudomonas. Furthermore, they are very expensive and during therapy some bacteria develop resistance to other beta-lactams and to aminoglycosides. This induction of resistance to several classes of antibiotics during therapy is very disturbing, and it is most important that use of third generation cephalosporins be restricted to treatment of (1) gram negative meningitis, (2) organisms resistant to other antibiotics and (3) gram negative infection in patients with renal failure (where aminoglycosides are contraindicated). Oral third generation cephalosporins are likely to be marketed soon; the potential for overuse of these drugs will be considerable.

The fluroquinolones (norfloxacin, ciprofloxacin, ofloxacin, perfloxacin and enoxacin) are modifications of nalidixic acid. Development of resistance to these agents during therapy has been described, but it is much less common than with nalidixic acid. All the quinolones are well absorbed after oral administration, and ciprofloxacin can be given intravenously. They are active against a wide range of gram positive and gram negative bacteria, and ciprofloxacin is active against mycoplasma, ureaplasma, chlamydia, mycobacteria (including M. tuberculosis) and rickettsiae. Antagonism with other antimicrobial agents is rare, and synergy may occur with ticarcillin, piperacillin, imipenem, rifampicin and, occasionally, aminoglycosides. Unfortunately, high doses of quinolones in juvenile animals damage cartilage, and this will limit the use of these drugs in children and pregnant women (although no damage has been observed in the few children treated).

Many new antifungal agents are being produced. Amphotericin has been improved by packaging it in liposomes, so that it concentrates in the reticuloendothelial system and spares the kidneys (ampholiposome). The azoles (miconazole and ketoconazole) have been modified to produce itraconazole, fluconazole, SCH39304 and saperconazole. Fluconazole can be given orally

or IV and it has good penetration in the CNS; it is active against cryptococcus, candida, coccidioidomycosis and other fungi and is more effective in vivo than in vitro. Fluconazole may cause liver damage. SCH39304 and saperconazole are still in the trial stage, as are the unrelated antifungals LY121019 and nikkomycin.

Acyclovir has an established place for the treatment of varicella, zoster and herpes simplex infections; newer agents active against these viruses include A1340 (a prodrug of acyclovir that is well absorbed orally), phosphonoformate (used topically and, perhaps, IV) and BVdU (a thymidine analogue that can be given orally). Cytomegalovirus infection in immunocompromised patients can be treated with either gancyclovir or BVdU. Azidothymidine is not a cure for established AIDS, but it slows the development of the disease. Tribavirin (ribavirin) is active against RSV, but its efficacy in clinical practice is unproven.

S.II.2

INTERFERON AND TUMOR NECROSIS FACTOR IN THE PATHOGENESIS OF HUMAN IMMUNODEFICIENCY VIRUS INFECTION

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ABSTRACT

Cytokines including interferon (IFN) and tumor necrosis factor (TNF) are potent modulators of immune processes. They are synthesized in response to microbial infections and inflammation. With other cytokines, IFN and TNF form a complex network of interaction resulting in programmed differentiation and function of the responsive cells. In light of their multiple biological effects, we have postulated that dysregulation of these cytokines may contribute to the pathogenesis of HIV infection. In this paper, we demonstrated that the expression of IFN-α receptors are down-regulated in patients with AIDS. Consequently, we have determined that HIV-infected cultured cells and cells from AIDS patients show hyporesponsiveness to IFN action. TNF, as a major mediator of inflammation and sepsis, is capable of inducing the replication of HIV. This is due to the activation of transcription factor NF-*k*B binding to the promotor of HIV by TNF. We have also demonstrated that TNF synthesis and its receptor expression are upregulated in HIV infection. Therefore cytokines including IFN and TNF play an important role in regulating responses to microbial infection. Dysregulation of these cytokines and their receptor expression may contribute to the pathogenesis of AIDS.

INTRODUCTION

Cytokines are soluble polypeptides responsible for cell to cell communication and play crucial roles in many biological processes including microbial infections, inflammation, immunity, and hematopoiesis[1,2]. In 1969, the first cytokines were discovered following demonstration of a group of factors produced by mitogen activated lymphocytes. These lymphokines are potent modulators of immune responses, growth and mobility of leukocytes. Recent advances also indicate that factors similar in function are produced by non-lymphoid cells including macrophages/monocytes, fibroblasts, endothelial cells, and transformed tumor cell lines[1,2]. The complex interaction of cytokines forms a network of cytokine cascade resulting in programmed growth, development, differentiation, and function of cells and tissues[3,4]. In lieu of their multiple biological effects, it is conceivable that dysregulation of cytokine expression may contribute to the development of diseases. In this paper, we will discuss the role of IFN and tumor necrosis factor TNF in the pathogenesis of Human Immunodeficiency Virus (HIV) infection.

IFNs are naturally occuring proteins capable of eliciting antiviral, antineoplastic, and immunomodulatory activities. They can be classified into three major groups: α, β, and on the basis of its biological and physiochemical properties[5]. IFNs are produced by animals and cultured cells in response to inducers including viral infections and double-stranded RNA[5]. Cells exposed to IFN show enhanced activities of 2'-5'-linked oligoadenylate (2-5A) synthetase and a protein kinase[6]. The 2-5A synthesized in turn activates latent endoribonuclease L which cleaves single-stranded RNA including messenger RNA. This results in cessation of celullar growth and inhibition of viral replication. IFNs also have immunomodulatory effects including enhancement of natural killer cell activity and induction of TNF[5].

TNF-α (cachectin) and TNF-β (lymphotoxin) are cytotoxic polypeptides released from activiated monocytes/macrophages, and lymphocytes respectively[7,8], in response to inflammation, bacterial or viral infection. In addition to their role in the elimination of pathogens, TNFs are thought to contribute to cytotoxicity including tumor destruction[7]. However, high levels of TNF in vivo can be detrimental because they induce severe metabolic acidosis, hypotension, and hemorrhagic necrosis of vital organs[8]. On the cellular level, TNF causes degranulation, production of superoxide radicals, induction of procoagulant activity and suppression of thrombomodulant resulting in thrombosis[9]. Thus, TNF mediates sepsis and inflammation, induces cachexia, and suppresses hematopoiesis. Previous studies reported that IFN-α can markedly enhance the cytotoxic effects of TNF on susceptible tumor cells and virus-infected cells[10]. The mechanisms underlying this synergy including antiviral activities between TNF-α and IFN-α remain to be delineated.

DYSREGULATION OF THE IFN SYSTEM IN AIDS

In light of its molecular actions in the inhibition of viral replication, IFN appears to play a critical role in immune responses to acute viral infections, e.g., varicella, herpes simplex, and influenza. Accordingly, attempts have been made to utilize IFN in the treatment of viral infections including varicella-zoster, cytomegalovirus and chronic hepatitis B[11-13]. The clinical efficacy of IFN on chronic Hepatitis B is controversial depending on the dosage, dosing interval, and the group of patients treated[14]. Nevertheless, it has been shown that continuous administration of high doses of IFN-α intravenously resulted in paradoxical suppression of the immune system in patients[15]. We have therefore postulated that persistent high levels of IFN in vivo in chronic viral infection could be detrimental to the immune system, despite its importance in host defence against acute infections. In fact, high levels of an acid-labile IFN-α, in some cases more than 1000 U/ml, have been observed in the sera of patients with HIV infection[16,17]. The presence of this IFN subtype in HIV-infected individuals has been associated with the progression of disease from asymptomatic state to fulminant AIDS, and is implicated in the pathogenesis of AIDS. To substantiate the hypothesis on the deleterious effects of high endogenous levels of IFN, we investigated the contribution of the acid-labile IFN-α to the dyregulation of the IFN system including expression of its receptors and IFN-inducible 2-5A synthetase enzyme in HIV infection.

Although previous reports indicated that IFN-α inhibits the replication of HIV in vitro resulting in reduced reverse transcriptase activity and decrease in viral yields[18], the clinical efficacy of IFN-α in HIV infection remains to be investigated, in particular in fulminant AIDS patients. It has also been shown that some AIDS patients with Kaposi's sarcoma showed tumor regression in response to recombinant IFN-α therapy[19]. Since IFNs elicit antiviral and antineoplastic activities by binding to specific high affinity receptors on the cell surface[20], we evaluated the role of IFNs as therapeutic agents in AIDS by investigating the expression of IFN-α and γ receptors on blood mononuclear cells (PBM) from patients with HIV group III (Centers for Disease Control surveillance criteria), group IVc (fulminant AIDS), and HIV-seronegative normal controls[17]. The equilibrium binding characteristics of ^{125}I-IFN-α and γ to PBM were analyzed by Scatchard analysis to determine receptor numbers and dissociation constants. We have demonstrated a progressive reduction in IFN-α receptor expression on PBM during the progression of HIV infection (Fig. 1 and Table 1). This down regulation of IFN-α receptors was consistent with elevated levels of serum acid-labile IFN-α in the patients. Treatment of PBM from the group IVc patients with exogenous IFN-α in vitro resulted in minimal induction 2-5A synthetase activity in comparison to controls, consistent with hyporesponsiveness of the cells to IFN action. In contrast, the expression of IFN-receptors in both groups of HIV-infected individuals remained normal[17]. Thus the decrease in IFN-α receptor expression and consequent hyporesponsiveness to IFN-α raise the question of the usefulness of IFN-α in the treatment of end-stage HIV infections.

TABLE 1. IFN-α receptor sites on PBM from normal controls and patients with HIV infection.

	Normal	HIV Group III	HIV Group IVc
Number of patients	17	8	7
Receptor sites	500 ± 250	315 ± 230 ($p<.05$)	92 ± 88 ($p<.001$)

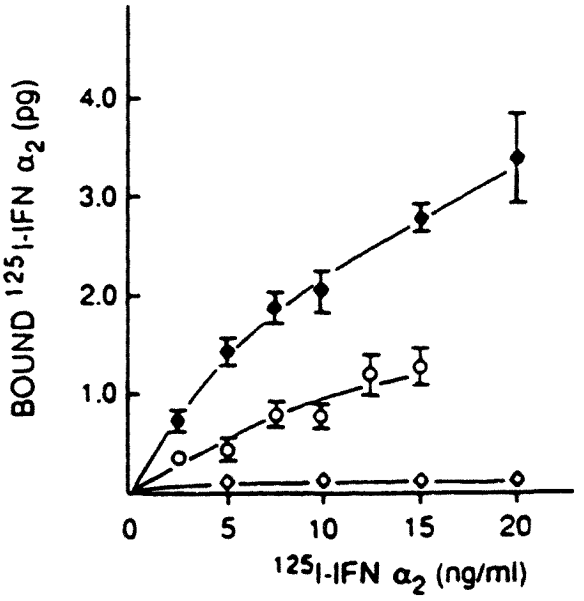

Figure 1
Down regulation of IFN-α receptor expression in vivo in PBM from patients with HIV infection.

IFN-α receptor binding assays were performed on $4x10^5$ cells in a volume of 200 µl, incubated at 4h at 4°C, with the indicated concentrations of ^{125}I-IFN-α_2. Specific binding activities were obtained after nonspecific binding activities were subtracted from the total radioactivity counts. Each point represents the mean of triplicate incubations for each ^{125}I-IFN-α_2 concentration for each patient's cells, with error bars indicating one standard deviation. Scatchard analysis were performed to determine the number of receptor/cells and the equilibrium dissociation constants involved in the reaction. These curves are representative of the data summarized in Table 1.

♦ , control; o , HIV group III; ◊ , HIV group IVc.

It is possible that the IFN-α subtype found in the sera of HIV-infected individuals is initially induced to combat the virus and to prevent progression of the disease. This may have contributed to the long latency of HIV infection in the natural history of the disease. However, in the later stages of AIDS, it is apparent that persistence of high levels of IFN-α in vivo does not prevent the progression of immunodeficiency[16,17]. Mechanisms underlying HIV evasion of the antiviral activities of IFN-α are not well understood. Among the possible mechanisms are: (i) down regulation of cell surface antigens or receptors that are crucial in the mediation of antiviral actions

of IFN, (ii) disturbances of transmembrane signaling subsequent to IFN binding to its receptors, (iii) inhibition of IFN-induced transcription factors binding to the promotor of IFN-stimulated genes including 2-5A synthetase resulting in lower rates of transcription, (iv) disturbances of IFN-induced mRNA splicing, packaging, or transport to the cytoplasm, (v) instability of the IFN-stimulated gene transcripts, or (vi) suppression of translation of the mRNA encoding IFN-inducible proteins responsible for antiviral actions. In addition, abnormal expression of IFN may contribute to some other biological processes, in particular the activation of the TNF system, resulting in enhancement of HIV replication (see below).

With regard to IFN-α receptors, the detailed mechanisms underlying the reduced expression of IFN-α receptors in vivo in PBM from patients with fulminant AIDS remain to be determined. This observation could be partly acounted for by high levels of the acid-labile IFN-α present in AIDS sera, causing increased rate of internalization of the receptors[17]. To investigate whether HIV by itself can induce the down regulation of IFN-α receptors in the absence of the acid-labile IFN-α, we have infected CD4 expressing cells in vitro with HIV-1 in the presence of polyclonal anti-IFN-α antibodies. We observed a progressive down regulation of IFN-α receptors during the process of HIV infection in vitro[21]. Interestingly, these HIV-infected cells also showed diminution in 2-5A synthetase induction in response to IFN-α treatment, similar to PBM isolated from AIDS patients. We are currently investigating whether this is due to reduced transcription or reduced stability of the mRNA encoding the proteins as discussed above. In the context of other cell surface antigens in HIV-infected cells, previous reports, in agreement with our observations, indicated that the expression of MHC type II antigen and interleukin-2 receptor is also down regulated in AIDS patients[22]. Thus, we have shown that the IFN system, including IFN synthesis, IFN-α receptor expression, and its inducible genes, is dysregulated in HIV infection and my contribute to development of immune deficiency.

TUMOR NECROSIS FACTOR IN HIV INFECTION

Since TNF is a pleiotropic molecule with multiple modulatory effects on the immune system, dysregulation of its synthesis in vivo may contribute to the pathogenesis of disease processes. Recent reports indicated that high serum levels of TNF correlate with the morbidity and mortality of patients with meningococcemia and fulminant hepatitis[23,24]. In experimental models on meningitis, it has been shown that TNF is a mediator of inflammation and its presence in the cerebrospinal fluid appears to be predictive of neurological damage[25,26]. In accord with these observations on inflammatory diseases, we have shown that TNF synthesis is also enhanced in patients with Kawasaki disease[27]. Therefore, dysregulated induction of high levels of TNF may contribute to the pathogenesis of inflammatory diseases.

In the context of chronic viral infections, we postulated that dysregulation of the IFN and TNF system may contribute to the replication of HIV and progression of AIDS. To substantiate our hypothesis, we investigated whether the acid-labile IFN-α present in AIDS sera can regulate TNF receptor expression in tissue culture cells[28]. The expression of TNF receptors was determined by performing saturation binding studies with ^{125}I-TNF-α on cells pretreated with AIDS sera or recombinant human IFN-α or -γ . Similar to IFN receptor experiments, Scatchard analysis was employed to determine the number of TNF receptor sites per cell on the cell surface. Cells not treated with AIDS sera or IFNs were used as controls. The results showed that (Table 2) the acid-labile IFN-α present in AIDS sera is capable of inducing the expression of cellular receptors for TNF. The extent of receptor induction depended on the concentration of the IFN present in the sera. Also, there was no significant induction of TNF receptors when the AIDS sera were preneutralized with polyclonal anti-IFN-α antibodies. The results indicated that the acid-labile IFN-α is the factor mainly responsible for TNF receptor induction[28].

In addition to receptor studies, we have previously reported that the basal level of TNF synthesis by PBM from patients is enhanced during the progression of HIV infection in vivo[29]. Moreover, the acid-labile IFN present in AIDS sera contributes to the pathophysiological changes in sepsis by rendering the cells from AIDS patients hypersensitive to endotoxin stimulation (Fig. 2) resulting in further synthesis of TNF[30]. It therefore appears that the TNF system is activated in patients with HIV infection. This activation may be a contributing factor to some of the physiological disturbances including the wasting syndrome observed in AIDS.

TABLE 2. Regulation of TNF receptor expression by the acid-labile IFN-α present in AIDS sera, IFN-α_2, and IFN-γ_1.

	TNF RECEPTOR SITES PER CELL			
	Controls	AIDS sera	IFN-α_2	IFN-γ_1
HeLa cells	3800 ± 1200	6200 ± 1600*	4800 ± 1300	5200±1450**
(n=6)	(100%)	(163%)	(126%)	(136%)

HeLa cells were treated with IFN-α_2 (300 U/ml), IFN-γ_1 (300 U/ml), and sera from six different AIDS patients at 37° C for 12h. The concentration of the acid-labile IFN-α in the undiluted AIDS sera was determined to be 512 U/ml and the final concentration used in the incubation medium for TNF receptor induction was 128 U/ml. The results were analyzed for statistical significance by employing the non-paired Student's test.

* $p<0.02$, ** $p<0.05$.

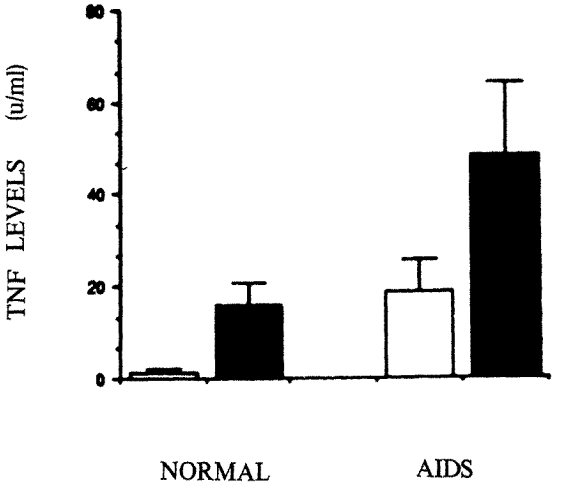

Figure 2
Synthesis of TNF by blood monocytes from patients with HIV infection.

Blood monocytes ($0.5x10^6$) from normal controls (n=14) and patients with group IVc HIV infection (n=7) were incubated at 37°C for 16h in the presence (solid bars) or absence (open bars) of LPS (10 µg/ml). Triplicate samples were assayed for TNF mediated cytotoxicities.

Results studies reported that TNF induces the replication of HIV in a chronically infected T-cell clone in vitro[31]. Molecular mechanisms underlying this process have been partially elucidated. Transfection experiments demonstrated that TNF-α specially activates the HIV promotor resulting in increased transcriptional activities[31]. The TNF stimulation of HIV replication appears to be mediated by the binding of transcription factor NF-*k*B to a specific oligonucleotide sequence, i.e., NF-*k*B site, in the enhancer region of HIV promotor[32]. Other cytokines may also play a role in the activation of HIV replication. For instance, granulocyte-

macrophage colony stimulating factor (GM-CSF) can enhance HIV replication as measured by increases in reverse transcriptase activities[33]. In addition to its effects on viral replication, TNF can induce auto-destruction of cloned T-cells when these cells were stimulated to produce large quantities of the cytokine[34]. Therefore, it is conceivable that significant levels of TNF produced by cells in vivo, in response to bacterial endotoxin or other viral antigens derived from opportunistic infectious agents, could activate the expression of HIV and play a role in the pathogenesis of AIDS.

THERAPEUTIC IMPLICATIONS

Since cytokines form a complex network of interaction resulting in modulation of biological activities, understanding the cellular basis of their regulation in vitro and in vivo may provide insight into designing therapeutic regimens for patients with HIV infection. Investigations to date indicated that different cytokines have distinct effects on the production of HIV by infected cells in vitro. It has been demonstrated that pretreatment of macrophages with IFN-α or IFN-β results in less productive infections when challenged with HIV in vitro[35]. In contrast, TNF and interleukins (including IL-1 and IL-6) did not protect the macrophages from subsequent HIV infection[35]. In fact, TNF and GM-CSF could induce the replication of HIV in macrophages as discussed above.

In light of the role of endotoxin in inducing HIV replication[36], which is mainly mediated by TNF action, we investigated the effect of IFN-α in ameliorating the inductive activity of endotoxin. We showed that pretreatment of U1 cells (a subclone of HIV-infected promonocytic U937 cells) with IFN-α suppresses the action of endotoxin in inducing HIV replication[37]. Similar results have been observed with the use of IFN-α on the effects of phorbol esters on HIV induction[38]. Therefore it appears that IFN-α may play a protective role in early stages of HIV infection in suppressing the retroviral replication.

On the basis of these observations on the complexity of the immune system and the interaction of cytokines with HIV, it is important that immunomodulators should be evaluated in vitro to elucidate the mechanisms of action before clinical trials are performed. In addition, AIDS patients who receive these cytokines should be monitored closely to detect potential undesirable effects on the immune system and the underlying HIV infection.

CONCLUSION

In summary, cytokines including TNF and IFN play an important role in regulating immune responses to HIV infection. However, dysregulated expression of the cytokine systems may contribute to the pathogenesis of immunodeficiency in HIV infection. For example, dysregulation of the IFN system may afford an opportunity for the retrovirus to evade the antiviral effects of IFN-α in late stages of HIV infection. Therefore IFN-α could be useful in early stages of HIV infection but of limited use in patients with fulminant AIDS. TNF, as a mediator of inflammation and host defence, paradoxically is an inducer of the viral replication. Consequently, the use of anti-TNF antibodies should be considered for HIV-infected individuals during episodes of opportunistic infections. Thus, understanding the biological basis of disease processes and the mechanisms involved in immune defects in HIV infection should provide insight into designing therapeutic measures to halt the progression of AIDS.

ACKNOWLEDGEMENTS

The author wishes to thank Mr. J. Livesey and S. Der for their technical expertise, and Drs. R. Gold, S. Read, and B. Williams for their helpful comments. The research is supported by grants from the National Health Research and Development Program and the Federal Center for AIDS, Ottawa, Canada. A. S. L. is the recipient of a Young Investigator's award from the Canadian Infectious Disease Society, Royal College of Physicians of Canada.

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S.II.3

INFECTIONS IN PRIMARY IMMUNODEFICIENCIES

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Primary immunodeficiencies are relatively rare but should be suspected if the infections are recurrent, not responding to usual treatment, of unusual pathogens or with unexpected complications. Over the last 18 months, a group of children were diagnosed to have well-defined primary immunodeficiencies in our department : 6 boys with chronic granulomatous disease (CGD), one boy with hypogammaglobulinaemia associated with low B cell number and one girl with the moderate phenotype of leucocyte adhesion deficiency (LAD).

5 of the 6 boys with CGD have a positive family history. 3 of them are brothers and they presented within the first year of life with recurrent salmonella sepsis, persistent lung infiltrates and hepatosplenomegaly. The 4th boy presented with recurrent pseudomonas otitis media and finally died at 5 months old of pseudomonas sepsis and meningitis; he had an elder brother who died after an identical pattern of infections. The 5th boy had an elder brother who had recurrent fever and died of TB meningitis; he himself had recurrent fever, salmonella sepsis, TB and liver abscess. The 6th boy has no family history and presented with protracted pneumonia and fever at 6 months old; he interestingly had a prolonged and severe reaction to the BCG.

The boy with hypogammaglobulinaemia presented at 1 year old with pseudomonas gangrenosum and sepsis; he then developed septic arthritis and osteomyelitis of the left knee while on antibiotics.

The girl with LAD presented with persistent omphalitis, recurrent soft-tissue infections and marked leucocytosis.

S.II.4

STUDY ON HEPATITIS B VACCINE - SIX YEARS FOLLOW-UP

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It is well known that vertical transmission of HBV from HBsAg positive mothers to the newborn infant is a major problem and that HBV-vaccine is safe and efficient in interrupting the maternoinfantile transmission. However its long term protection rate needs to be assessed through further studies, and only then can we recommend a schedule of booster vaccination to maintain protection of these children from HBV infection.

I would like to present the result of our 6-year follow-up on the use of HBV vaccine in neonates to interrupt the transmission from asymptomatic mothers with positive HBsAg.

In 1982, healthy neonates born to HBsAg positive mothers in the Obstetric and Gynecologic Hospital, Shanghai Medical University were randomised into 4 groups:

A. NIAID (U.S.A.) group 16 ug/0.4 ml/dose x 3
B. Beijing (82-1) group 20 ug/0.5 ml/dose x 3
C. Beijing (82-1) group 20 ug/0.5 ml/dose x 3 + HBIG 200 IU/dose x 1
D. placebo group

The characteristics and number of cases of the 4 groups are listed in Table 1. A total of 99 cases were recruited and followed up for 6 years.

TABLE 1. Characteristics of mothers and infants by study groups

	Study Groups			
	NAID	BBPRI	BBPRI/HBIG	PLACEBO
No. of infants	25	2	23	26
Birth weight (mean g±SD)	3144.3	3218.6	3187.1	3206.4
Apger score (5 min mean)	9.1	9.0	9.2	9.1
No. of male infants (%)	11(44)	13(52)	14(61)	12(48)
No. of cesarean births (%)	4(16)	3(12)	3(13)	5(20)
No. of mothers HBeAg Positive (%)	13(52)	16(60)	9(39)	11(44)

The follow-up were carried out in the Children's Hospital Shanghai Medical University from 3 months of age, and HBsAg, AntiHBs (Abbott) were tested at each visit. The titer of the AntiHBs ≥ 10 mIU/ml was considered as protective.

The vaccines were injected at 0, 1 and 6 months and follow-up were carried out at 0, 1, 3, 6 month and annually for 6 years with physical examination, SGPT, HBsAg, Anti-HBs.

The 26 infants of the placebo group were vaccinated intradermally with NIAID vaccine 4 ug/0.1 ml/dose x 3 in infancy, according to the program of 0, 1 and 6.

RESULTS

Greater than 60% of the patients in the NIAID group, BBPRI group and BBPRI + HBIG group were observed to have persistence of anti-HBs titre ≥ 10 mIU/ml at 5 years, 3 years and 4 years respectively (Table 2).

TABLE 2. Anti-HBs positive response in four groups during the six-year follow-up period

Period of follow-up (year)	Study Groups							
	NAID		BBPRI		BBPRI/HBIG		PLACEBO	
	No.	%	No.	%	No.	%	No.	%
1	23/25	92	22/25	88	22/23	96	3/26	12
2	16/21	76	19/25	76	18/23	78		
3	7/9	77	8/12	67	10/13	77		
4	12/16	75	6/14	43	10/16	63		
5	8/12	67	4/13	31	5/11	45		
6	4/9	45	2/10	20	3/11	27		

We calculated the percentage of cases which met the definition of having protective Anti-HBs, i.e. ≥ 10 mIU/ml. The percentages of each group with protective Anti-HBs in each subsequent year for 6 years were:

A. NIAID group: 84%, 71%, 78%, 69%, 50%, 44%(Table 3)
B. BBPRI group: 80%, 60%, 42%, 21%, 15%, 10%(Table 4)
C. BBPRI + HBIG: 96%, 70%, 62%, 44%, 27%, 9%(Table 5)

TABLE 3. Persistence of Hepatitis B vaccine-induced anti-HBs reaction in the NIAID vaccine group

Anti-HBs	No. (%) of infants whose anti-HBs turned to non-protective at different ages (year)					
(mIU/ml)	1	2	3	4	5	6
Negative	2(8)	5(24)	2(22)	4(25)	4(33)	4(44)
< 10	2/13(8.7)	1/16(6)	0	1/12(8.3)	2/8(25)	1/5(20)
10-100	5/23(22)	1/16(6)	1/7(14)	1/12(8.3)	1/8(13)	2/5(40)
>100	16/23(70)	14/16(88)	6/7(86)	10/12(83)	5/8(63)	2/5(40)
Total	25	21	9	16	12	9
≥ 10	21/23(91)	15/16(94)	7/7(100)	11/12(92)	6/8(75)	4/5(80)
Protective efficacy	21/25(84)	15/21(71)	7/9(78)	11/16(69)	6/12(50)	4/9(44)

TABLE 4. Persistence of Hepatitis B vaccine-induced anti-HBs reaction in the BBPRI vaccine group

Anti-HBs	No. (%) of infants whose anti-HBs turned to non-protective at different ages (year)					
(mIU/ml)	1	2	3	4	5	6
Negative	3(12)	6(24)	4(33)	8(57)	9(69)	8(80)
< 10	2/22(9.1)	4/19(21)	3/8(38)	3/6(50)	2/4(50)	1/2(50)
10-100	4/22(18)	6/19(32)	2/8(25)	2/6(33)	2/4(50)	1/2(50)
>100	16/22(73)	9/19(47)	3/8(38)	1/6(17)	0	0
Total	25	25	12	14	13	10
≥ 10	20/22(91)	15/19(79)	5/8(63)	3/6(50)	2/4(50)	1/2(50)
Protective efficacy	20/25(80)	15/25(60)	5/12(42)	3/14(21)	2/13(15)	1/10(10)

TABLE 5. Persistence of Hepatitis B vaccine-induced anti-HBs reaction in the BBPRI /HBIG vaccine group

Anti-HBs	No. (%) of infants whose anti-HBs turned to non-protective at different ages (year)					
(mIU/ml)	1	2	3	4	5	6
Negative	1(4)	5(22)	3(23)	6(38)	6(55)	8(73)
< 10	0	2/18(11)	2/10(20)	3/10(30)	2/5(40)	2/3(67)
10-100	4/22(18)	4/18(22)	3/10(30)	4/10(40)	3/5(60)	1/3(33)
>100	18/22(82)	12/18(67)	5/10(50)	3/10(30)	0	0
Total	23	23	13	16	11	11
≥ 10	22/22(100)	16/18(89)	8/10(80)	7/10(70)	3/5(60)	1/3(33)
Protective efficacy	22/23(96)	16/23(70)	8/13(62)	7/14(44)	3/11(27)	1/11(9.1)

TABLE 6. Number (%) of HBsAg positive infants and patients with Hepatitis B in the study groups during the six-year follow-up period

Event	Study Groups			
	NIAID	BBPRI	BBPRI/HBIG	PLACEBO
HBsAg positivity	3(12)	4(16)	3(13)	11(42)
Patients with HB	0	1(4)	1(4.3)	8(31)

The efficacy decreased yearly in the study groups. The results suggested the need of booster vaccination at the 5th, 3rd and 4th year for patients in group A, B and C respectively. In group A, 3 infants became HBsAg positive but were asymptomatic. In group B, 4 infants became HBsAg positive, one of whom developed hepatitis. In group C, 3 infants became HBsAg positive, one of whom developed hepatitis. In the placebo group, 11 of the 26 infants became HBsAg positive at one year of age and 8 cases developed chronic hepatitis B in the 5-year follow-up, thereby demonstrating the need of being vaccinated early in the neonate.

The variety of the vaccines used (e.g. different methods of manufacturing), different doses and different procedures could affect the efficacy and the duration of their protective effect. It is generally agreed that there is a need for booster vaccination after several years.

The children born to HBsAg positive mothers were followed up by measuring HBVDNA, HBsAg and AntiHBs. 4 out of 32 babies were HBsAg positive in their peripheral venous blood right after birth. 2 of them received HBV vaccine and the other 2 had no HBV vaccination. The 2 babies with vaccination became HBsAg negative 1 and 3 month after birth, while the other 2 without vaccination had persistently positive HBsAg and HBVDNA for 3 (lost contact) and 6 years (Table 7).

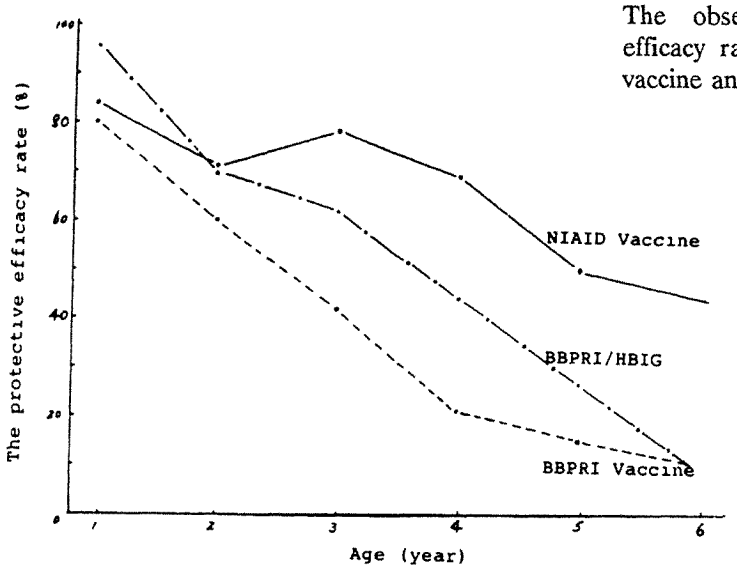

Figure
The observed decrease of protective efficacy rates in NIAID vaccine, BBPRI vaccine and BBPRI/HBIG group

TABLE 7. The outcome of HBVDNA. HBsAg and AntiHBs in babies born to HBsAg positive /mothers with the relation of HBV vaccine

Case no.	HBVDNA						HBsAg							AntiHBs					
	1	3	6	12	3yr	6yr	0	1	3	6	12	3yr	6yr	1	3	6	12	3yr	6yr
5	+	+	+	+	+	/	+	+	+	+	+	+	/	-	-	-	-	-	/
6	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-	-	-	-	-
23	-	-	-	-	-	-	+	+	-	-	-	-	-	-	+	+	+	+	+
31	-	-	-	-	-	-	+	-	-	-	-	+	-	+	+	+	+	+	+

In 1978, we selected 50 infants born to asymptomatic mothers with positive HBsAg and 100 infants of HBsAg negative mothers for follow-up. The infection rate of infants born to HBsAg positive mothers was 27.8% and 72.2% at age 1 and 10 years respectively, demonstrating the high infection rate after infancy. On the other hand, the infection rate of infant born to HBsAg negative mothers at age 10 years also reached 36.8%. Although lower than the 72.2% infection rate seen in the HBsAg positive mother group, it demonstrated that in HBV endemic region, early vaccination of infants born to even HBsAg negative mothers and booster vaccination are needed (Table 8, 9).

1978:
HBsAg + mothers: 50 and their children
HBsAg - mothers: 100 and their children

1988:
HBsAg + mothers: 18
HBsAg - mothers: 19

TABLE 8. Children of HBsAg + mothers (18)

	HBsAg		AntiHBs		Total
	+	-	+	-	
< 1 year	4 (22.2%)	14	1 (5.6%)	17	5 (27.8%)
10 years	7 (38.9%)	11	6 (33.3%)	12	13* (72.2%)

TABLE 9. Children at 10 years

	HBsAg		AntiHBs		Total
	+	-	+	-	
+ Mothers' (18)	7 (38.9%)	11	6 (33.3%)	12	13* (72.2%)
- Mothers' (19)	4 (21.0%)	15	3 (15.8%)	16	7** (36.8%)

* 1 child with both positive HBsAg and AntiHBs at the same time
** 2 children with both positive HBsAg and AntiHBs at the same time

S.II.5

HEPATITIS B - EFFICACIES OF VACCINATION

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Infection with hepatitis B virus (HBV) is common in Chinese people. The HBsAg carrier rate in general population of Taiwan is 15-20%, it is estimated that the majority of carriers are infected in early infancy or childhood. In attempt to interrupt perinatal transmission of HBV, our study done in infants born to HBeAg positive carrier mothers showed that combination of HBIG and plasma vaccine could reduce carrier rate to 11% (4/35) in the immunized group as compared to 78% (40/51) of control group. To infants born to HBeAg negative mothers, hepatitis B vaccine alone could offer enough protection. Our another study done in preschool children revealed various reduced dosage schedules could also provide good immunogenicity. After five years' follow-up, none of the above vaccinees became HBsAg positive. We conclude that hepatitis B immunization is efficacious in preventing HBV infection.

SYMPOSIUM III

S.III.1

CHANGING PATTERN OF CHILDHOOD ASTHMA IN TAIWAN

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As a result of industrialization and other unknown factors, the prevalence of childhood asthma in Taiwan increases rapidly from 1.3% in 1973 to 6.0% in 1985. The asthmatic attacks are mainly perennial, although there are 2 small peaks in the late April and early November. The male to female ratio is 1.5 : 1 in the general surveys but the ratio is 5 : 1 in the allergy clinic. The most important allergen is house dust mite (D. pteronyssinus) followed in order by molds, used kapok and rice straw. Animal danders and pollens do not play an important role. No remarkable change of allergen distribution has been found in the past decade. Two-thirds of the patients have been benefitted by immunotherapy (hypo-sensitization) as evidenced not only by decreased severity but also by a number of changes of immunological function. Metered-dose inhalers of β_2 agonists and steriods are now the first line antiasthmatic medications, but slow-releasing theophylline and oral β_2 agonists are used widely for chronic asthma. Although steroid-dependent asthma accounts for 5% of the total patients, the fatality is still infrequent in this area.

S.III.2

A TEN-YEAR NATION-WIDE SURVEY OF HOSPITALIZED CHILDREN WITH WHEEZING IN CHINA

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Wheezing in early childhood is a rather common symptom. It is quite difficult to diagnose asthma in a young child who presents with the first episode of wheezing. Accurate diagnosis allows early and proper management of atopic children. An accurate diagnosis of a wheezy infant or young child based mainly on clinical manifestations is by no means easy even in big centres, and may become more difficult in small medical units throughout China. Based on this view point, a ten-years nationwide retrospective study was carried out (1979-1988) to assess the prevalence of wheezy illness in hospitalized children. All cases involved in our retrospective survey were based only on hospital records. Many of the diagnosis were still based on the concept that asthmatic bronchitis and asthma were different disease entities. We hope that the analysis will still be helpful in the planning of our future prospective survey on asthma.

MATERIAL AND METHOD

The extent of the survey covered three geographical areas, namely, the east section, the mid-south section (including the mid-south and south west administrative divisions) and the north section (including the north, north-west and north-east administrative divisions). Data were collected from case records. The survey involved 1,879,770 hospitalized children (0-14 years) admitted into 133 hospitals of 22 provinces and municipalities in China during the period of 1979 to 1988. There were 102,219 wheezy children diagnosed to be suffering from bronchiolitis, asthmatic bronchitis and asthma. M/F ratio of the wheezy children was 1.97:1 and that of children with bronchiolitis, asthmatic bronchitis and asthma were 2.7:1, 1.9:1 and 1.8:1 respectively. 5.43% of all hospitalized children were admitted because of wheezing and 3.14% were admitted because of asthmatic bronchitis and asthma.

DISEASE DISTRIBUTION (Table 1)

TABLE 1. Children hospitalized because of wheezing in different localities (% of all hospitalized children between 1979-1988

Disease	East Section 1025557	Mid-South Section 446331	North Section 407882
Bronchiolitis	26646(2.60)	12370(2.77)	3326(0.82)
Asthmatic Bronchitis	26938(2.63)	12211(2.74)	6303(1.55)
Asthma	10100(0.98)	2334(0.52)	1991(0.49)
Total	63684(6.27)	26915(6.03)	11620(2.86)

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In the east and mid-south section wheezy children accounted for 6.23% and 6.03% of all hospitalized children respectively, which were significantly higher than that in the north section. Particularly, children suffering from bronchiolitis in the north section was only about 1/3 of those found in the east or mid-south section, and those of asthmatic bronchitis plus asthma were approximately 2/3 of those seen in either of the other two sections. It is noteworthy that the percentage of children admitted with brochiolitis was half as much as asthmatic bronchitis as seen in the north section.

AGE OF ONSET

Our data showed that 96.71% of children with bronchiolitis have their first episode of wheezing before two years old. About 70% of children with asthmatic bronchitis and asthma were first seen before three years of age (Table 2).

TABLE 2. Age distribution of hospitalized wheezy children

Disease	Total No.	Age (years) 0-	1-	2-	3-	6-	9- < 15
Brochiolitis	42342	86.60%	10.11%			3.2%	
Asthmatic Bronchitis	45452	41.34%	28.84%	16.30%	10.18%	3.34%	
Asthma	14425	3.22%	4.10%	6.65%	30.20%	26.83%	34.04%
Total	102219	54.71%	17.58%	9.10%	9.15%	4.29%	4.67%

YEAR-RATE VARIATION

No significant year-rate variation was found through the ten-year analysis of 949,140 in-patient children in 83 district hospitals. The fluctuation in hospitalization rate of bronchiolitis, asthmatic bronchitis and asthma were 1.03 - 2.09%, 1.83 - 2.26% and 0.57 - 0.97% respectively (table 3).

TABLE 3. Year rate of hospitalization of wheezy children

Year	Percentage (%) of those hospitalized children with different disease Bronchiolitis	Asthmatic Bronchitis	Asthma
1979	1.03	1.97	0.83
1980	1.70	2.06	0.80
1981	1.69	1.83	0.57
1982	2.09	1.82	0.58
1983	1.78	1.78	0.54
1984	1.76	1.99	0.58
1985	1.63	2.26	0.69
1986	1.54	2.09	0.70
1987	1.87	2.04	0.75
1988	1.84	1.95	0.78

S.III.3

EXPERIMENTAL STUDY ON SURFACTANT REPLACEMENT THERAPY IN ANIMAL MODELS

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Since Enhorning demonstrated that exogenous surfactant prepared from animal lung could improve the lung mechanics in premature rabbits, many reports have shown that surfactant replacement is an effective way in prevention and treatment of RDS. The surfactant preparation can be obtained from different sources. We report here an experimental study of surfactant replacement therapy in two animal models using surfactant prepared from pig and calf lung extract. Two animal models were employed, a lung lavage model representing secondary surfactant deficiency and 27 days premature rabbits as RDS model.

METHOD

Pig and calf lung surfactant extract were prepared using the method of Enhorning and Shapiro with some modifications.

In the lung lavage model, 25 rabbits weighing 1.9 - 2.4 kg were used. Anesthesia was induced with 40 mg/kg sodium phenobarbital i.v.. Respiration was maintained by a volume cycled ventilator with pure oxygen through endotracheal intubation. Surfactant was washed out by repeated lung lavage with normal saline. The end point of lavage was indicated by an arterial oxygen tension of less than 120 mmHg. 25 animals were divided into four groups, 7 in the control group and 6 in each of the 3 surfactant treated groups. The Pigsurf (surfactant prepared from pig lung) was instilled into trachea in 3 groups. The doses for each group were 50 mg/kg, 100 mg/kg and 50 x 2 mg/kg respectively. After surfactant administration the animals were maintained on the same ventilator settings for a period of 6 hours. The animals were then killed and the lungs weighed. The lung water was determined by heating the lung in 110°C to constant weight. The arterial blood gases, total compliance and surface tension were measured before and after lung lavage, and after surfactant administration successively. Saturated phosphatidylcholine (SPC) and protein of lavage fluid were measured before surfactant administration and at the end of experiment. Total compliance was measured with a pressure transducer and the surface tension was measured by pulsating bubble technique. The SPC was measured by thin layer chromatography. Protein was measured according to the method of Lowry.

34 premature rabbit fetuses from 7 litters at 27.75 days of gestation were used. The uterus of the pregnant rabbit was exposed under i.v. anesthesia with sodium phenobarbital. While the fetuses were still in the uterus, an intracranial injection of xylocaine was given to inhibit respiration. They were then delivered and weighed. The fetal trachea was exposed into which a 5 mm metal tube was inserted. The fetuses were divided into 4 groups. For comparison, 3 surfactant preparations were used, i.e. Pigsurf from pig lung, Calsurf and Infasurf (CLSE, Ony Inc. N.Y.) from calf lung. In concentration of 30 mg/ml and 100 mg/kg body weight, different surfactant preparations were instilled into the trachea of the study groups, N.S. was instilled in the control group.

For studying the lung mechanics of the first breath in fetuses, a special device for recording the pressure volume change was developed. Changes of lung volume were produced by the movement of a syringe plunger back and forth, which was driven by a D.C. motor. A displacement transducer was connected to the plunger for measuring the changes of lung volume. A pressure transducer was connected to the system which measures the changes of pressure during the changes of lung volume. The fetus was placed in 37°C water bath. A fine catheter connected the metal tube from trachea to the system. When the plunger moved, the signals of changes of pressure and volume were recorded on a X-Y recorder to obtain the pressure-volume curve. Opening pressure, static total compliance and V_5 (the lung volume at pressure of 5 cm H_2O in deflation phase) were calculated on the curve. The results were expressed as ml per kg body weight. At the end of the experiment the fetuses were fixed in formalin for further morphologic study to measure the alveoli area and number.

RESULTS

Lung Lavage Experiment

2 rabbits died of surfactant deficiency in the control group. All rabbits in the study groups were alive at the end of the experiment. The changes in lavage fluid are shown in table 1. After surfactant administration the SPC and protein were all significantly increased. However, no significant differences were found in the value of protein between the control and the study groups.

Table 1. Effect of surfactant on lavage fluid

		SPC mg/g dry lung			protein mg/g dry lung			Tmin dyn/cm		
		B	A	P	B	A	P	B	A	P
Control	mean	0.19	0.20	> 0.20	7.49	38.52	< 0.01	27.57	37.26	> 0.05
(n=7)	SD	0.09	0.15		4.12	13.24		4.70	9.13	
50 mg/kg	mean	0.18	1.27	< 0.001	7.07	27.40	< 0.01	25.37	18.91	< 0.05
(n=6)	SD	0.10	0.37		3.06	7.59			1.58	4.98
100 mg/kg	mean	0.12	2.42	< 0.01	9.42	40.64	< 0.05	29.24	17.14	< 0.05
(n=6)	SD	0.07	1.04		4.98	26.94		6.42	5.49	
50x2 mg/kg	mean	0.12	1.38	< 0.01	6.40	28.33	< 0.05	28.82	18.66	< 0.05
(n=6)	SD	0.05	0.73		3.26	19.30		5.12	4.69	

SPC = saturated phosphatidylcholine Tmin = minimal surface tension
B = before surfactant administration
A = after surfactant administration

The changes of total compliance (expressed as V_{10}, the lung volume at pressure of 10 cm H_2O in deflation phase), arterial PO_2 and PCO_2 are shown in Fig. 1 - 3.

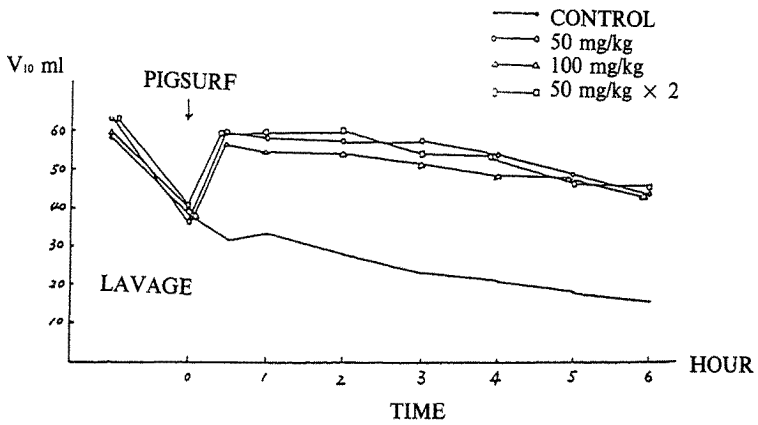

Fig. 1
Effect of surfactant on compliance

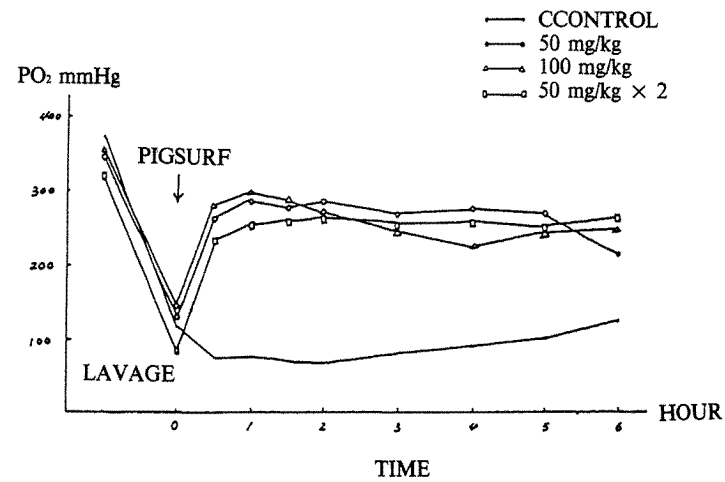

Fig. 2
Effect of surfactant on PO_2

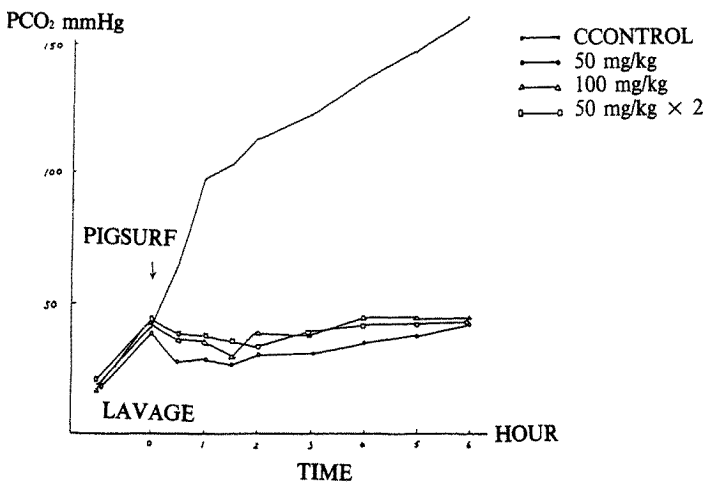

Fig 3
Effect of surfactant on PCO_2

Before surfactant treatment, the V_{10} after lavage in the three study groups were 38.0, 38.2 and 38.2 ml respectively. This increased to 59.6, 56.5 and 57.3 ml 30 minutes after instillation of 50, 100 and 50 x 2 mg/kg of Pigsurf respectively. Comparing with the control the differences in the first 3 hours were significant, after that the values in the index groups were still higher, but no significant differences were found.

After 1,3 and 6 hours of surfactant therapy the PO_2 in the 50 mg/kg group were 82, 77 and 60% of the value before lavage respectively. In the 100 mg/kg group they were 84, 69 and 70% respectively. In 50 x 2 mg/kg group the PO_2 value was lower than 100 mg/kg group at the beginning, but became higher at 6 hours. In the control group the PO_2 showed a slight increase after 3 hours and the arterial PCO_2 increased higher than 150 mmHg at the end of the experiment. The PCO_2 of study groups were slightly decreased or unchanged. The data of lung water are shown in table 2. The residual fluid volume was obtained from the total amount of lavage fluid minus the harvest fluid volume. In the control group the residual fluid volume was not more than those of the study groups, but the total lung water was significantly higher.

Table 2. Data of lung water

	body weight kg			residual fluid ml			lung water %		
	mean	SD	P	mean	SD	P	mean	SD	P
Control (n=7)	2.09	0.13		26.43	4.31		90.72	0.80	
50 mg/kg (n=6)	2.12	0.12	> 0.20	31.00	4.00	> 0.05	87.61	0.84	< 0.001
100 mg/kg (n=6)	2.09	0.16	> 0.20	32.33	5.57	> 0.05	88.42	2.40	< 0.05
50x2 mg/kg (n=6)	2.11	0.13	> 0.20	27.17	5.31	> 0.20	87.90	3.56	> 0.05

Premature Rabbits

The pressure-volume curves of the surfactant treated and the control animals are shown in Fig. 4, the results of opening pressure, compliance and V_5 are shown in table 3.

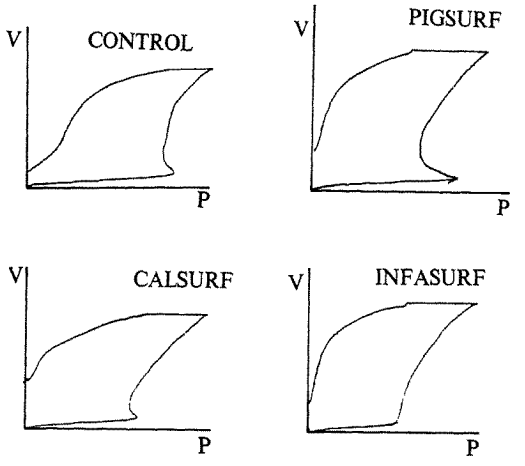

Fig. 4
Pressure-volume curves in premature rabbits after surfactant instillation

Table 3. Effect of surfactant on lung mechanics in premature rabbits

	Opening pressure mmHg				Compliance				V5 ml/kg ml/cm H_2O/kg			
	n	mean	SD	P	n	mean	SD	P	n	mean	SD	P
Control	12	29.83	3.43		11	2.83	0.67		12	68.19	12.53	
Pigsurf	4	32.03	4.00	> 0.05	3	3.84	0.71	< 0.05	4	78.12	16.14	> 0.05
Calsurf	12	20.93	2.24	< 0.001	11	3.50	1.48	> 0.05	12	77.78	16.83	> 0.05
Infasurf	6	18.93	0.88	< 0.001	5	3.69	0.71	< 0.05	6	76.85	10.04	> 0.05

Table 4. Effect of surfactant on lung morphology in premature rabbits

	Alveoli number				Alveoli area			
	n	mean	SD	P	n	mean	SD	P
Control	10	101.3	14.2		10	48.1	5.5	
Calsurf	13	73.3	11.5	< 0.01	13	59.3	4.3	< 0.02

* Project supported by the National Fund of Natural Sciences

The improvement in opening pressure, compliance and V_5 with Calsurf and Infasurf were similar. Although the compliance value after Calsurf treatment was not significantly lower than that of the control, it was significantly different from that after Infasurf treatment. The effect of Pigsurf on compliance and V_5 were as good as Infasurf and Calsurf, but the opening pressure after Pigsurf was higher than that observed after Infasurf and Calsurf treatment, being as high as that observed in the controls.

The change of alveoli area and number are shown in table 4. After Calsurf was instilled the alveoli area expanded significantly, so that the number of alveoli decreased when counted under the microscopic field.

DISCUSSION

By washing surfactant out from the lungs, the lung lavage model showed the typical characteristics of surfactant deficiency. At the end of lavage, analysis of the lavage fluid revealed a decrease in SPC and an increase in surface tension resulting in a decrease in the lung compliance (V_{10}). The blood gas analysis gave a picture of respiratory failure.

At low lung volume the elastic recoil of the lung depends mainly on surface tension. After surfactant administration the increase in V_{10} indicated an improvement in the elastic property of the lung. The increase in PO_2 in surfactant treated group was caused by the amelioration of atelectasis which resulted in the improvement of lung mechanics. The slight increase in PO_2 in the control group after 3 hours might be due to the removal of lung fluid by absorption. As the ventilator settings remained constant throughout the experiment, the progressive rise in PCO_2 to a very high level in the control group indicated that the ventilation of the surfactant deficient lung was very poor. Ventilation was much better in the surfactant treated groups due to the improvement of compliance. It is important to mention that after 6 hours of experiment, the increase in protein in the lavage fluid was found not only in the control group with surfactant deficiency, but also in the surfactant treated groups as well. The increase in protein was the result of damage to the capillary endothelial cells from repeated lavage and surfactant deficiency, which could not be repaired in short time.

The lung water content was higher in the control group. It is possible that the surfactant deficient lung was incapable of keeping the lung dry. It is unlikely to be caused by lavage since the residual fluid in the control group was no more than that observed in the surfactant treated groups. It shows that surfactant administration can promote fluid absorption from alveoli, but it is unlikely to help in the removal of protein exudate from the alveolar space.

It should also be mentioned that neither blood gases nor lung mechanics returned completely to normal after surfactant therapy. Studies in vitro and in vivo had demonstrated that protein exudate significantly inhibited surfactant function. This may be an important factor responsible for the above findings. Factors such as the severity of surfactant depletion in experimental rabbits or the quality of surfactant preparation merit further investigation.

As regard to the dosage of surfactant, there was no difference in the initial effect of the low (50 mg/kg) and high (100 mg/kg) dose. With high dose or repeated dose (50 x 2 mg/kg), there was more sustained improvement in hypoxemia. It is suggestive that in severe surfactant deficiency, one single dose of surfactant may not be enough and additional doses are preferable.

Premature Rabbits

The premature rabbit model is a well accepted model for the study of RDS. It is not as complicated as the lung lavage model and secondary factors may influence the lung function in the latter model. Studying the process of lung expansion in the first breath in premature rabbits is a good model to assess the effect of surfactant preparations. We have used opening pressure, static compliance and V_5 on pressure-volume curves to evaluate the function of surfactant preparations. The static compliance measured at end of inflation reflects the function of surfactant to expand the lung in high lung volumes. V_5 which is the lung volume at 5 cm H_2O in deflation phase, reflects the effect of surfactant against lung collapse. In addition the opening pressure is a measure of the even distribution of surfactant. Infasurf (CLSE) was used for comparison with our surfactant preparations, i.e. Pigsurf and Calsurf. Compare with the control group, all the three preparations had similar effects on improvement in compliance and V_5. Infassurf and Calsurf gave better response on opening pressure. The uneven distribution of Pigsurf was indicated on the pressure-volume curve in the inflation phase. The effect on lung expansion by Calsurf instillation can be identified in morphologic study of alveoli area and number also.

In summary our surfactant preparations from pig and calf lung were efficacious for improvement of lung mechanics and hypoxemia as supported by experimental administration of surfactant in lung lavage model and premature rabbits. The results from pressure-volume curve study in premature rabbits suggest that surfactant preparation from calf is better than that from adult pig and has similar effects as Infasurf (CLSE). We believe that it is appropriate to plan for clinical trials on surfactant replacement therapy in premature newborn at high risk from developing RDS.

Acknowledgement

We are indebted to Goran Enhorning M.D. for his kind guidance in premature rabbit experiment. We wish to thank Shu Jin Shen M.D. for her kind help in editing the manuscript.

S.III.4

THE INCIDENCE AND EPIDEMIOLOGY OF CONGENITAL HEART DISEASE IN SHANGHAI

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The purpose of this survey is to study the incidence and epidemiology of congenital heart disease in Shanghai. The investigation was carried out in Yang Pu (1 October 1984 - 30 September 1985) and Xu Hui (1 February 1987 - 31 January 1988) These two districts have the biggest population among all the ten districts in the City.

Twenty thousand and eighty-two live born infants were recruited from the two districts in a year. Among them there were 10,393 males and 9,689 females. A one-year prospective follow-up was carried out. All the infants were examined by qualified pediatricians immediately after birth, at 3 months, 6 months, 9 months and 12 months.

Totally 138 cases of congenital heart disease were diagnosed. The diagnoses were confirmed by autopsy (25), operation (27), catheterisation and angiocardiography (5), doppler echocardiography (75) and clinical only (6). The incidence of congenital heart disease in these two districts was 0.687%. Of the 138 cases, 68 cases were male and 70 were female with the incidence of 6.54% and 7.22% respectively.

Regarding the types of congenital heart disease, there were 108 cases (78.26%) in the acyanotic group, including 78 cases of ventricular septal defect (56.52%), 11 cases of atrial septal defect (7.97%), 10 cases of patent ductus arteriosus (7.25%), 4 cases of aortic stenosis (2.90%), 2 cases of atrial ventricular canal (1.45%), 1 case of coarctation of the aorta (0.72%), 1 case of mitral cleft (0.72%) and 1 case of dextrocardia (0.72%). There were 30 cases (21.74%) in the cyanotic group, including 8 cases of pulmonary valvular stenosis (5.79%), 7 cases of transposition of great arteries (5.07%), 7 cases of Tetralogy of Fallot (5.07%), 3 cases of interruption of aortic arch (2.17%), 2 cases of truncus arteriosus (1.45%), 1 case of pumonary atresia (0.72%), 1 case of tricuspid atresia (0.72%) and 1 case of single ventricle (0.72%). In this group of patients with congenital heart disease, the incidence of ventricular septal defect (56.52%) was the highest. It was higher than that in the North America and Europe. Obviously the incidence of aortic stenosis (2.90%) and coarctation of the aorta (0.72%) were much lower than that in the western world. Interestingly, there was not a single case of hypoplastic left heart syndrome in this series.

In this group of patients, 38 cases died in the first year of life with a mortality of 27.54%. The causes of death were pneumonia (23), resistant heart failure (8), severe hypoxia (4), intracranial hemorrhage (1), pulmonary hemorrhage (1) and undefined cause (1). Among the 70 cases of isolated ventricular septal defect 24 cases (34%) had a spontaneous closure of their defect in the first year of life.

The epidemiological survey of this series included family history, parity, maternal age and maternal health during pregnancy including threatened abortion, toxemia, contact with toxic agent, upper respiratory infection. Using 1:2 matching analysis for statistical treatment, it was concluded that upper respiratory infection during early pregnancy was implicated with an increase in the incidence of congenital heart disease ($P < 0.001$). The relative risk reached was 6.25. The relative risk of family history was 3.33 which suggested that those who had a positive family history, had a greater risk of congenital heart disease than those who had a negative family history.

S.III.5

PAEDIATRIC ANGIOPLASTY AND VALVULOPLASTY IN HONG KONG

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During the period January 1987 to December 1989 interventional cardiac catheterisation was performed in 90 children : 65 valvular pulmonary stenosis, 12 pulmonary atresia with intact interventricular septum post-close pulmonary valvotomy, 7 coarctation of aorta, 4 aortic stenosis, 1 pulmonary artery stenosis and 1 renal artery stenosis. The results were good for patients with classical pulmonary stenosis with the mean right ventricular systolic pressure dropped from 84 mmHg to 50 mmHg and the mean gradient dropped from 63 mmHg to 29 mmHg. Dilatation was considered inadequate in 5 patients and only 1 has required a second dilatation so far. Results were less rewarding in patients with dysplastic pulmonary valves and those after close pulmonary valvotomy for pulmonary atresia with intact interventricular septum; only 50% of these have satisfactory gradient relief. For native coarctation of aorta in infancy, good initial result was obtained but restenosis was frequent. For coarctation restenosis after previous surgery, results were much better. Balloon dilatation was successful for the one patient with renal artery stenosis and failed for the patient with postoperative stenosis of the main pulmonary artery.

S.III.6

"ORIENTAL" VENTRICULAR SEPTAL DEFECT

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INTRODUCTION

"Oriental" ventricular septal defect (VSD) denotes a defect at the outlet part of the interventricular septum immediately beneath the aortic and the pulmonary valve rings. Various names have been used to describe this defect, namely, supracristal, subarterial infundibular, subpulmonary, subpulmonic, type II or more recently, doubly committed subarterial VSD. This defect is much more common in the Southeast Asian ethnic groups than the West (18-36% vs 5-7%)[1,2], henceforth the name "oriental" is used. This defect is unique in that i. it rarely closes spontaneously[3], ii. it frequently associates with aortic valve prolapse and aortic regurgitation and iii. aneurysm of aortic sinus of valsalva may develop[1]. The high incidence of aortic valve involvement has prompted close monitoring with repeated aortography[4] or early surgical closure[5]. We reviewed our experience of "Oriental" VSD to evaluate the natural and unnatural history of the defect which might enable us to formulate an optimal therapeutic approach for this problem.

MATERIAL AND METHOD

Between the year 1980-1989, 135 cases of "Oriental" VSD were admitted to the Grantham Hospital for investigation and treatment and they form the subjects for this study. Diagnosis was made echocardiographically using criteria established by Sutherland et al[6] and/or angiographically as described by Soto et al[7] and/or by surgical inspection. All underwent cardiac catheterisation and angiography and 110 underwent echocardiographic examination. The clinical, echocardiographic, cardiac catheterisation and/or surgical features of these patients were studied. The echocardiographic features of 22 children with perimembranous ventricular septal defect were also studied to serve as controls.

CLINICAL CATEGORISATION

According to the clinical behaviour and the associated anomalies the 153 cases of "Oriental" VSD could be subdivided into 4 categories:

Group I: 22 cases presented early in life (ranging between 5 days and 2.3 months of age) with severe heart failure. 62.5% were males and 37.5% were females (male to female ratio = 1.7:1). All but 2 of them were associated with coarctation of aorta. 5 were admitted in shock state. All required surgical repair of the aortic coarctation with or without pulmonary artery banding soon after admission to hospital. None had aortic regurgitation upon presentation.

Group II: 48 cases presented in later infancy (ranging between 2 months and 2 years of age). All presented with heart failure requiring drug treatment with digoxin and diuretics but none had coarctation of the aorta. 57.5% were males and 42.5% were females (male to female ratio = 1.4:1.). All underwent cardiac catheterisation which revealed significant pulmonary hypertension (systolic pulmonary arterial pressure more than 50% of the systolic systemic arterial pressure) and/or a large left to right shunt. None had significant aortic valve regurgitation.

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Group III: 34 cases presented as a small to moderate sized VSD between 2 years and 12 years of age (mean age = 7.5 years). The male to female ratio was 1.5:1. None were associated with coarctation of the aorta. All were asymptomatic. All underwent cardiac catheterisation which showed that 80% had a small left to right shunt (Qp to Qs ratio of less than 2 to 1) and a normal or minimally elevated pulmonary arterial pressure. Seven cases had aortic regurgitation and in 2 the aortic regurgitation was moderately severe.

Group IV: 31 cases presented between 14 years and 65 years of age. 28 of them had aortic regurgitation which is severe in 14. Four patients had concomitant aortic valve endocarditis. The male to female ratio was 3.5 to 1. Thirteen cases had an aneurysm of sinus of valsalva with aortic regurgitation. In 5 cases the aneurysm had ruptured into the right ventricular outflow tract. None had aortic coarctation.

ANATOMIC FINDINGS

1. The defect

Location: The defect was situated at the outlet septum guarded superiorly by the fibrous contact point of the aortic annulus and the pulmonary annulus. Echocardiographic subcostal and precordial views which showed the left ventricular outflow tract could image the defect just beneath the pulmonary valve (figure 1). In hearts with perimembranous VSD the defect was found to be in direct contact with the central fibrous body adjacent to the tricuspid valve.

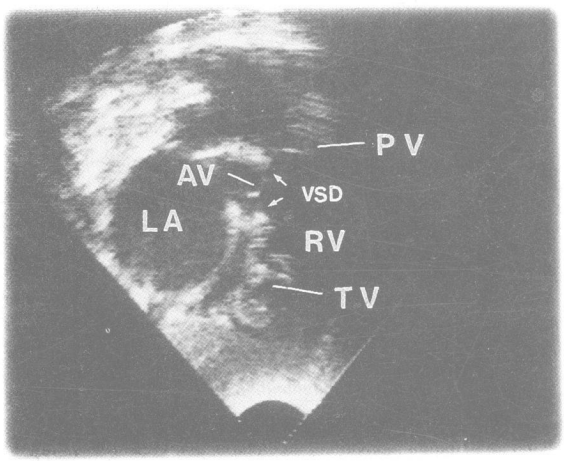

Figure 1.
Echocardiographic subcostal view showing the right ventricular outflow tract. The infundibular septum is completely absent leaving a large "Oriental" ventricular septal defect (VSD) behind. The left atrium (LA) is enlarged. AV = aortic valve, PV = pulmonary valve, RV = right ventricular, TV = tricuspid valve.

Size: The size of the defect was variable. The defect was large in Group I and II, but was pin-hole in size in Group III. In 15 of Group III and 19 of Group IV the defect was large but was partially closed by the prolapsed right coronary leaflet.

Malalignment: In all of Group I cases, the aortic and pulmonary annulus contact point was found to be posteriorly displaced and was malaligned with the rest of the ventricular septum (Figure 2). Consequently the left ventricular output was streamed preferentially towards the pulmonary outflow tract and the main pulmonary artery was disproportionately larger than the ascending aorta. Certain degree of aortic isthmal narrowing was invariably present and true coarctation of the aorta was found in all but 2 cases. This phenomenon was not observed in any other groups.

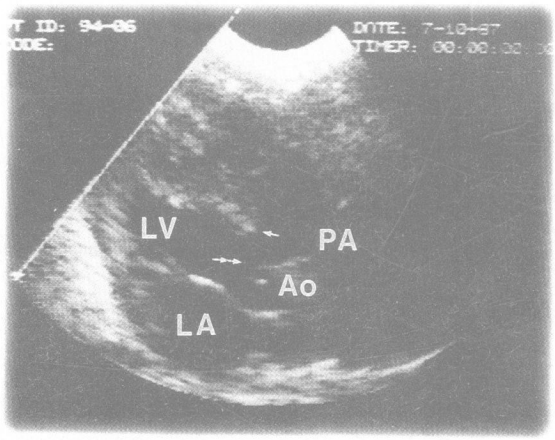

Figure 2.
Echocardiographic left ventricular long axis view showing that the crest of the ventricular septum (single arrow) is malaligned with the junction between the aortic and the pulmonary valve (double arrows). The ventricular septal defect is large. LV = left ventricle, Ao = aorta, LA = left atrium.

2. The right aortic coronary sinus

In hearts with perimembranous VSD the right aortic coronary sinu wall was covered with the right ventricular infundibular septal musculature giving it mechanical support. This could be demonstrated using long axis echocardiographic views of the left ventricular outflow tract and the ascending aorta (Figure 3).

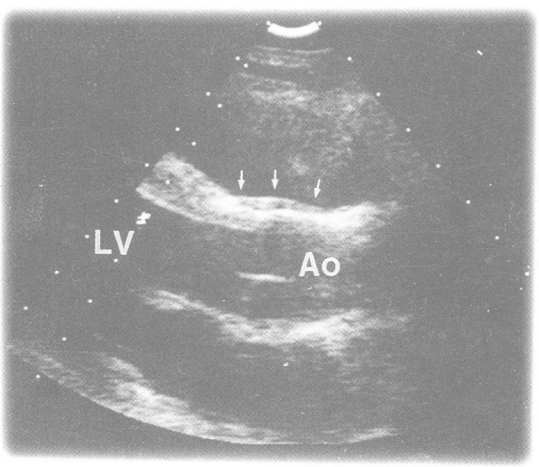

Figure 3.
Precordial echocardiographic long axis view of the left ventricle in a patient with perimembranous ventricular septal defect. The right ventricular infundibular musculature (arrows) is covering the anterior aspect of the aortic right coronary sinus wall. Ao = aortic valve, LV = left ventricle.

In hearts with "Oriental" VSD, this right ventricular infundibular muscular cover of the anterior aortic coronary sinus wall was absent in all cases studied (Figure 4). This muscular deficiency extended from defect at the contact point of the aortic and pulmonary annulus near the commissure between the right and left coronary leaflets rightward for a variable distance over the right aortic sinus wall (Figure 5). Consequently the right aortic sinus wall was 1. denuded of muscular support, and 2. protruding or prolapsing into the right ventricular outflow tract and 3. part of the corresponding facing pulmonary leaflet arose directly from the denuded right aortic sinus wall. Prolapse of aortic right coronary sinus was not found in Group I but it was found in 21% of Group II, 58% of Group III and 73% of Group IV cases. 13 patients in Group IV (42%) had an aneurysm of sinus of valsalva and in 5, the aneurysm had ruptured into the right ventricular outflow tract.

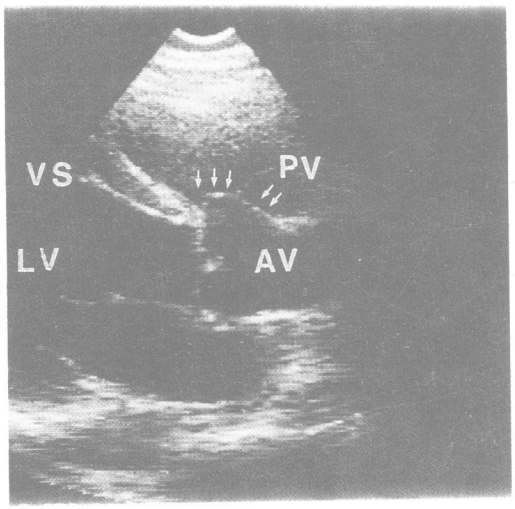

Figure 4.

Precordial echocardiographic long axis view of the left ventricle (same as in figure 3) of a patient with a tiny "Oriental" ventricular septal defect. The right ventricular infundibular muscular cover of the aortic right coronary sinus wall is absent (arrows). The pulmonary valve (PV) arises from the denuded and dilated aortic coronary sinus wall. AV = aortic valve, VS = ventricular septum, LV = left ventricle.

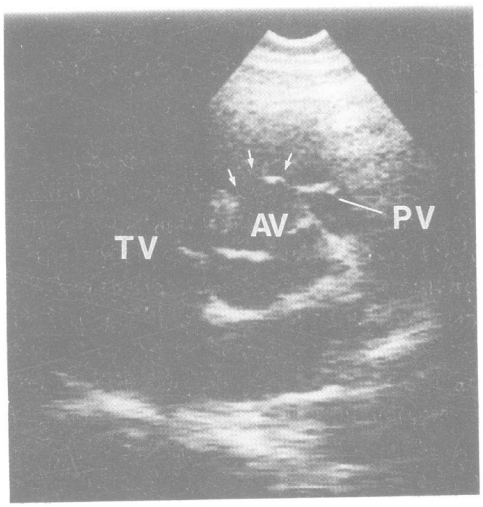

Figure 5

Precordial echocardiographic left ventricular short axis view at the level of the aortic valve (AV). The right ventricular infundibular musculature was absent (arrows). The right coronary sinus wall is thin and protruding into the right ventricular outflow tract. PV = pulmonary valve, AV aortic valve, TV = tricuspid valve.

3. The Right Coronary Aortic Valve Leaflet

The right aortic valve leaflet prolapsed beneath the aortic valve ring partially closing the ventricular septal defect in 11% of Group II, 50% of Group III and 75% of Group IV cases. Seller's grade II or more aortic regurgitation was found on angiography in 4% of Group II, 20% of Group III and 77% of Group IV cases. Aortic regurgitation or aortic valve prolapse was not found in Group I. In the 33 cases with aortic regurgitation, prolapse of both the aortic valve leaflet and the right coronary sinus wall was found in 69% and aortic valve leaflet prolapse alone was found in 20%.

FOLLOW UP

Of those who did not have surgical repair of the VSD, 24 had follow up cardiac catheterisation and angiography 1 to 10 years after the initial presentation, 17% either developed or showed worsening of aortic regurgitation. Of the 60 patients who did not have aortic valve prolapse or regurgitation at the time of surgery, none of them showed aortic valve prolapse or regurgitation on echocardiographic examination 1 to 10 years after surgery. In 11 patients aortic regurgitation was already present at the time of surgical repair of the VSD. Seven of them showed significant improvement or disappearance of aortic regurgitation, 2 showed no change while 2 had worsening of aortic regurgitation as demonstrated by cardiac catheterisation and angiography 2 to 6 years after surgery.

DISCUSSION

It is obvious from our study that "Oriental" VSDs could present with a wide clinical spectrum dependent on i. the size of the VSD, ii. associated malalignment of the aorta-pulmonary junction, iii. age of the patient, iv. associated aortic valve leaflet and/or sinus complications and v. secondary infection. Patients in Group I and Group II are cases with large anatomic defects. Additionally, Group I has posterior malalignment of the aorto-pulmonary junction resulting in streaming of left ventricular output into the pulmonary artery, a large main pulmonary artery, a much smaller ascending aorta and a narrowed aortic isthmus. The high prevalence of coarctation of aorta in Group I is probably the morphologic consequence of the defect. In the occasional cases without true coarctation, the aortic isthmus is invariably smaller than normal.

It is interesting to note that patients in Group I and Group II do not have significant aortic valve or aortic sinus complications at the time of presentation. This could be due to the young age at presentation such that there was not enough time for aortic complications to develop. Secondly, the defect size in Groups I and II was large and the pulmonary pressure was usually elevated such that the left to right shunt velocity through the defect was low, not creating enough dragging force at the aortic valve by the Venturi effect[8].

The majority of patients in Group III represent cases with a small defect (at least functionally), a relatively normal pulmonary pressure with or without a varying degree of aortic valve and aortic sinus prolapse and/or aortic valve regurgitation. In 40% of cases in Group III and Group IV the defect was partially closed by the prolapsing aortic valve leaflet and appeared smaller than it really was. Patients in Group IV were young adults whose presentation was with significant aortic valve or aortic sinus complications. The VSD was only an incidental finding. This clinical spectrum suggests that the aortic valve and sinus lesions in "Oriental" VSDs were acquired lesions resulting from both anatomic and haemodynamic predisposition.

The haemodynamic predisposition to aortic valve complication due to the VSD jet deforming the aortic valve leaflet has been well described by Tatsuno et al[8]. However, the anatomic predisposition to both the aortic valve and aortic sinus prolapse has been stressed. Van Praagh et al studied the pathologic specimens of 4 cases of this VSD and suggested that the prolapse of the aortic valve was a result of the location of the VSD, its relation with the aortic valve and the lack of muscular support beneath the aortic valve leaflet[9]. Tatsuno et al pointed out that the muscular support of the aortic annulus and the aortic right coronary sinus was also deficient in specimens of heart with VSD and prolapsed aortic valve leaflet. Our echocardiographic study confirmed Tatsuno's finding and demonstrated that this muscle deficiency was present above and below the aortic valve and was present in every case of "Oriental" VSD studied. Our present study also confirmed the association of "Oriental" VSD and aneurysm of sinus of valsalva. The absence of normal right ventricular infundibular musculature lining of the right coronary sinus wall in "Oriental" VSDs may be responsible for the progressive dilatation and thinning of the aortic sinus wall which then herniates with time and eventually ruptures into the right ventricular outflow tract. This occurred in 31% of our Group IV cases.

We have also observed that the aortic sinus wall could be so thinned that it could not be distinguished echocardiographically from the aortic valve leaflet tissue and both the right coronary sinus and the right coronary aortic valve leaflet prolapsed into the right ventricular outflow tract. Although it could be argued that the prolapsing structure might just be the dilated aortic leaflet, with the use of real-time cross-sectional echocardiography the insertion point of the right coronary leaflet was still found to be aligned with that of the non-coronary leaflet and the upper margin of the aneurysmal structure clearly extended superiorly into the aortic wall, suggested that the "prolapsed structure" consisted of the valve leaflet as well as the right aortic sinus wall tissue.

In our study, aortic regurgitation was strongly associated with combined aortic valve and aortic sinus prolapse. Thus surgical closure of the VSD before the occurrence of the aortic sinus and leaflet deformity might prevent development of aortic regurgitation. Indeed this was supported by the longitudinal follow up of those cases whose VSDs were surgically closed before aortic sinus or leaflet prolapse showing no late development of aortic regurgitation. On the other hand, closure of VSD in the presence of aortic regurgitation did not necessary result in disappearance or improvement of aortic regurgitation although the majority might do. Kusuhara suggested that if the aortic regurgitation fraction was more than 25% of the left ventricular stroke volume, simple VSD closure was usually not adequate and aortic valve valvuloplasty or even aortic valve replacement might be required to control aortic regurgitation[10].

Infective endocarditis of the aortic valve which is associated with significant mortality and morbidity, is a serious complication of "Oriental" VSDs. Our study shows that this is a common occurrence in adults with an haemodynamically unimportant "Oriental" VSD. Because of the unfavourable natural history elective surgical closure of an uncomplicated "Oriental" VSD in childhood to prevent the various late complications appears to be a justified approach to this common Oriental problem.

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S.III.7

CRITICAL AORTIC STENOSIS IN EARLY INFANCY - ANATOMICAL AND CARDIOGRAPHIC SUBSTRATES OF SUCCESSFUL OPEN VALVOTOMY

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In order to establish non-invasive criteria by which to manage young infants with critical aortic stenosis, 20 heart specimens under 3 months of age were examined and the clinical course and real time echocardiograms of 20 patients in the same age group who underwent open valvotomy were reviewed.

The heart specimens showed a spectrum of valvar, ventricular and vascular abnormalities which could be accurately identified by echocardiography. A small left ventricular cavity was usually associated with a narrow ventriculo-arterial junction, small ascending aorta, and narrow subaortic region. In these hearts, the mitral valve had a single or grossly hypoplastic papillary muscle with short or "arcuate" tendinous cords. A dilated left ventricular cavity had wider inflow and outflow orifices, and the tension apparatus of the mitral valve was either normal or supported by hypertrophic papillary muscles at the other end of the spectrum.

The survivors ($n=5$) and non-survivors ($n=5$) of open valvotomy showed significant differences in the echocardiographic dimensions of the left ventricle($p<0.005$), the subaortic region ($p<0.05$), the ventriculo-junction ($p<0.05$), the ascending aorta ($p<0.005$) and the mitral valve orifice ($p<0.001$). Babies with unfavorable cardiac anatomy tended to present earlier ($p<0.05$) and with a lower systemic blood pressure ($p<0.05$), and they required prostaglandin E2 to maintain right ventricular support of the circulation via a persistent arterial duct. This study suggests that patients with a small left ventricle (echocardiographic inflow dimension < 25 mm), a narrow ventriculo-aortic junction (<5mm) and a small mitral valvar orifice (<9 mm) will not achieve a satisfactory surgical result from aortic valvotomy.

SYMPOSIUM IV

S.IV.1

APNEA IN INFANCY AND CHILDHOOD

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I. PRENATAL BREATHING

It is now well established that breathing does not start at birth but occurs intermittently long before in utero. Fetal breathing (FB) movements have been recorded from as early as 0.5 gestation in fetal lambs. Initially FB, or specifically diaphragmatic activity is part of nearly continuous irregular and seemingly random twitching and writhing of all somatic muscles including the lateral rectus muscle of the eye and later changes into a distinct breathing pattern separate from body movements[1,2].

FB differs in several significant ways from adult respiration and it may be useful to discuss the characteristics of FB as a point of reference for the discussion on the development of postnatal breathing. Towards term FB is characteristically very irregular in both amplitude and frequency but the most distinguishing feature is the periodic nature and very loose coupling to the metabolic requirements of the fetus. FB has been most extensively studied in the fetal sheep and in this species breathing activity occupies approximately 40% of the time and occurs almost exclusively during rapid eye movement (REM) sleep. The nature of the coupling between REM sleep and FB is not known but appears to be mediated by midbrain mechanism because cutting the neuraxis at the midcollicular level will cause continuous fetal respiration[3].

Since the fetus does not control its own oxygenation on teleological grounds, one would predict weak respiratory reflexes. On this point there is some uncertainty. The peripheral chemoreceptors are responsive well before birth[4,5,6] and elimination of these receptors has been shown to reduce the vigour of FB suggesting that they provide a tonic drive to FB[7]. However, the great variation in the fetal sensitivity to CO_2 and in minute FB during different episodes of REM sleep in the absence of changes in fetal blood gases, the frequent apneas even during hypercapnia in REM sleep[8] and the great sensitivity of FB to adverse conditions[9] indicate that the chemoreflexes are easily overridden by more powerful influences on FB. In fact, denervation of the peripheral as well as central chemoreceptors (lesions of the intermediate areas "S" on the ventral medulla) in chronically prepared fetuses does not stop spontaneous FB nor all the respiratory response to hypercapnia. (Jansen & Chernick unpublished).

The fetal response to hypoxia is paradoxical in that it causes depression of FB instead of stimulation[10,11]. If, however, the fetus is pretreated with 5HT[12] or the fetal PaO_2 is first raised and then reduced, the fetal response is one of transient stimulation followed by depression[13] similar to the response observed in the immediate neonatal period of many species[14]. This indicates again that the peripheral chemoreflexes are overruled by active inhibitory mechanisms that in this situation have been localized in the upper lateral pons[15].

It is obvious that FB is dominated by inhibitory influences but the nature of this inhibition is poorly understood. A number of inhibitory agents and transmitters have been identified in the fetal brain but so far no unified concept has emerged. Of special interest is adenosine which has been shown to be released during hypoxia and antagonized by theophylline in the newborn[16] and may be responsible for the depression of FB in this situation.

It has become axiomatic that the fetus does not make breathing movements during non-REM (NREM) or quiet sleep but this may be to some degree species dependent. For instance, in the human fetus FB also occurs in state IF, interpreted to be equivalent to NREM sleep[17]. Even in the fetal lamb breathing can be induced during NREM sleep by perfusing the cerebral ventricles with mock CSF containing low HCO_3 concentrations[18], or by pretreatment with large doses of 5HT[12]. The most dramatic FB response during NREM sleep can be elicited by inhibition of prostaglandin synthesis by prolonged infusions of indomethacin or meclofenamate[19]. Conversely PGE_2 injected into the fetus depresses FB[20]. The precise site of action in either case has not been determined but has been localized to the CNS caudal to the cerebral cortex and rostral to T1[21,22]. After pretreatment with inhibitors of prostaglandin synthesis FB appears to be very similar to postnatal breathing which has led to the suggestion that prostaglandin may be involved in the transition from periodic fetal to continuous postnatal respiration [19,20]. The prostaglandin connection is further strengthened by the coincident observations of raised plasma levels of PGE_2 and reduced FB in the days before birth[23] and reduced levels of PGE_2 and increased breathing postnatally[24].

The mechanism by which prostaglandins influence fetal or postnatal breathing and whether a decrease in PGE_2 is in fact essential for the establishment of postnatal breathing remains to be established.

II. ONSET OF BREATHING AT BIRTH

Birth is a momentous event for the fetus by any measure and a critical factor in coping in a new environment is the establishment of effective independent respiration. If birth proceeds quickly breathing may start smoothly without evidence of stress[25]. Generally, however, the fetus is asphyxiated to some degree and breathing starts out as a series of deep irregular gasps before effective rhythmic respiration is established.

Our understanding of the onset of respiration at birth has undergone a fundamental change during the last several decades. We now know that breathing does not start de novo at birth but that it is a continuation of movements and reflexes that have been established and "exercised" for a long time in utero.

People who were expecting to find a single factor responsible for the "initiation of breathing at birth" or in present terminology "onset of postnatal breathing" must be disappointed because a number of stimuli have been identified that alone or in combination can induce a respiratory pattern akin to that observed after birth.

Most of the experiments initially done on exteriorized fetuses have now been repeated on "acute" or "chronic" fetal sheep preparations in utero. In brief, these experiments have demonstrated that somatic sensory stimulation, e.g. mechanical or electrical stimulation of the skin or peripheral nerves[26,27] can be a powerful stimulus to breathing but is to some degree subject to the arousal state of the fetus[28]. Similarly cooling of the skin (but not the core) has also been shown to stimulate continuous breathing in fetuses with normal blood gases in utero[29]. Conversely, fetal asphyxia in utero in the absence of other sensory stimuli can also initiate postnatal type breathing[30]. The observations with inhibitors of prostaglandin synthesis (indomethacin & meclofenamate) and the implication regarding the onset of breathing at birth have already been discussed. In this regard it is interesting to note that neither the respiratory response to indomethacin[21,31], nor the establishment of pulmonary ventilation at birth (asphyxia) is dependent on the carotid body chemoreceptors[32]. Whether or not the sudden release from a (proposed) placental inhibitor at birth is a factor in the establishment of continuous breathing has been variously confirmed[30] or disproved[33,34]. Until techniques of maintaining fetal sheep on artificial placentas have improved sufficiently to allow definitive conclusions, this question will have to be held in abeyance.

Birth, of course, is a complex interaction of a multitude of influences, but in all this the importance of arousal should not be underestimated. Finally, it appears that nature deemed the onset of pulmonary ventilation too important to rely on only one mechanism. It is also obvious, however, that the control mechanism is not fully mature at birth. The newborn animal and human infant demonstrate large swings in breathing and during the postnatal period the respiratory reflexes become atuned and coupled more tightly to the metabolic requirements. It is during this time of transition from fetal to adult type of control that the newborn is most vulnerable to respiratory complications and failure.

III. MATURATION OF THE CONTROL OF BREATHING

a. Receptors and Reflexes

1. Carotid bodies. The functional status of the carotid body chemoreceptors has been controversial almost from the beginning of fetal research when Barcroft and Karvonen[35] injected large doses of NaCN into the fetal circulation and failed to elicit the expected respiratory response.

Attempts to record from the sinus nerve directly[4,6,36,37] have only added to the confusion. Today we know that the carotid body chemoreceptors are responsive during fetal life and can be stimulated to elicit respiratory reflexes[11] and there is also evidence that they provide a tonic drive to spontaneous FB[7]. All considered, however, the evidence of spontaneous carotid body activity during fetal life is not impressive; the chemoreflexes are obviously subservient to more powerful influence such as sleep states and the central hypoxic depression of FB.

Considering the comparatively low fetal arterial PO_2 (by adult standards) the fetal chemoreceptors must have a high activation threshold. After birth the arterial PO_2 rises and the chemoreceptor threshold follows suit. How the carotid body threshold is reset after birth is not known. Acker et al[38] measured the difference between arterial and carotid body tissue PO_2 in fetal and newborn lambs and found the gradient to be negligible in the fetus but increasing rapidly during the immediate postnatal period. These investigators speculated that resetting of the carotid body sensitivity involved either a change in the perfusion of the carotid body or a drastic change in its metabolism and O_2 consumption. Although both suggestions are plausible, studies on newborn animals[39,40] have indicated a much longer time span (days to weeks) involved in the resetting of the respiratory chemoreflexes than the establishment of gradients within the carotid bodies (minutes to hours) would indicate.

At the present, therefore, the process of the resetting of the respiratory threshold from fetal to adult levels of PaO_2 is still an open question.

2. Aortic Bodies. The aortic bodies appear to be physiologically less important than the carotid bodies and even less is known about normal activity during fetal life. Ponte and Purves[5] were able to record spontaneous activity from fetal aortic body chemoreceptors that responded appropriately during asphyxia and Dawes et al[41] demonstrated a redistribution of blood flow during hypoxemia that was abolished by section of the vagus or aortic nerves. Reeves et al[42] did similar experiments on fetal calves and found the aortic bodies to be important only in deteriorating or deeply anesthetized fetuses. It should be pointed out, however, that all of these experiments were done on exteriorized fetuses - not an ideal preparation for the study of the cardiovascular control[43]. These experiments should now be repeated on physiologically stable chronically instrumented fetal animals.

We are not aware of any studies delineating postnatal changes in sensitivity of the aortic body chemoreceptors.

3. Central chemoreceptors. The central chemoreceptors are believed to be responsive to H^+ and CO_2 and to mediate the respiratory drive to CO_2 that cannot be accounted for by the peripheral chemoreceptors. The precise location and mechanism of stimulation, H^+ or CO_2 in the CSF, ECF or blood, has been controversial from the start but need not unduly concern us here. For this discussion it is important to remember that the ventrolateral surface of the medulla has been shown to be responsive to H^+ and to stimulate or depress breathing when superfused with acid or alkaline mock CSF respectively[44].

The functional status of the central chemoreceptors during fetal life is not known. Hypercapnia stimulates FB activity as early as 0.5 gestation but considering the great variability in respiratory output between different episodes of spontaneous breathing activity at the same blood gases the central chemoreceptors are not likely providing the main drive during spontaneous FB. In chronically instrumented fetuses Hohimer et al[18] were able to influence fetal breathing by perfusing the cerebral ventricles with mock CSF containing either high or low concentrations of HCO_3. Low HCO_3 CSF stimulated FB frequently also during NREM sleep. This is surprising because hypercapnia stimulates FB only during REM sleep or wakefulness[8,45] and indicates that the perfusion technique had stimulated different or additional mechanisms than respiratory acidosis.

In the exteriorized, anesthetized fetal lamb superfusion of the ventral medulla with acid mock CSF will not initiate breathing[46] but superfusion is effective within minutes of clamping the umbilical cord[47]. Similarly, hypercapnia will stimulate breathing within moments of birth in sino-aortic denervated lambs[48]. Similar responses have been reported for newborn lambs[48] guinea pigs, rabbits[47] and rats[49]. Individually these were not exhaustive studies but together they indicate functional and competent central chemoreceptors at birth. These studies do not indicate, however, that the central chemoreceptors are mature and fully developed at birth. In fact, experimental evidence suggests they are not and that further maturation in sensitivity and effectiveness proceeds postnatally[50,51].

4. Vagal & Chest Wall Reflexes. Reflex activity from the lungs and chest wall play a comparatively greater role in determining the pattern of breathing in the newly born than in the adult. Why these reflexes decrease after birth is not known but does parallel a diminution in a number of prenatal non-respiratory reflexes.

Heads paradoxical reflex is vagally mediated hyperinflation (respiratory augmentation) triggered by distension of stretch receptors in the large airways[52,53]. This reflex is present in the newborn of many species including the human and may be important in aeration of the lung at birth. The reflex diminishes after a few weeks of life but can still be elicited in the adult[54,55]. Sighing in newborn infants, characterized by a double inspiration may be triggered by Head's reflex. It has been suggested that sighing may help establish a normal FRC at birth and prevent airway closure during the first few days of life[56]. Detailed physiologic studies characterizing the maturational changes of this reflex after birth have not yet been undertaken.

Vagal afferents influence respiratory timing by several reflexes dependent on specialized receptors which respond to specific stimuli. Again these play a prominent role in the control of breathing in the newly born. Laryngeal chemoreceptors present in the epithelium of the epiglottis and larynx are innervated by the superior laryngeal nerve, a branch of the vagus nerve. In animals, water or milk of another species will stimulate these receptors and cause severe apnea and periodic gasping[57]. In awake newborn animals, stimulation of the superior laryngeal nerve causes repeated apnea but breathing is sustained by an arousal mechanism[58]. This reflex also disappears with maturation[57,59]. Stimulation of these receptors probably has no role in the pathogenesis of apnea of prematurity but there is some speculation about a possible role in the sudden infant death syndrome[57].

Slowly adapting stretch receptors in the lung are responsible for the inflation inhibitory reflex and prolongation of expiratory time (Hering-Breuer reflex). This reflex provides volume feedback from the lungs to prevent over-expansion. It is active in the term infant but in adult man this reflex is not triggered with usual tidal volumes[60]. In the term infant the Hering-Breuer reflex is influenced by sleep state being present during NREM sleep but is not during REM sleep[61].

Irritant receptors, also called rapidly adapting stretch receptors, are located in the airways and lungs and cause a shortening of expiratory time. However, in infants below 35 weeks gestation stimulation of the carina by a soft catheter may result in a slowing of ventilation or apnea rather than increased respiratory effort. This paradoxical response was suggested to be related to immaturity of vagal myelination[62]. Further study of the maturation of the reflex response to stimulation of irritant receptors innervated by the vagus and the influence of sleep state are warranted. J (juxta-alveolar) receptors are located near pulmonary capillaries within alveolar walls and have been implicated in the tachypnea of pulmonary edema. When stimulated these receptors also cause apnea, rapid shallow breathing, bradycardia and inhibition of monosynaptic reflexes[63]. In kittens, these reflexes are absent or weak prior to 7 days of age but fully developed by 10 days of age[64]. No studies of these receptors have been done in the human infant but it has been postulated that they may be responsible for the apnea associated with pulmonary edema secondary to patent ductus arteriosus in preterm infants. In contrast to the diaphragm, intercostal muscles are richly supplied with muscle spindles which can initiate reflex influences on breathing pattern[65]. Segmental intercostal reflexes are extremely important in maintaining intercostal muscle tone in the newborn infant and help to stabilize the very compliant chest wall and therefore maintain FRC. These reflexes are inhibited during REM sleep which also is associated with reduction in FRC[66,67].

Newborn infants have a potent intercostal-phrenic inhibitory reflex. Inspiration is terminated prematurely when a rapid rate of inward motion of the rib cage occurs[68]. This reflex is particulary important during REM sleep when distortion of the neonatal rib cage is accentuated and may be responsible for apneic spells in some preterm infants.

b. Integrative Functions in the Newborn

1. Behavioural Influences and Sleep. Behavioural activities such as speech, deglutition, singing, etc. have a profound effect on ventilatory patterns and the control of breathing. Few studies have been done to elucidate the influence of behaviour on respiratory control in the newborn infant. Spontaneous swallowing shortens inspiratory duration and may prolong expiration when the swallow occurs at a high lung volume. Feeding by breast or bottle in newborn lambs[69] or human infants[70] compromises breathing and is associated with a marked diminution in the ventilatory response to CO_2. Newborn infants sleep at least 80% of the time and in preterm infants over 50% of that time is spent in REM sleep. By 6 months of age there is an adult pattern of 80% NREM and 20% REM sleep[71]. In term newborn infants REM sleep is associated with an increase in ventilation but respiratory frequency and tidal volume become highly variable[72,73]. Because of the increased ventilation $PaCO_2$ is also slightly lower in REM sleep. Surprisingly PaO_2 is also lower presumably because of ventilation - perfusion mismatching in the lung. REM sleep is also associated with a diminution of the Hering-Breuer and monosynaptic reflexes as indicated previously.

2. Hypoxia and hyperoxia. The newborns of all species studied to date have a peculiar biphasic ventilatory response to steady-state hypoxia, an initial increase in ventilation followed by a decrease to below baseline levels[14]. In contrast the adult response consists of a sustained hyperventilation. It is not known when the response matures in the human neonate; it is still biphasic in preterm infants at 25 days of age[74]. The mechanism responsible for the biphasic response in the newborn has been the subject of considerable controversy. Some suggestions

are that the secondary decrease in ventilation is caused by central hypoxic depression[75], decrease in metabolic rate during hypoxia[76] and to a loss of excitatory stimuli from peripheral chemoreceptors presumably by adaptation[77]. Hypoxic release of endogenous opiates has also been implicated as a possible mechanism for the depressed ventilation during severe hypoxia[78]. However, in human infants the ventilatory depression to 15% oxygen breathing was only partially reversed by naloxone, a specific opiate receptor blocker[79]. The increased ventilation during hypoxia following naloxone was not above baseline levels and therefore endogenous opiates play only a minor modulating role. Aminophylline will reduce hypoxic ventilatory depression in newborn animals in the absence of increased circulating catecholamine levels[80]. The reason why aminophylline is effective is not known but the drug is known to influence putative neurotransmitters such as dopamine, serotonin and adenosine. Whether or not aminophylline alters carotid body function in the newborn has not been studied.

The ventilatory response to hypoxia is also influenced by sleep. The biphasic response in newborn infants is only present during wakefulness and REM sleep whereas during NREM sleep a sustained hyperventilation is seen[81]. However, other responses have been reported for the newborns of other species[14 82] and upon reading the literature on the topic it is clear that the influence of sleep on the response to hypoxia remains to be sorted out.

Studies of the ventilatory response to hyperoxia indicate that as early as 1 hour after birth there is a reduction in ventilation in response to hyperoxia but the depression is transient and followed by hyperventilation[14]. This biphasic response to 100% oxygen breathing is present in both preterm and term infants and is qualitatively and quantitatively similar to the response seen in the adult. The initial hypoventilation is attributed to elimination of tonic carotid body activity. The hyperventilation is probably mediated by a central increase in PCO_2 caused either by a decrease in cerebral blood flow or by interference with CO_2 transport in the brain.

3. Hypercapnia. Considerable attention has been paid to the respiratory response to hypercapnia of the newborn. However, interpretation of these results is confounded by the presence of vascular shunts, unstable respiration, a compliant chest wall, and the influence of different states of arousal in addition to maturational differences between postnatal and postconceptional age. The control of postnatal breathing is obviously influenced by the maturation of several mechanisms and systems, but in a general way it can be stated that the respiratory sensitivity to CO_2 is low immediately after birth and increases during the first several weeks of postnatal life[83 84]. After birth the carotid body chemoreceptors are reset to a higher threshold of PO_2[6] and possibly to a different threshold of PCO_2 as well, although this has not yet been studied. There is also evidence of a postnatal increase in the sensitivity of the central chemoreceptors in newborn lambs[50]. A substantial O_2-CO_2 interaction occurs in the adult carotid body[85] and one can assume this to be the case in the newborn as well.

The sleep and activity state obviously affects the response to CO_2. The sensitivity to CO_2 of the human infant has been reported to be reduced during phasic REM sleep compared to NREM sleep which apparently was not secondary to greater chest distortion during REM sleep. It was concluded that the difference in respiration was attributable to the inherently smaller tidal volumes produced during active sleep[86].

4. Acidemia. Because of the blood brain barrier which maintains CSF pH within narrow limits metabolic acidosis affects respiration in the adult only by way of the peripheral chemoreceptors. In fact acute stimulation of the carotid bodies by H^+ will increase breathing and decrease the CO_2 in the blood and CSF which acts to limit the hyperventilation. According to Evans et al[87] the blood brain barrier in fetal sheep is intact long before birth but more recent work indicates that this may not be the case[51]. Prolonged I.V. infusion of

HC1 in newborn lambs and goats resulted in a steady decrease of the pH CSF. Respiration increased immediately presumably by stimulating the carotid bodies but not further to reflect the steady acidification of the CSF. These investigators argue that the central H^+ sensing mechanisms as well as the peripheral chemoreceptors are immature at birth resulting in a blunted respiratory response[50,51].

IV. DISORDERS OF RESPIRATORY CONTROL

1. Periodic breathing in newborn infants is characterized by period of ventilatory efforts lasting 10-15 seconds interrupted by periods of apnea which usually last from 5-10 seconds[88,89,90,91]. This type of breathing pattern may occur in both REM and NREM sleep. Most preterm infants exhibit periodic breathing and the incidence decreases with increasing postconceptional age. Even term infants born at sea level will have frequent respiratory pauses during REM sleep which disappear by 52 weeks postconceptional age. In the adult respiratory pauses during sleep are exceptional and are generally associated with a burst of rapid eye movements.

The pathophysiology of periodic breathing is not well understood. Because the shape of the CO_2 response curve is not different during periodic breathing compared to regular breathing[14], it is unlikely that an alteration in the sensitivity to CO_2 is responsible for the phenomenon, although administration of 2-4% CO_2 will abolish periodic breathing[92]. Administration of oxygen will also abolish periodicity perhaps by decreasing cerebral blood flow and increasing brain PCO_2. Breathing hypoxic gas mixtures will induce periodic breathing and indeed periodic breathing is more common in fullterm infants born at altitude than at sea level[93]. This suggests that hypoxia may play a role in the genesis of periodic breathing. Indeed blood transfusion of anemic preterm infants is associated with a marked reduction in the incidence and duration of periodic breathing[94]. Whether hypoxia is the sole explanation remains unclear. Another possibility is that the synaptic excitatory drive of respiratory neurons in the brainstem may be more susceptible to minor inhibitory influences in the preterm infants because of a lack of dendritic arborization[95]. This could account for the unstable ventilatory pattern.

2. Apneic spells lasting longer than 10 seconds and associated with depressed heart rate are also commonly seen in preterm infants and increase in incidence with increasing prematurity. There are several varieties of apnea: (a) central apnea, during which there is no respiratory effort; (b) obstructive apnea, during which air flow is interrupted but respiratory efforts continue; (c) mixed apnea which contains elements of central and obstructive apnea; (d) breath-holding apnea in which there is a pause during expiration and is terminated by further expiration preceding the next inspiration. Over 90% of apneic spells in otherwise healthy preterm infants are of the central type and only about 5% are of the breath-holding type[89]. Mixed and obstructive apneas account for less than 3% of apneas. About 20% of preterm infants will have severe idiopathic apnea requiring intervention. Treatment is by cutaneous stimulation, low concentrations of oxygen, theophylline or caffeine and when unresponsive to these measures intravenous doxapram has been used[91] (Table 1). These drugs are believed to be effective secondary to CNS stimulation.

Table 1. Drugs used for neonatal apnea

Drug	Route	Dose	
		Loading	Maintenance
Caffiene citrate	P.O., I.V.	20 mg/kg	2.5 mg/kg bid
Theophylline	P.O., I.V.	6 mg/kg	2 mg/kg bid
Doxapram HCL*	I.V.	0.5 - 2.5 mg/kg/hr	

* may contain benzyl alcohol preservative

Severe apnea may also be found in the preterm infant in association with other conditions. Twenty percent of infants with apnea have an intracranial hemorrhage and it is postulated that the cause is CNS depression. More than half of the preterm infants with apnea have associated conditions which reduce lung compliance (patent ductus arteriosus, hyaline membrance disease, bronchopulmonary dysplasia, congenital heart disease). The genesis of apnea under these conditions may be related to respiratory muscle fatigue or to activation of the intercostal-phrenic inhibitory reflex if the chest wall gets sucked in during inspiration[91].

V. APNEA IN OLDER CHILDREN

Apnea or severe alveolar hypoventilation in older children may be (a) transient -usually associated with obstructive sleep apnea, (b) congenital - the most severe form of central hypoventilation syndrome (CHS) has its onset typically in the neonatal period or early infancy, (c) late onset central hypoventilation syndrome - the underlying abnormality is likely congenital in origin or (d) acquired - related to a structural lesion in the brainstem. The latter three categories must be treated with mechanical ventilation. In some centers diaphragmatic pacing has been successful when there is no intrinsic abnormalities of the lung[96].

The commonest cause of obstructive sleep apnea in children is related to adenotonsillar hypertrophy. The clinical findings indicate a history of snoring or difficulties breathing during sleep, often associated with enuresis. During wakefulness there may be mouth breathing, an adenoidal facies or pectus excavatum. If severe, the sequelae are cor pulmonale, pulmonary edema, failure to thrive and poor appetite, hypersomnolence or delayed development and learning problems. Surgical treatment (adenoidectomy or T & A) should not be delayed.

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S.IV.2

INFECTION IN INTENSIVE CARE

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Nosocomial infection is a major problem in intensive care units. Handwashing is by far the most important preventive measure. Other measures of proven efficacy are adequate staff numbers, adequate space between patients, the availability of isolation facilities, adequate supervision and training on infection control, and strict control of the use of antibiotics. Antibiotic use should be restricted to the treatment of proven infection, short-term treatment of suspected infection (stop antibiotics after 48 hours of negative cultures) and a single dose at the start of high-risk surgical procedures. If prophylaxis against peptic ulceration is required, sucralfate should be used in preference to antacids or H2 antagonists because high gastric pH predisposes to bacterial colonisation of the stomach.

Measures that do not reduce the risk of nosocomial infection include prophylactic antibiotics (except for one dose with surgery), routine cultures (of staff, patients or equipment), gowns, ultraviolet lights, antiseptic mats, and use of antiseptics for cleaning floors.

Conventional measures for the treatment of severe sepsis in intensive care include antibiotics, draining pus, intravenous colloid or crystalloid, dopamine, noradrenaline, paralysis and ventilation, oxygen, bicarbonate, blood, platelets and fresh frozen plasma.

Experimental therapies for the treatment of severe sepsis in intensive care include measures to remove endotoxin (exchange transfusion, plasmafiltration), neutralise endotoxin (J5 antibodies, high titre plasma), remove mediators (haemofiltration), antagonise mediators (steroids, naloxone), and improve immunity (granulocyte transfusion, immunoglobulin).

S.VI.3

DEVELOPMENTAL DYNAMICS OF THE TEENAGER

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Every living organism has within it the potential for growth. For humans, this growth embraces change which manifests as maturation and adaptation with expression through both biological and behavioral characteristics. This biobehavioral interaction triggers a cascade of events which interacts with family, friends and community to create the uniqueness of each individual. The pressure for change and adaptation, the paucity of life experience, and the biological forces of development expose the growing child to the benefits and adversities of both human and natural elements. Adolescence then becomes a potentially perilous period of exploration and change. To focus only on the physical events of puberty ignores this important biobehavioral interaction. Psychological and social adaptations are driven by maturational forces based not only in the neuroendocrine axis, but also the milieu of the culture. Disease and dysfunction in teenagers often has its roots in several aspects of the growth process encouraging an integrated development approach to the teenagers problem.

S.IV.4

UNSUSTAINED SEXUAL PRECOCITY

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10 girls with unsustained breast development and vaginal spotting were presented. Regression of pubertal changes followed vaginal spotting but recurrent episodes occurred in 4 patients (group Ib). The clinical and hormonal data on the patients [Group Ia (n=6) and group Ib (n=4)] and 23 girls with central precocious puberty (Group II) were compared (Table).

	Age (yrs)	Ht. SDS (CA)	E_2 (pmol/L)	bLH (IU/L)	pLH (IU/L)	bFSH (IU/L)	pFSH (IU/L)
Ia	2.54 (1.6 - 4.3)	0.22 ± 0.3	< 30	< 0.3	0.5 ± 0.7	< 0.3	0.4 ± 0.06
Ib	1.49 (0.33 - 2.16)	1 ± 0.3	146 ± 62	< 0.3	< 0.3	< 0.3	< 0.3
II	5.66 (0.25 - 7)	1.65 ± 0.32	115 ± 23	1.7 ± 0.3	29.1 ± 3.7	2.16 ± 0.3	14.6 ± 1.8

b : basal; p : peak

Patients in group Ib were found to have ovarian cysts varying in size from 2.2 - 6 c.c. at the time of breast enlargement. The basal & GnRH stimulated bioactive levels of FSH (determined by the rat granulosa cell aromatase assay) in group Ib patients were low. This suggested that the clinical presentation of group Ib patients could not be explained by the presence of bio FSH which was not immunoreactive.

S.IV.5

DEPRESSION IN HONG KONG CHILDREN SUFFERING FROM THALASSAEMIA MAJOR

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This study aimed to examine twenty-five patients aged 9-15 years, 12 boys and 13 girls, suffering from β-thalassaemia major for the presence of depression. Twenty five normal children, matched for age and family background, were included as the control group. Both patients and control, were interviewed individually, the former after correction of anaemia by blood transfusion. The Children's Depression Scale (CDS) (Australian Council for Educational Research) was used for assessment and the Hong Kong Welchsler Intelligent Scale for Children, for the intelligent quotient (I.Q.) of patients. Parents of both groups were also interviewed for information on the family. Analysis of data showed that although the higher total depression score in patients, when compared with the control, fell short of that indicating statistical significance, four patients, all over 10.5 years, had been identified to be at risk for depression while none was found among the control (Chi Square $p < 0.05$). Total depression score of these four when compared with the twenty one non-depressed patients showed significant difference in all the subscales. Patients as a group were found to have normal I.Q., and the effect of sex and puberty on depression was examined. Further detailed study was indicated to better identify the factors for depression in some of our patients.

S.IV.6

PHYSICAL FITNESS IN HONG KONG CHILDREN

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There is no one set of physical fitness statistics for primary and secondary school children based on a simple and standard set of tests which can be easily applied in all schools. The purpose of this study is therefore to produce one.

Physical Fitness statistics of school children of both sexes between the age of 6 to 12 were obtained. Between November 89 to February 90, around 7,000 school children from 17 schools chosen from Hong Kong, Kowloon and the New Territories underwent 7 tests. The tests include body height, body weight, one minute sit-ups, sit and reach, grip strength of both hands, skin fold measurements at the triceps and 6 or 9 minute run.

The results of Phase I of this study gives the mean and the percentiles of all 7 tests for children between the ages of 6 to 12 based on their age or height.

With the availability of such standardized tables and charts a meaningful physical fitness award scheme can be launched in October 1990 to (1) test the physical fitness of all primary school children, (2) give relevant guidance on fitness exercises based on the individual need, (3) repeat tests after 3-4 months to evaluate the progress made, (4) select children whose physical fitness falls below the 10th percentile for medical examination and (5) publish log books containing the relevant charts and guidelines on fitness exercises to be distributed free to all school children.

Paediatricians are urged to cooperate in ruling out medical illnesses which necessitates the restriction of exercises aimed to improve physical fitness.

S.IV.7

CONGENITAL NEPHROTIC SYNDROME (CNS): DIAGNOSIS, PATHOGENESIS AND RESULTS OF RENAL TRANSPLANTATION

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Our experience with 58 infants with nephrotic syndrome in the first year of life will be reviewed. The age of onset of edema and severe proteinuria appears to be the critical diagnostic factor which was predictive of the eventual outcome and management. Only 1 of 50 CNS infants with onset <3 months of age has had a remission, whereas 6 of 8 older than 3 months have achieved remission. Early renal pathology cannot reliably identify those infants who may have remission. Management includes tube feedings (120 - 140 Kcal/kg), control of edema, infection, hypocalcemia and hypothyroidism. Bilateral nephrectomy and dialysis may be necessary to achieve growth and to facilitate ultimate renal transplantation. Further evidence that the primary defect in glomerular permeability is a deficiency of heparan sulfate proteoglycan anionic sites in the glomerular basement membrane will be presented. The results of renal transplantation in 28 infants over the past 18 years will be described.

S.IV.8

ACID-BASE DISORDERS IN RENAL DISEASES

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INTRODUCTION

Acid-base disorders are commonly encountered in pediatric practice and result from the gain or loss of either hydrogen ion or base in the extracellular space[1,2,3].
The clinical presentation depends upon the capacity of the kidneys and lungs, the organs primarily responsible for the regulation of acid-base balance, to maintain the body's pH at 7.4.

The Bronsted-Lowry definition of an acid as a substance that dissociates almost completely into hydrogen ion and its conjugate base, and a base as a substance that accepts hydrogen ion, have been universally accepted[3,4]. A strong acid dissociates almost completely into hydrogen ion and its conjugate base. A weak acid does not dissociate as readily.

BUFFERING SYSTEMS

The first line of defense against severe acid-base changes relies on the buffering systems in the blood (Figure 1). Forty-seven percent of non-bicarbonate buffers consist of hemoglobin and oxyhemoglobin, organic phosphates, inorganic phosphates, and plasma proteins[1,2]. Fifty-three percent of the buffering capacity of whole blood resides in plasma bicarbonate and the erythrocyte bicarbonate[3,4].

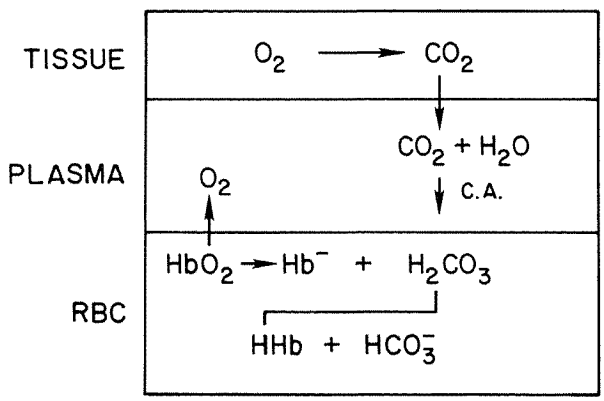

Figure 1:
Interactions between red blood cell (RBC) buffering and plasma/tissue oxygenation. Carbon dioxide (CO_2) freely diffuses from tissue into plasma and through the action of carbonic anhydrase (C.A.) combines with water (H_2O) to become carbonic acid (H_2CO_3) which dissociates into bicarbonate (HCO_3^-) and hemoglobin (Hb) buffered hydrogen ion (HHb). The oxygen (O_2) released from RBC, crossing the cellular membrane into the plasma and the reduced hemoglobin (Hb^-) stays in the RBC to serve as the buffer.

The bicarbonate-carbonic acid buffering system depends on interactions governed by the Henderson-Hasselbach equation: $pH = pK + \log \frac{HCO_3}{SpCO_2}$ where pK is the dissociation constant

of carbonic acid, HCO_3 the bicarbonate anionic component, S and pCO_2 are the solubility factor and the partial pressure of carbon dioxide, respectively. The dissolved CO_2 in plasma equilibrates with the alveolar CO_2 (Figure 2). The CO_2 and HCO_3 cross the erythrocyte membrane to equilibrate with intracellular HCO_3. The respiratory response to an acid-base disturbance is abrupt, occurring and maximizing within minutes; whereas, the renal response to an acid-base disturbance maximizes over the course of 3-5 days.

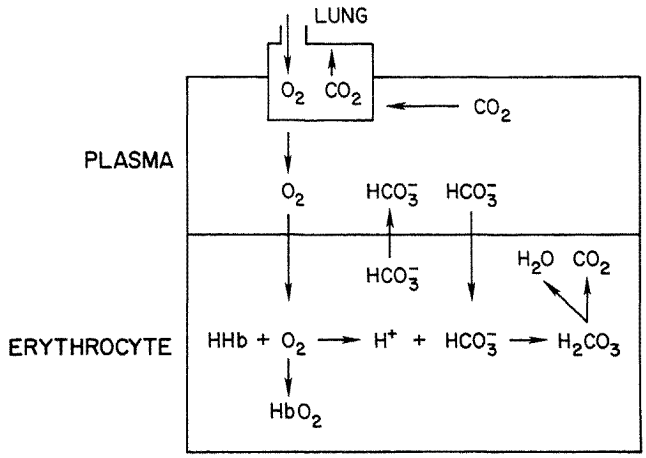

Figure 2:
The interrelationship between the CO_2 in the alveolus, the tissue and the red blood cell (RBC). Carbon dioxide (CO_2) is dissolved in the tissue and is in equilibrium with the CO_2 in the alveolar air which is exhaled through the lungs. Oxygen (O_2) enters through the lung into the tissue, passing the RBC membrane and enters into the cell. Oxygenation of hemoglobin (Hb) releases a hydrogen ion (H^+). Subsequently, the hydrogen ion reacts with bicarbonate (HCO_3^-) to form carbonic acid (H_2CO_3) which can dissociate into water (H_2O) and carbon dioxide (CO_2). The bicarbonate (HCO_3^-) freely diffuses across the cell membrane. HbO_2 = oxyhemoglobin, HHb = reduced hemoglobin.

RENAL ACIDIFICATION MECHANISMS

The kidneys are primarily responsible for the reabsorption of bicarbonate, formation of titratable acid and ammonium ions[4]. Bicarbonate reabsorption occurs primarily in the proximal tubule and is operationally linked to sodium reabsorption. The formation of titratable acid is facilitated primarily by filtered phosphate. With the pK of organic phosphate at 6.8., urinary phosphate contains considerable buffering capacity. From the glomerular ultrafiltrate's pH of 7.25 to the distal tubular urinary pH of 5.8, filtered phosphate provides the bulk of buffering capacity[1]. After the urinary pH reaches 5.6, the buffering capacity of filtered phosphate is almost exhausted and other urinary buffers, such as creatinine and uric acid begin to buffer the secreted hydrogen ion until the final urinary pH of 4.4 is reached.

In the past, ammonia formed from the action of glutaminase on glutamine was thought to diffuse out of the renal cells to buffer the hydrogen ion, resulting in the formation of ammonium[4]. However, in view of the fact that the pK of ammonia is 9.3, most available ammonia is already in the ammonium form at the glomerular ultrafiltrate pH of 7.3. This precludes urinary ammonia from acting as a urinary buffer. The current concepts[1] are as follows. The action of glutaminase on glutamine results in the formation of ammonium and bicarbonate. The reabsorption of bicarbonate regenerated by renal ammoniagenesis contributes to the normal renal handling of hydrogen ion.

METABOLIC ACIDOSIS AND ALKALOSIS IN RELATIONS TO THE KIDNEY

The two primary mechanisms accounting for development of metabolic acidosis are : 1) the gain of acid and 2) the loss of base. One example of the gain of acid is the ingestion or infusion of acidifying salts, such as ammonium chloride and arginine hydrochloride[2]. In addition, metabolic acidosis develops from lactic acid accumulation, retention of hydrogen ion due to chronic renal insufficiency or the inability to establish a sharp pH gradient across the distal tubule in renal tubular acidosis[5].

The most common cause of metabolic acidosis in infants and children is the loss of base, secondary to infantile diarrhea[4]. The loss of bicarbonate in proximal, Type II renal tubular acidosis, is another example of metabolic acidosis developing from the loss of base.

There are two primary mechanisms for the development of metabolic alkalosis: 1) the loss of acid and 2) the gain of base. Examples of the loss of acid to account for the development of metabolic alkalosis include the use of diuretics, hyperaldosteronism, vomiting such as due to pyloric stenosis and nasal gastric suction[2,3]. Accompanying the metabolic alkalosis from the loss of hydrochloric acid is the significant loss of potassium chloride which gives rise to total body potassium deficiency[6].

It is difficult in normal situations for metabolic alkalosis to develop from therapeutic excess of base because of the kidney's ability to reabsorb normally between 4,000 and 6,000 mEq/day of bicarbonate in infants and adults, respectively. Therapeutic excesses are only a very small fraction of such a large bicarbonate load being handled by the kidneys. However, if there are concurrent defects in sodium, potassium or chloride, the renal ability to handle excess base is compromised and metabolic alkalosis may then develop[6].

RENAL TUBULAR ACIDOSIS

The primary renal disease giving rise to metabolic acidosis is exemplified by classic, Type I, distal renal tubular acidosis[7]. The child presents with failure to thrive, polyuria, and polydipsia. The laboratory features are characterized by hypokalemia, and hyperchloremic metabolic acidosis secondary to a deficiency to the distal sodium-hydrogen ion exchange. The sodium lost in association with bicarbonate wasting results in volume contraction, and increased aldosterone secretion, which give rise to the renal potassium wasting and hypokalemia. The sustained metabolic acidosis requires bone buffering of hydrogen ion, resulting in hypercalciuria. The chronic metabolic acidosis also stimulates mitochondrial oxidation of citrate, resulting in hypocitraturia[8]. The reduction of this calcium chelator, in the face of hypercalciuria and alkaline urine, predispose to the consequential nephrocalcinosis, which may lead to chronic renal insufficiency.

Renal tubular acidosis is treated by giving as much alkaline therapy as is necessary to achieve sustained correction of the metabolic acidosis. In a long-term study of distal renal tubular acidosis in children it has been shown that the dosage of alkaline therapy varies from between 2 to 7 mEq/kg body weight/day. With sustained correction of metabolic acidosis in renal tubular acidosis, there is significant improvement in weight and height[7].

Renal tubular acidosis usually occurs randomly. However, there are familial cases of renal tubular acidosis which appear to be transmitted by an autosomal dominant trait[9]. Type I renal tubular acidosis can also be associated with sickle cell anemia, elliptocytosis, and Ehlers-Danlos syndrome. In addition, it should be noted that an autosomal recessive form of renal tubular acidosis in association with nerve deafness has been described[10,11]. Finally, an autosomal recessive renal tubular acidosis associated with osteopetrosis has also been described[12].

FIXED NON-METABOLIZABLE ACIDS

There are two principal categories of acids (Figure 3). The first is metabolic acids which are handled by the liver and lungs, with equilibrating CO_2 during gas exchange in respiration[13]. The second category of acids is the so-called fixed, non-metabolizable acids handled by the kidneys as net acid excretion, which consists of titratable acid and ammonium[2,13].

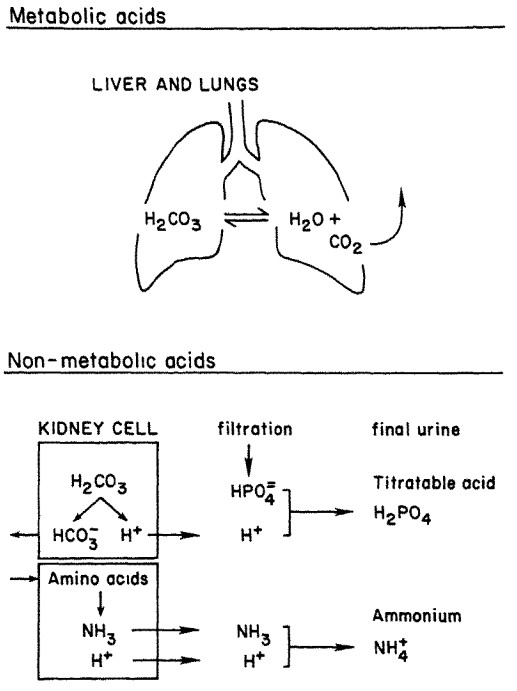

Figure 3:
The two major categories of acid: metabolizable, (metabolic acid), and non-metabolizable, (non-metabolic) acids. Carbonic acid (H_2CO_3) dissociates into water (H_2O) and carbon dioxide (CO_2) when it is exhaled through the lungs. The hydrogen ions (H^+) coming from non-metabolic acids are excreted as titratable acid, mainly phosphate ($HPO_4^=$) buffered H^+ and ammonium (NH_4^+). Carbonic acid (H_2CO_3) in kidney cells is dissociated into bicarbonate (HCO_3^-) and H^+. Through the action of glutaminase on glutamine, ammonia (NH_3) is produced.

The rate of endogenous non-metabolizable acid production from intermediary metabolism[14] has been estimated to be 1 mEq/kg/day in the adult. In order to maintain acid-base balance, the rate of net acid excretion equals endogenous acid production. It has been demonstrated that endogenous acid production can be approximated by the measurement of sulfate and organic anions in the urine[15]. This concept is visualized in Figure 4. The oxidation of methionine and cysteine result in the production of sulfate, which is excreted. For each molecule of sulfate in the final urine, 2 molecules of hydrogen ion are returned as fixed, non-metabolizable acid requiring net acid excretion. In addition, the many organic acids which are not metabolized by the liver or eliminated as CO_2 via the lungs, also obligate renal net acid excretion. Thus, by measuring urinary organic anions, this second component of endogenous acid production can be extrapolated[14,15].

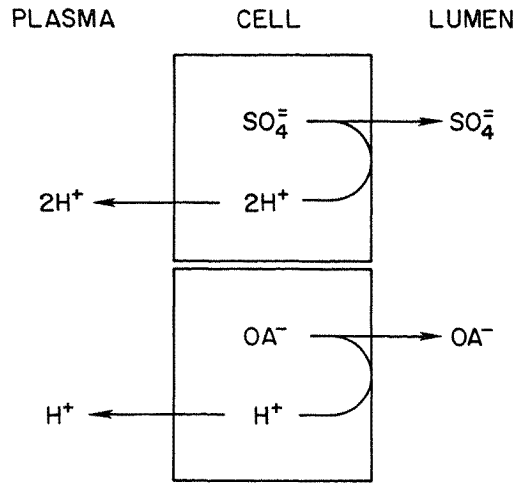

Figure 4:
Concept of Relman and associates (Relman AS, Lennon EJ, Lemann J, Jr: Endogenous production of fixed acid and the measurements of the net balance of acid in normal subjects. J. Clin. Invest. 40:16521, 1961) concerning endogenous acid production. In the metabolism of cysteine and methionine, sulfuric acid is produced. For each molecule of sulfate ($SO_4^=$) excreted into the urinary lumen, two molecules of hydrogen ions (H^+) are produced. These have to be excreted by the kidney as fixed, non-metabolizable, net acid. For each molecule of organic anion (O.A.$^-$) a molecule of H^+ is produced again obligating the renal excretion of the hydrogen as net acid. The sum of SO_4 and O.A. provides an estimation of the endogenous acid production.

Normal children or adults can handle the 1-2 mEq/kg/day (or 50 μEq/min/1.73 sq.m.) of acid production, because this is matched by an equal quantity of net acid excretion[16]. However, with impaired renal function in chronic renal failure (Figure 5), the compromised renal net acid excretory ability cannot respond to the acid load, and metabolic acidosis is encountered.

METABOLIC ALKALOSIS

A close interrelationship exists between alkalosis and potassium depletion[6]. It appears that metabolic alkalosis begets potassium depletion. Initially prompted by the renal excretion of bicarbonate in response to metabolic alkalosis, the bicarbonate excretion is accompanied by potassium excretion. This potassium loss is further aggravated by continued vomiting and significant potassium depletion may ensue. If metabolic alkalosis and potassium depletion persist, the kidneys paradoxically begin to excrete an acid urine instead of an alkaline urine. The mechanism for this "paradoxical aciduria" is complex[6]. This is most likely the result of hypochloremia which prevents adequate proximal reabsorption of sodium, resulting in the need for large sodium reabsorption in the distal tubule. In the face of severe potassium depletion, this ion is retained and the other positively charged hydrogen ion is excreted. This then is the best explanation for the "paradoxical aciduria" of metabolic alkalosis. When this chloride deficiency is reversed despite continued potassium deficiency, the "paradoxical aciduria" is averted and bicarbonaturia is resumed, resulting in correction of the alkalosis.

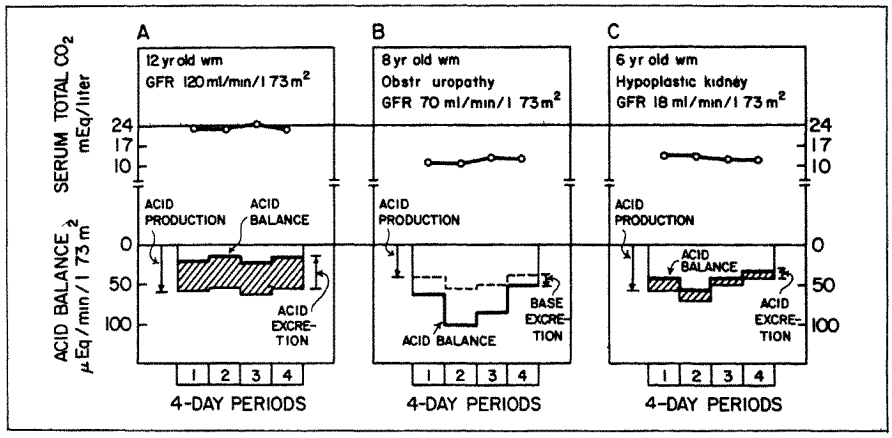

Figure 5:
Net acid balance in a normal subject and in patients with chronic renal insufficiency. A: In physiological conditions, normal acid production of 50-60 μEq/min/1.73 sq.m. is balanced by an almost equal amount of net acid excretion. With acid balance, the serum CO_2 remains in the normal ranges. B: Net acid balance in an eight-year-old, white male (WM), with obstructive uropathy and a reduced glomerular filtration rate (GFR) 70 ml/min/1.73 sq.m. The endogenous acid production remains about the same, but there is net base excretion resulting in positive balance of acid ranging from between 60 to 100 μEq/1.73 sq.m. This is reflected in the development of metabolic acidosis with serum total CO_2 of 10 mEq/L. C: Six-year-old, white male with hypoplastic kidney and glomerular filtration rate of 18 ml/min/1.73 sq.m. The net acid excretion being significantly impaired resulting in positive net acid balances of 50 μEq/min/1.73 sq.m. This is reflected in the sustained metabolic acidosis of serum total CO_2 of 10 mEq/L. From Chan JCM: Nutrition and Acid Base Metabolism. Fed Proc 40:2423-2428, 1981.

Metabolic alkalosis may also result from various chloride deficiency syndromes[17,18], such as congenital chloride diarrhea, surreptitious vomiting, the vomiting of pyloric stenosis, hydrochloric acid gastric suction, cystic fibrosis, and the milk chloride deficiency syndrome. In addition, Bartter syndrome and diuretic abuses are additional causes of metabolic alkalosis.

Bartter syndrome[19] is usually associated with hyponatremia, metabolic alkalosis and hypokalemia. The primary chloride reabsorption defect in the loop of Henle results in renal potassium wasting, hypokalemia, and elevated prostaglandin E_2. Despite elevated plasma renin activity and angiotensin II concentrations, the blood pressure of patients with Bartter syndrome is normal because of the vasodilatory effect of the elevated PGE_2. This syndrome may be associated with growth retardation if the onset of Bartter syndrome is in a child who is less than five years of age. Other typical features are defective renal concentration, possibly secondary to the persistent hypokalemia, and juxtaglomerular apparatus hyperplasia. The treatment is to remove the underlying cause and to provide potassium chloride at 1-2 mEq/kg day in 3-5 divided doses. Occasionally, the addition of spironolactone, 15 mg/kg/day, or triamterine, 10 mg/kg/day or amiloride, 0.3 mg/kg/day has been helpful[19]. If hypomagnesemia is encountered, careful doses of magnesium sulfate, 10-15 mEq/kg/day should also be administered[19].

SALICYLATE INTOXICATION

Salicylate has three primary actions which have a bearing on acid-base balance. It increases alveolar ventilation and also CO_2 production. Hyperventilation and respiratory alkalosis are

paramount features of salicylate overdose. In addition, salicylate increases the production of organic acids and may result in the development of metabolic acidosis[20]. It is the interplay between the degree of respiratory alkalosis and metabolic acidosis which determines the final blood pH. The treatment is to provide enough fluid and to alkalinize the urine, due to the increased solubility of salicylate in alkaline urine. Special therapeutic measures, such as peritoneal dialysis are indicated if there is semi-coma or coma, convulsions, marked hyperventilation, oliguria or respiratory depression and pulmonary edema[21]. These clinical features are reflected by a profound depression in plasma bicarbonate, and pCO_2 elevated, steady state, plasma salicylate concentration and rising blood urea nitrogen[22].

ACKNOWLEDGEMENTS

Supported by National Institutes of Health Grants RO1 31370 and T32 DK 07526-02. The authors thank Marilyn Reilly for secretarial assistance and Martha D. Massie, R.D., for editorial assistance.

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S.IV.9

TWO DECADES OF BONE MARROW TRANSPLANT (BMT) - REVIEW OF PUBLISHED RESULTS

M.Y. Cheng
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A literature review was made on the mortality and morbidity data in BMT in paediatric patients.

The study groups included : (1) Acute lymphoblastic leukaemia (2) Acute non-lymphoblastic leukaemia (3) Leukaemia in Down's syndrome (4) Infant leukaemia (5) Chronic myelogenous leukaemia (6) Preleukaemic syndromes (7) Solid tumours (8) Severe aplastic anaemia (9) Fanconi anaemia (10) Dyskeratosis congenita (11) Osteopetrosis (12) Thalassaemia major (13) Congenital immunodeficiencies (14) Hereditary metabolic disorders.

Most of these studies had small number of patients and short follow-up. However, the data presented represent the best knowledge that we know up to today regarding BMT in children. The data are sometimes useful in counselling of patients for BMT. In children with acute leukaemia, we are badly in need of data on the morbidity and mortality of a group of new leukaemics who eventually end up having BMT.

PROCEEDINGS OF THE SCIENTIFIC MEETING

Posters

P.1

AN UNUSUAL CAUSE OF SCOLIOSIS AND LEG LENGTH DISCREPANCY

W. Goh[1], T. Ng[2], C.F. Fung[3], V. Wong[1]
[1]Departments of Paediatrics, [2]Pathology and [3]Surgery, University of Hong Kong

A 2-year-old boy with normal perinatal history and development was referred to orthopaedic surgeons for scoliosis and unequal limb length. The child was referred to the paediatrician for assessment. MRI of the spinal cord showed syringohydromyelia at T4 to T6 and T8 to T11 levels with enlarged cord at C6 to T2 levels. Neoplastic lesion had to be excluded. The child subsequently had a laminectomy from T8 to T11 and was found to have ganglioglioma involving whole spinal cord.

Ganglioglioma is a rare CNS tumour accounting for 0.4% to 7.6% of intrinsic CNS tumours. They occur most frequently in children and young adults, 80% of cases presented before the age of 30. They are commonly found in the cerebral hemisphere especially temporal lobes, floor of 3rd ventricle, brainstem, cerebellum. Spinal cord is an uncommon site, there are only 15 cases of spinal gangliogliomas reported so far. The majority (11) cases are in the cervical cord and only one with the whole spinal cord being involved.

A brief summary on the clinical picture, radiological finding, histological features, prognosis and treatment of ganglioglioma will be presented.

P.2

THE OUTCOME OF PREMATURE INFANTS

W. Goh, V. Wong, K.Y. Wong
Department of Paediatrics, University of Hong Kong

The outcome of premature infants being referred to the Duchess of Kent Child Assessment Centre in the period July 1985 - December 1989 was reviewed.

196 patients aged between 5 months and 19 years were included for analysis. 16 children were excluded because of conditions like trisomy, dysmorphism, congenital infection which could contribute to physical and mental delay. Among 196 patients, 114 (58%) were physically and mentally normal. Of the remainder 82, 69 have cerebral palsy, diplegia in 40 (49%), quadriplegia in 11 (13%), hemiplegia in 7 (8.5%), triplegia in 4 (5%), mixed C.P. in 4 (5%), one each with ataxia, dyskinesia and monoplegia. 2 children had clumsiness. 11 children under age of 3 had delay in neuromaturation. 12 children had visual impairment and 11 had hearing impairment. 10 developed hydrocephalus.

The functional morbidity and intellectual function of children above age 3 with physical handicap are analysed.

P.3
A CLINICAL DOCUMENTATION OF PAEDIATRIC GAIT
Vivian Chan Bacon-Shone
Duchess of Kent Children's Hospital, Child Assessment Centre, Hong Kong

This paper introduces the Gaitway system, using a small group of children aged between four and eight years who are either normal in their development or who only have a disarticulation problem. The study was done in the physiotherapy department of Duchess of Kent Children's Hospital. Six walking trials were recorded, with three trials recorded barefoot and three with shoes. A walking distance of about 10-13 steps was recorded in each walking trial. The system provides an easily applicable clinical tool for the measurement of the temporal and spatial parameters of walking. These parameters include the step length, stride length, single support time, double support time, cadence and maximum velocity of the gait cycle. The study serves as a pilot investigation into the normal variation of these parameters in growing children. The data was also related to the height and intelligence quotient of the children. The system is easy to operate, but requires some cooperation from the child in order that useful measurements can be recorded. It appears to be a useful piece of equipment for highlighting different gait characteristics and for the documentation of walking patterns.

P.4
BRAINSTEM EVOKED POTENTIAL STUDY IN CHILDREN WITH AUTISTIC DISORDER
V. Wong, S.N. Wong
Department of Paediatrics, University of Hong Kong

Brainstem auditory evoked potential (BAEP) was compared in 109 children with infantile autism (IA), 38 children with autistic condition (AC), 19 mentally retarded (MR) and 20 normal children. The brainstem transmission time (BTT) was significantly increased in both the IA and AC groups as compared to normal and in the IA versus MR group. There is no difference in BTT between IA and AC groups. The autistic characteristic may be related to dysfunction of the brainstem which affects the processing of the sensory input through the auditory pathway. The brainstem lesion may be part of a generalised process of neurological damage that accounts for the deviant language, cognitive and social development in autistic disorder.

P.5
OUTCOME OF BABY WITH SEVERE BIRTH ASPHYXIA
B. Lam
Department of Paediatrics, University of Hong Kong

The perinatal events of 40 term neonates who had severe birth asphyxia were reviewed and correlated with the neurological outcome at a mean age of 2 1/2 years. Severe birth asphyxia was defined as Apgar Score of ≤ 3 at 1 min or severe neurological abnormalities attributed to perinatal hypoxia. Majority (68.5%) of the babies had abnormal fetal heart pattern before delivery. Persistent fetal bradycardia was most likely to be associated with poor outcome. The neurological staging, the need for assisted ventilation for more than 24 hours and severe renal impairment were the best predictors of neonatal death and subsequent poor neurological outcome. None of these babies had necrotising enterocolitis. The overall mortality was 10% and 14.2% of babies had moderate to mild neurological sequelae.

P.6
NEONATAL HYPERBILIRUBINEMIA IN CHINA
GUAN Xiji
Sun Yat-Sen University of Medical Sciences, Guangzhou, Guangdong, People's Republic of China

In China, hyperbilirubinemia is still one of the most important sign in neonatal period. The main causes of neonatal hyperbilirubinemia in 514 cases from 1983 to 1985 were infection, blood type incompatibility, G-6-PD deficient in order. In both data of 268 hospitalized neonates of infection and 302 neonates of autopsy showed that sepsis was the first important cause of death. More BO incompatibility in Northern whereas AO in Southern China.

Modified Brewer test was used as a screening method to estimate methemoglobin reducing rate. Nitroblue tetrazolium method was used to quantitate G-6-PD activity. Three groups have been studied in G-6-PD deficiency since 1977: (1) Prenatal preventive group, consisting of 42 families: 11 deficient neonates with a previous family history of infant loss due to pathological jaundice or G-6-PD deficiency; 31 with one or both parents deficient in G-6-PD. For prospective mothers who were likely to give birth G-6-PD deficient neonates, phenobarbital and/or Chinese herbs were prescribed; (2) Cord blood screening group, consisting of 66 neonates, whose cord blood were to be G-6-PD deficient; (3) Morbidity group, consisting of 282 neonates, diagnosed to be G-6-PD deficient. The neonates of group (1) and (2) were similarly prevented with phenobarbital. The results of prenatal preventive method showed that it is a more effective way to prevent and treat neonatal hyperbilirubinemia.

P.7
CLINICAL GENETIC DISORDERS IN TAIWAN
Tso-Ren Wang
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Clinical approach to genetic syndromes relies on the personal and family histories, the measurements and the "total pattern" of anomalies. Achondroplasia, Cornelia de Lange syndrome, Freeman-Sheldon syndrome, hypohidrotic ectodermal dysplasia, Klippel-Trenaunay-Weber syndrome, neurofibromatosis, osteogenesis imperfecta, rhizomelic chondrodysplasia punctata, tuberous sclerosis, Waardenburg syndrome, and X-linked hypophosphatemic rickets are examples in our study population.

Cri du Chat syndrome, Down syndrome, Turner syndrome are rather common in our cytogenetic studies.

Accompanied by the clinical information, biological material especially urine from the patients is put on multicomponent analytical system. Quantitative detection of amino acids by ion exchange chromatography and gas chromatography mass spectrometry for organic acids provide facilities for the research, diagnosis and follow-ups of phenylketonurias and methylmalonicacidemia.

P.8
MUTATIONAL ANALYSIS OF DUCHENNE/BECKER MUSCULAR DYSTROPHY (DMD/BMD)
Y.L. Lau[1], G. Srivastava[2], V. Wong[1], K.H. Fu[2], F. Ho[2], C.Y. Yeung[1]
Departments of [1]Paediatrics and [2]Pathology, Queen Mary Hospital

Duchenne and Becker muscular dystrophy (DMD/BMD) affects approximately 1 in 3000 male births. There were no reliable methods of carrier detection and prenatal diagnosis in this disease until the recent advances in elucidating the dystrophin gene. The aim of this study is to define the mutations of patients from 23 DMD/BMD families with the cDNA probes from Dr. L. Kunkel in order to provide genetic counselling. The cDNA probes used are 1-2a, 2b-3, 4-5a, 5b-7 and 8. Two restriction enzymes (Hind III/Bgl II) were used for most of the probes. The methodology is the established Southern blotting using DNA extracted from peripheral white blood cells. Deletional mutations were detected in 7 families using probe 8 with both Hind III and Bgl II. Mutations giving rise to novel fragments with and without deletions were detected in 2 families using probe 5b-7 with Bgl II. In 1 family, deletion was detected with probe 2b-3. The frequency of mutations detected so far is 44 % and the major sites of mutations are the same as those reported in Caucasians. Prenatal diagnosis and carrier detection will be feasible in these 10 families.

P.9

A REVIEW OF MULTIPLE CONGENITAL ANOMALY SYNDROMES IN HONG KONG

S.T.S. Lam and A.S. Chau
Clinical Genetic Service, Department of Health, Hong Kong

The study of multiple congenital malformations (MCA) disorders occupies a central position in medical genetics. During a seven years' period, 3996 index patients and their families were referred to the Clinical Genetic Service. Of the probands, 1707 were diagnosed as MCA syndromes. This represented 42.7% of total referrals. Ten commonest conditions accounted for 53% of patients suffering from this category of genetic diseases. These included Down syndrome, Turner syndrome, trisomy 18, trisomy 13, Noonan syndrome, hemifacial microsomia, Cornelia de Lange syndrome, Cri du Chat syndrome, Prader Willi syndrome and Williams syndrome. A multidisciplinary approach is emphasized in the diagnosis and management.

P.10

AIR POLLUTION, RESPIRATORY SYMPTOMS AND ASTHMA IN CHILDREN OF HONG KONG

AJ Hedley[2], A Tam[1], J Liu[2], CM Wong[2], J Chan[2], TH Lam[2], SG Ong[2].
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To determine whether atmospheric pollution in Hong Kong is related to an increased incidence and prevalence of respiratory symptoms, respiratory diseases and asthma, 3859 children aged from 8 to 10 studying in 11 different primary schools were interviewed and examined in April/May 1989. 2016 children were from schools located in Kwai Ching district (KC), a highly industrialized and densely populated area with poor air quality standards, while 1843 were from Southern District (SD), which is principally residential and less polluted. 3732 parents responded to a respiratory health questionnaire, while all children answered a supervised questionnaire. Physical examination and spirometry were performed in 3590 children. The 2 groups were comparable in height, weight, and gender.

Preliminary analysis of the 11 schools indicated that more children from KC had frequent episodes of sore throat, phlegm, wheeze, and consulted their doctors more often. However, there was no significant difference in the reported prevalence of asthma (8%) in the two districts. More parents and children were current or ever smokers in KC than SD; 15% of boys and 6% of girls had smoked by age 10. On examination, more KC children had cough and chest deformity. Spirometry values were not significantly different between the 2 districts. In 3.1% of children, FEV_1/FVC was <0.8. Respiratory morbidity appears to be more common in KC children. A histamine challenge test will be done as a followup to confirm the declared asthmatic status of the children. In a pilot study 94 subjects were tested. Histamine challenge had a sensitivity of 78% (7 out of 9 asthma cases detected) and a specificity of 75% (64 out of 85 non-asthma identified).

P.11

A STUDY ON THE USE OF VOLMAX IN CHILDHOOD

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Oral preparations of bronchodilators are still very useful for asthmatic children who have difficulties to learn how to use inhalation preparations properly. An open clinical trial was conducted on two groups of asthmatic children to compare the effects of the two kinds of oral bronchodilators, Volmax and Theo-Dur. The results, expressed as the changes in pulmonary functions, PEER and the "asthmatics diary" (symptom records), indicated that while having equal therapeutic benefits, Volmax produces less side effects than Theo-Dur; and for using Volmax, individualization of doses and monitoring of serum concentration are not needed as with Theo-Dur. Therefore, we conclude that Volmax is a nice alternative drug in treating childhood asthma.

P.12

SURFACTANT REPLACEMENT THERAPY IN RDS

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Since Fujiwara (1981) reported the successful result of surfactant replacement therapy in RDS, several surfactant preparations from different species were developed. The results of clinical trials from these preparations all demonstrated that surfactant replacement can improve lung mechanics and hypoxemia in RDS babies. This is a pilot clinical trial of surfactant replacement therapy.

PATIENTS AND METHODS

Four babies were involved in this study. The mean birth weight was 1862 ± 390 g, the mean gestational age was 34.5 weeks. The diagnosis of RDS was confirmed on clinical basis and X-ray findings. All babies were admitted before 6 hours of age and received mechanical ventilation through endotracheal tube. A surfactant preparation from calf (Infasurf, Ony Inc. N.Y.) was slowly instilled into each bronchus before 12 hours of age with a mean total dose of 114 mg/kg (47-164 mg/kg). Two babies received Infasurf twice, the intervals of the two administrations were 20 and 46 hours respectively. For better distribution of surfactant, the preparation was given in aliquots within a period of 10 to 30 minutes.

The transcutaneous oxygen tension levels were recorded with a Radiometer transcutaneous blood gas monitor during the course of the treatment. Chest films were taken before and after surfactant administration. The granularity, air bronchogram and opacity on the X-ray film were evaluated with a scoring method (scoring 1-4, 4 represented the most severe case).

RESULTS

After surfactant instillation, the mean transcutaneous oxygen tension increased from 73 ± 53 to 163 ± 60 mmHg within 3 hours; in some cases the oxygen tension reached the highest level within 30 minutes. Generally speaking, the period of improved oxygen tension did not persist longer than 12 hours. The chest films showed improvement of atelectasis by the presence of much better aeration. The scores of the X-ray findings are shown in table 1. After surfactant administration the granularity, the air bronchogram and opacity were all improved.

Table 1. Effect of surfactant on X-ray scores of RDS babies

	Granularity	Air bronchogram	Opacity
Before treatment	2.5	2.0	2.5
After treatment	1.3	1.3	1.5

(The results are the mean of scores of 6 pairs of x-ray films)

Regarding prognosis, one baby was extubated after 4 days mechanical ventilation and was discharged at the age of 20 days. Two babies died of intracranial hemorrhage at 3 and 4 days respectively. The treatment was discontinued in one baby at the age of 6 days due to pneumonia.

DISCUSSION

Although surfactant administration has been shown to be efficacious in the treatment of RDS, more detailed information concerning its clinical applications are not available. From our limited pilot study, we believe that the following points are important and should be considered in future clinical trials.

1. We need more reliable methods for the assessment of surfactant function in RDS babies. We can obtain useful information from serial blood gas analyses and X-ray examinations, but we need more specific methods in biochemical and physiological studies, e.g. the phospholipid assay on tracheal aspirates can reflect the components of surfactant on the surface of alveoli and the measurement of total compliance can reflect the lung mechanics.

2. The method of surfactant instillation is most critical. The position of the endotracheal tube should be in the right place, i.e. main trachea. For prevention of vigorous cough, which can blow out the instilled surfactant, the preparation should be given very slowly and in small aliquots. The body position should be changed during the course of instillation.

3. The effectiveness of Infasurf was evidenced by the improvement of hypoxemia and atelectasis. However, the duration of improvement varied considerably. In some cases it was no longer than 12 hours, which might be partly due to the production of exudative protein which inhibited the surfactant function. Our pilot study suggested that in high risk RDS infants, a single dose of surfactant was not enough and it was of important to offer an additional dose.

4. There are many complications in premature newborns with RDS. It is difficult to clarify the influence of surfactant administration on the complications of RDS because of small number of cases in this pilot study. Nevertheless, our result indicated that the survival rate of RDS depended not only on surfactant therapy but many other factors also. Therefore, for the efficacious application of surfactant therapy and decrease of the mortality of RDS, sophisticated perinatal care for prevention and treatment of other complications is warrented.

* Project supported by the fund of national natural sciences

Acknowledgement

We are indebted to Goran Enhorning M.D. for his kind help in giving Infasurf for experiment. We wish to thank Shu Jin Shen M.D. for her kind help in editing the manuscript.

P.13

HAEMATOLOGICAL FINDINGS ON β-THALASSAEMIA TRAIT IN HONG KONG CHINESE

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The study aimed to collect haematological data from 98 parents who were obligatory β-thalassaemia trait (βTT) because they have children diagnosed to have β-thalassaemia major. Nativity in all except three was Guangdong Province. Laboratory determinations conducted on venous blood samples included haemoglobin (Hb), red cell count (RCC), haematocrit, mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC), preparation for Hb H inclusion bodies, Hb electrophoretic study, quantitation of Hb A_2, Hb F, and serum ferritin (S.F.) levels. The mean Hb level was 13.2 ± 0.9 g/dl for male, 11.6 ± 1.0 g/dl for female. MCV, MCH, MCHC, Hb A_2, and F levels showed no sex difference. All had S.F. greater than 12 ng/dl. MCV, directly measured by the electronic Coulter Counter, was less than 80 fl in all parents. MCV is more useful than Hb level in the detection of trait carriers and the above data supported MCV 80 fl as the effective cut off point in the screening for βTT in the Hong Kong population.

P.14

CORD BLOOD IMMUNOGLOBULIN AND COMPLEMENT LEVELS IN PREMATURE AND TERM NEWBORNS IN HONG KONG.

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Complement and immunoglobulins are integral parts of humoral immunity. Their lower levels in premature newborns is contributory to their susceptibility to infection. Levels of complement and imuno globulins vary with different populations and with different methods of measurements. In order to determine the levels of C_3, C_4, IgG, IgM, and IgA in Chinese newborn infants of varying gestational age, 449 consecutive samples of cord blood were collected and the levels measured by a centrifugal analyser (Cobas Bio, Roche). Maturity ranged from 24.3 to 43.6 weeks and birth weight ranged from 0.75 to 4.05 kg. Among them 74 were SGA infants, 351 were AGA infants and 24 were LGA infants. The relationship between maturity (M) and IgG (G) was determined by linear regression to be : $\log G = 2.11 + 0.024\ M$ ($r=0.57$, $p<0.0001$). The corresponding equation for C_3 and C_4 were : $\log C_3 = 2.26 + 0.040\ M$ ($r=0.42$, $p<0.0001$); $\log C_4 = 0.85 + 0.043\ M$ ($r=0.32$, $p<0.0001$).

Compared to studies from other populations, the slope of the curve relating IgG to maturity was smaller, reflecting a higher level of IgG in the very immature infants. This was true even when corrected for SGA infants. Also the IgG levels reached full term values earlier compared to studies in other populations. The levels of C_3, C_4, IgM and IgA are comparable to other populations. These data suggest a more mature placental function in Southern Chinese mothers compared to those in other countries.

P.15

ABNORMAL RENAL AND SPLANCHNIC ARTERIAL DOPPLER PATTERN IN PREMATURE BABIES WITH SYMPTOMATIC PATENT DUCTUS ARTERIOSUS

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Patent ductus arteriosus is frequently implicated to cause ischaemia to major organs by diastolic shunting of blood from aorta to pulmonary artery. We studied the blood flow velocity pattern in the thoracic descending aorta (Ao), celiac(CA), superior mesenteric(SMA) and both renal arteries (LRA, RRA) by pulsed Doppler technique in 8 premature babies with PDA before (Pre) and after (Post) its closure by surgery or indomethacin, and compared them to 9 normal babies (N) of similar maturity and birth weight. Relative magnitude of diastolic to systolic flow was measured semiquantitatively by the ratio of velocity-time integral in the diastolic to that in systolic phase (A_d/A_s).

The Doppler pattern before treatment showed that diastolic flow was reversed in the aorta, SMA, RRA and LRA, and was diminished in CA. After closure of PDA, flow became forward in all arteries studied, which was similar to the Doppler pattern in normal babies. A_d/A_s ratio was negative and significantly smaller in all arteries in Pre group as compared to Post or N group.

Our data supports the diastolic steal phenomenon in PDA which may contribute to ischemic damage to abdominal organs in premature babies.

P.16

SONOGRAPHIC FINDINGS IN INFANTS WITH PURULENT MENINGITIS

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Fifty-three cases with purulent meningitis scanned by realtime ultrasound through fontanelle from September 1987 to August 1989 in Shanghai Children's Hospital were reviewed. A series of abnormal findings including echogenic sulci, extra-axial fluid collections, ventriculomegaly, abnormal parenchymal echogenicity, evidence of ventriculitis and brain abscess and cystic degeneration were observed in 36 cases with complications. These findings directly reflect the pathological changes in the brain, therefore, sonography is indicated in those patients with meningitis who are suspected clinically with complications, being an imaging modality of choice as long as the fontanelle is open. This retrospective study shows the significance of sonography in diagnosis, guidance of treatment and prognosis of purulent meningitis. The necessity of periodical follow-up by ultrasound is also emphasized.

P.17

A STUDY OF CELL-MEDIATED IMMUNITY IN HISTIOCYTOSIS X

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To clarify changes in cell-mediated immunity in histiocytosis X (HX), we detected T-lymphocyte subsets by using Leu system monoclonal antibodies and lymphocyte transformation (LT) in 42 cases with HX and 30 control children. The results showed that Leu 3a (18 ± 7.6) of pre-treated (PT) cases was significantly lower than that (29.4 ± 8.4) of control group ($p < 0.001$) and Th/Ts ratio declined in PT cases (0.71 ± 0.26) as a results of Th decrease. After a period of 6 to 8 months treatment, Th reached normal level. The value of t-cell subsets were found normal in cured cases. The LT activity was found significantly decreased in early stage HX cases; and after treatment for 6 to 8 months, LT returned to normal level, but their Ts response to ConA remained lower than that of control group. The LT response of cured HX were similar to those control group. These results suggested that HX is associated with changes in cell-mediated immunity, esp. with T-cell subsets abnormality, and that detection of T-cell subsets and cell-mediated immunoactivity may be useful in monitoring the therapeutic effects and prognosis of HS. Since 1982, 41 cases with HX who had multiple organ involvements were treated with both chemotherapy and thymic extract, 87.8% of the cases went into remission. This finding suggested again the association between HX and abnormal immunoregulatory mechanism.

P.18

SERUM IMMUNOGLOBULIN CONCENTRATIONS IN HEALTHY CHINESE CHILDREN

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This study was undertaken to establish reference ranges for serum Ig concentrations in over 800 healthy Chinese aged 0.1 year old to adulthood. The various Ig isotypes were measured by rate nephelometry (COBAS BIO, Roche). The standard serum was standardised against the WHO reference. The inter-assay variation was 5 - 10% of the mean for all 3 Ig isotypes. The serum IgM concentrations were consistently higher in females than in males in all age groups. The raw data were log normalised and the mean ± 1.96 SD of the log value are presented after anti-log as following:

Age(years)	Number(M/F)	IgG(mg/dL)	IgA(mg/dL)	IgM(mg/dL)
0.2(0.1-0.3)	41(19/22)	513(269-977)	16(<10-44)	50(26-100)
0.5(0.4-0.6)	36(13/23)	427(251-724)	22(<10-51)	68(37-123)
0.85(0.7-1.0)	28(16/12)	537(331-871)	32(11-93)	98(39-245)
1(0.6-1.5)	53(27/26)	568(346-932)	33(13-86)	94(43-207)
2(1.6-2.5)	32(23/9)	724(447-1148)	48(20-112)	110(54-219)
3(2.6-3.5)	42(18/24)	871(525-1445)	78(45-112)	138(81-229)
4(3.6-4.5)	92(41/51)	912(617-1349)	100(46-214)	141(72-269)
5(4.6-5.5)	173(82/91)	933(617-1445)	118(58-240)	141(71-282)
6(5.6-6.5)	120(58/62)	955(676-1349)	123(63-234)	141(72-275)
8(6.6-9.5)	60(36/24)	1000(724-1380)	126(68-229)	129(65-257)
11(9.6-12.5)	57(39/18)	1000(661-1514)	123(52-282)	126(65-240)
14.5(12.6-16.5)	50(25/25)	1288(851-1950)	178(81-380)	162(79-324)
>16.5(adults)	80(30/50)	1367(900-2080)	246(134-453)	156(66-366)

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