Vol. XXVI No. 2 DECEMBER 1971

The Medical Journal of Malaya

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Editorial

The Institute for Medical Research, Kuala Lumpur

by A.A. Sandosham

THIS YEAR THE I.M.R. celebrated its seventieth birthday by opening its doors to the public. Huge crowds, which included the King and Prime Minister, invaded the premises for the first time and were given the opportunity of learning of the work of the Institute. Judging by the interest shown, it would appear there was need for a Public Relations Officer on the staff of the Institute. This seems to be a suitable occasion for the medical profession of Malaysia to look back on the origin and establishment of the Institute, its achievements in the past and its promises for the future.

The large-scale opening up of the country for agriculture, mining and trade with imported labour having little or no immunity to local infections towards the end of the last century brought in its train much morbidity and mortality. The need to study tropical diseases on the spot became apparent. Sir Frank Swettenham, the then President-General of the Federated Malay States, was a man of vision and saw this need and fostered the means for medical research in Malaya. He said: "These States have prospered exceedingly and I cannot imagine any better use to which some of our means may be devoted than a scientific and sustained research into the causes and, if possible, the means of preventing and curing such scourges as beri-beri and all forms of malarial fever . . . . ."

The time was opportune for the establishment of a research institute and the first Director, Dr. Hamilton Wright, arrived in 1900 and the institute was formally opened in February 1901. Since its foundation, there has been a steady output of pioneering work by the staff on beri-beri, malnutrition, malaria, typhus, filariasis, dysenteries, leptospirosis, melioidosis, helminthiasis, virus infections and blood diseases, to mention only a few of the main lines of enquiry.

The Institute has undertaken the production of vaccines against small-pox, typhoid, cholera and rabies. There have been many calls on the vaccine production department during local outbreaks and for prevention of diseases. The sale of vaccines is at the same time a source of revenue to Government and the unit has now moved into more spacious accommodation in Petaling Jaya.

Another important function of the I.M.R. is the laboratory diagnostic service provided for the hospitals, clinics and health centres. The ever-growing demand of clinicians and health workers on the laboratory divisions has been a source of strain on the staff who have perforce to neglect their research, the primary objective in founding the institute. It is necessary for the clinical laboratories of the General and District Hospitals to undertake more and more of the routine diagnostic work and turn to the I.M.R.

only for the more complicated techniques and as a reference laboratory for the country as a whole.

This requires adequate numbers of laboratory staff of all categories – professional (medical and non-medical scientists) and technical, and the I.M.R. has undertaken the additional task of training laboratory staff for itself and the hospital and health centre laboratories throughout the country. Young doctors are prepared for higher qualifications in pathology, biochemistry, bacteriology, haematology, etc. before being sent abroad. Courses of studies are organised at the I.M.R. for training students as medical laboratory technologists.

The I.M.R. is now recognised as the national centre for the Central Coordinating Board for Tropical Medicine, one of the offshoots of the Southeast Asian Ministers of Education Organisation. As such, it undertakes 6-month courses for doctors, veterinarians and scientists of the Southeast Asia region, leading to the postgraduate Diploma in Applied Parasitology and Entomology. I.M.R. is, no doubt, qualified to undertake post-graduate training and, in fact, at one stage attempts were made to incorporate the institute into the Faculty of Medicine of the University of Malaya for this purpose.

Teaching at post-graduate level, however, would have been an almost impossible task but for the assistance given by the staff of the Hooper Foundation and the U.S. Army Medical Research Unit. Since the war, close liaison has been established with USAMRU, the US Public Health Service and the Hooper Foundation (University of California Medical Research and Training programme) who have brought their staff of researchers, equipment and finances to work in the premises and, in collaboration with the I.M.R. staff, on the health and medical problems of this country. The value of this arrangement was particularly obvious when with Merdeka, rapid Malayanisation was encouraged by giving attractive terms of compensation to the expatriates to leave the public service. This particularly affected the I.M.R. adversely as it was found that there were hardly any local researchers on the senior cadre and it was the availability of visiting scientists that helped the I.M.R. tide over the doldrums it had got into at one stage.

It is now rumoured that a Medical Faculty of the Universiti Kebangsaan may be established in association with the General Hospital and the I.M.R. If that is so, it is inevitable that some of the I.M.R. staff will be required to help in the teaching, especially in the para-and pre-clinical subjects. While all this is good and helpful for the quick development of the medical services of the country, there is a real danger that the primary objective of the foundation of the institute, namely research, will be receiving less and less attention as the urgency for the training of medical technologists, scientists, health workers and vaccine production and the need for the expansion of the diagnostic services for the medical department looms large.

Septic abortions

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SEPTIC ABORTION is a serious complication in early pregnancy and carries a high morbidity and mortality. It is difficult to find out the exact incidence of septic/criminal abortion in a population for the patients would not admit to a criminal abortion. Further, even if there were clinical signs of interference they would strongly deny it.

The only data available are those studies done on hospital admissions. In 1961/1962 Hooi, in a study of 1,000 cases of abortions at the General Hospital, Kuala Lumpur, had 239 cases of septic abortions, giving an incidence of 23.9 per cent.

The above study was carried out at the General Hospital, Kuala Lumpur, with a twofold aim:

(a) To study the clinical pattern of the disease

(b) To see if the introduction of the National Family Programme had any impact on the incidence of septic abortions.

Method and Material

This retrospective study was carried out at the Department of Obstetrics and Gynaecology, General Hospital, Kuala Lumpur. The cases under study were 1,000 abortion cases picked at random over the period 1968 to 1969. From these 1,000 cases, all the septic abortion cases were taken out for the study.

Diagnostic Criteria for Septic/Criminal Abortion

The following criteria were used:-

1. A confession or admission of criminal interference of the pregnancy.
2. Circumstantial evidence derived by clinical examination:-
   (a) Evidence of interference – trauma to vagina or cervix, foreign body in the vagina or in the cervical canal.
   (b) Evidence of complication, pelvic or abdominal peritonitis, septicaemia, perforation of the gravid uterus, and tetanus.
   (c) A temperature above 100.4° F. In the absence of temperature any evidence of intra or extra uterine sepsis as evidence of foul discharge through the cervical os.

Data:

The data obtained were tabulated as follows:

Table I

Incidence of septic abortion

Diagnosis	No. of cases	Incidence
Threatened abortion	210	21.0%
Incomplete/complete abortion	735	73.5%
Septic abortion	36	3.6%
Missed abortion	16	1.6%
Habitual abortion	3	0.3%
	1,000	100%

Table I shows that the incidence of septic abortion in 1968/1969 was 3.6%, a dramatic fall from 23.9% in 1961/1962 (Hooi 1963)

Table II Ethnic Group/Age of septic abortion

Ethnic	Age						
Group	15-19	20-24	25-29	30-34	35-39	40	Total
Malay	1	4	2	1	3	0	11
Chinese	1	3	6	0	1	1	12
Indian	1	2	3	5	0	2	13
	3	9	11	6	4	3	36

Table II shows that the majority of patients were in the age group 25-29. This was true for the Chinese but for the Malays, it was the age group 20-24 and for the Indians the age group 30-34.

Table III Ethnic Group/Parity of septic abortion

Ethnic	Parity		
Group	Primigravida	2 – 5	6+
Malay	1	7	3
Chinese	1	8	3
Indian	4	0	9
	6	15	16

Table III shows that for the Malays and the Chinese, the majority were in parity 2-5 group, but for the Indians, the majority were in the parity 6 group.

Table IV Ethnic Group/Gestation period

Gestation Period	Ethnic Group			
	Malay	Chinese	Indian	Total
4-8 weeks	4	4	3	11
9-11 weeks	2	3	5	10
12-13 weeks	3	4	1	8
14-16 weeks	1	0	4	5
16+ weeks	1	1	0	2

Table IV shows that the majority of cases were in the 4-8 weeks gestation period.

Table V Clinical features – Ethnic Group

Symptoms	Ethnic Group			
Signs	Malay	Chinese	Indian	Total
1. History or evidence of interference on vaginal exam.	5	7	3	15
2. Fever:				
(a) 99°F to 100.3°F	4	4	3	11
(b) Above 100.4°F	5	5	7	17
3. Offensive vaginal discharge	7	2	6	15
4. Abdominal pain	4	2	6	12
5. Pelvic peritonitis	1	1	0	2

Table V shows the clinical features. The majority of patients had multiple clinical features, fever and offensive vaginal discharge being the important signs.

Table VI – Choice of Antibiotics

Antibiotics	No. of cases
Crystalline Penicillin/Streptomycin	21
Tetracycline	10
Penbritin	2
Chloromycetin	2

Table VI shows that 21 patients (58.5%) received only a combination of crystalline penicillin and streptomycin, which was the drug of choice. If the patient was sensitive to penicillin, then she was given a course of tetracycline, 10 patients (27.7%).

Discussion –

Recent trends in the management of septic abortion.

I. The choice of antibiotics

Since the advent of antibiotics in the last two decades, the course of septic abortions has been markedly altered.

In the series of 336 cases managed by the Septic Abortion Unit of K.K. Hospital since March 1966 as reported by Chong (1969), ampicillin, cephaloridine and chloramphenicol were found to be very useful antibiotics with a high degree of efficacy.

Ampicillin dosage was 500 mg. 6-hourly for 4-5 days, given I.V. in the first 24 hours, then orally when the patient's condition had improved.

Cephaloridine dosage was 500 mg. 12-hourly for 5 days given I.M.

Chloramphenicol dosage was 500 mg. 6-hourly I.V. for the first 24 hours, then orally for another 3-4 days. Toxic effect was not seen in any of the patients using chloramphenicol and it appeared that a short term use of the drug is quite safe and justifiable in the management of ill patients.

Percentage sensitivity of organisms to antibiotics

Drugs	% of organisms sensitive
Amphicillin	71.2%
Chloramphenicol	73.1%
Cephaloridine	55.6%
Streptomycin	65.5%
Penicillin	33.6%

Jones W.R. (1967) reports in the Med. J. of Australia:

Antibiotics	% of organism sensitive
Streptomycin	100%
Chloromycelin	100%
Ampicillin	61%
Tetracycline	52%

The use of penicillin with streptomycin has been quite widely practiced while penicillin alone in massive doses has been employed with good results.

II. Treatment of shock

This could be endotoxic or haemorrhagic.

Endotoxic shock is a state of peripheral vascular collapse induced by a lipoprotein-carbohydrate complex contained in the O-somatic antigen present in the cell wall of the gram negative bacteria. Shock due to Cl. welchii or staphylococcal infection is probably caused by exotoxin.

Test for Endotoxin

Douglas and Beckman (1966) from the New York University School of Medicine describe a test for the demonstration of endotoxin in the circulation. Intravenous injection of 7-10 ml. of plasma from the patient is injected into rabbits with simultaneous intracutaneous injection of 100 pgm of adrenaline in the abdomen. A reaction of haemorrhagic necrosis within 8-24 hours indicates the presence of endotoxin in the patient's plasma. This test will be a great help in distinguishing endotoxic shock from hypovolemic shock.

In the analysis of causes of death following abortion in 28 cases by Utian (1968), a striking feature was the development of Ac. Pulm edema after starting transfusion in 5 cases after minimal I.V. fluid administration. This was also noticed in other studies (Ohio State Med. Ass. Committee 1961, Schwarz & Emich 1965). Furthermore C.C.F. was seen in 12 deaths.

It is probable that in some ill septic abortion patients, there exists a precarious cardiodynamic balance with susceptibility to fluid overload. Exaggerating or aggravating factors are renal damage with fluid retention, severe peripheral vasoconstriction, generalised myocarditis, bronchopneumonia and septicaemia. These patients present in a state of hypotension which is mistakenly thought to be due to hypovolemic shock. I.V. fluid therapy then exaggerates the imbalance and results in C.C.F., Pulm. edema and death if the cardiogenic component is not recognised. The necessity for the monitoring of fluid replacement by central venous pressure (CVP) manometry in these severely ill patients is therefore obvious.

Role of nor-adrenaline and metaraminol in endotoxic shock

Nor-adrenaline and metaraminol have often given satisfactory results in septic shock especially when

used in combination with steroids. These agents raise the B.P. by increasing the cardiac output, a beta adrenergic effect which is useful in an endotoxin depressed myocardium. Unfortunately, it is their alpha adrenergic properties which, although producing a temporary rise in B.P. through increased vasoconstriction, ultimately causes further deterioration. So endotoxin induced vasoconstriction is potentiated rather then opposed, leading to diminished tissue perfusion, increasing anoxia, acidosis and eventually organ failure.

So the combined use of vasodilators and adrenergic blocking agents were proposed. Drugs with primarily vasodilatative effect, eg. chlorpromazine, phenoxybenzamine, increase tissue perfusion by blocking vasoconstriction but lower the B.P. Therefore in order to maintain B.P. with vasodilators, one must give significant amounts of fluid, a procedure with risk in the face of mycocardial depression. These drugs have been given in conjunction with metaraminol and nor-adrenaline with beneficial effects but their combined use is complicated.

Cavanagh & McLeod used metaraminol (Aramine) on 35 patients between July 1959 and July 1965.

His classification of shock state is as follows:-

Severe	Systolic B.P. less than 50 mm. HG.
Moderate	" 50-80 mm.Hg.
Mild	Only transient hypotension was present and was excluded from the study.

Of the 35 patients in the series, 24 were in moderate shock, mean B.P. 68/36; 11 were in severe shock mean B.P. 22/12.

Metaraminol was given in 5% Dextrose I.V. The duration of administration varied from less than 1 hour to 96 hours. Metaraminol elevates both systolic and diastolic B.P. and increases the blood flow through cerebral, renal and coronary vessels. Cortiosteroids, used concomittantly with vasopressor agents, appeared to permit the maintenance of the patient on smaller doeses of vasoconstrictor drugs. In the series, 23 of the 35 patients survived with metaraminol.

In moderate shock, 21 of 24 survived. In severe shock, 3 of 11 survived. (The reason for such results will be obvious subsequently).

Du Toit et al. (1966) believe that the common denominator in the fatal outcome of endotoxic shock in man is inadequate tissue perfusion as seen in cardiac failure, hypovolemic shock or endotoxic shock and septicaemia. Their criteria for endotoxic shock is when transfusion sharply raised the J.V.P. without clinical improvement of the shock state. They did not use measurement of peripheral resistance, determination of the oxygen debt or the clinically warm or cold hypotensive state as their criteria.

The following is a brief report on the treatment of endotoxic shock with Insoprenaline by du Toit et al (1966).

Method

Arterial blood is taken for determination of acid-base balance and serum electrolytes which are quickly corrected. Continuous monitoring of urinary output and ECG. and administration of oxygen is done. Massive doses of I.V. antibiotics are given and patient digitalised.

If the JVP as measured by a manometer is below 12 cm. of water, Ringers lactate soln. and/or blood is given. All the patients, initially or after transfusion, had a JVP. of over 12 cm. of water with no improvement or very little, in their clinical condition. At this stage, a 1:450,000 isoprenaline infusion is begun with a dose rate of 0.5-4 pgm/min. A decrease in JVP below 12 cm. of water is matched with a further infusion of appropriate soln. until urinary excretion starts and/or systolic B.P. of 80-100 mm. Hg. is maintained. In their study, isoprenaline drip was no longer required beyond 36 hours.

In man, isoprenaline is a beta adrenergic receptor stimulator producing a 64% increase in cardiac output and dilatation of the capillary network, resulting in 48% decrease in peripheral resistance, i.e., isoprenaline improves tissue perfusion. Renal artery dilatation will improve glomerular circulation and therapy promote urinary excretion at a low arterial B.P.

The possible effects of endotoxin are varied:-

1) Intense constriction of arterioles and capillary sphincters in kidneys, liver and intestines.
2) Impaired cardiac function with myocarditis and reduced cardiac output.
3) Increased pulm. vascular pressure and vascular distension with pulm. edema.
4) Intravascular coagulation as a part of generalised Schwaitzman reaction with reduced venous return.

Role of steroids in endotoxin shock

The beneficial effects of hydrocortisone is:-

1) It alleviates the degree of adrenocortical insufficiency, supporting the patient in the present stress.
2) Hydrocortisone blocks the intense regional sympathomimetic action of endotoxins.

3) Hydrocortisone acts directly on peripheral vascular bed restoring vascular tone; it has an inotropic effect on the heart, and
4) Hydrocortisone decreases clinical toxicity and permits survival long enough to allow benefit from antibiotics.

Hydrocortisones are given in massive doses, ie., 0.5 – 1 gm. I.V. at first sign of hypotension and 100 mg. every hour or 0.5 gm. 6-hourly.

III. Surgical management in septic abortion

Whenever there is a nidus of infection, as in the uterine cavity, controversy exists as to the evacuation of the non-viable contents of the uterus.

Evacuation of the uterus immediately or very early has been advocated by Stallworthy (1947), Perera (1961), Schwartz & Emich (1965). Douglas & Bectman (1966) believe that the body defence mechanisms weaken in the face of continuing influx of bacteria or toxins. In fact, extension of infection with clinical deterioration, oliguria, evidence of infection by Cl. welchii and endotoxin shocks are reported as indications for early evacuation or hysterectomy.

Goodno et al (1963) and Moritz and Thompson (1966) argue that surgical treatment is a dangerous procedure on these ill patients and should be delayed till general, supportive and antibiotic therapy have improved their condition. They have produced excellent results by delaying the evacuation of the uterus till the patients were afebrile. Neuwirth & Friedman (1963) showed that early evacuation in febrile patients increased the incidence of post-operative pyrexia and hypotension.

In the series of 233 cases of K.K. Hosp., as reported by Sidhu (1969), total duration of pyrexia was very significantly less in the immediately evacuated group than the delayed one. Immediate evacuation means the uterus was evacuated within 24 hours of admission and antibiotic institution. Delayed evacuation means the uterus was evacuated when the patient was afebrile; however, if the patient remained febrile at the end of 72 hours, the uterus was evacuated without delay.

Post-operative pyrexia was more frequent in the immediate group, but that lasted for only 24 hours in 70% of the cases developing pyrexia after evacuation. Though only 24.5% developed post-operative pyrexia in the delayed group, 60% of these (24.5%) had pyrexia lasting more than 24 hours after evacuation. In the immediate group, other complications were negligible, whereas in the delayed group, there was further spread of infection even after the evacuation in the form of pyrexia, thickened appendages, tubo-ovarian masses and pelvic abscess.

Another group of very ill patients with complications had individual treatment like laparotomy, colpotomy or immediate evacuation if bleeding was excessive.

Utian (1968) advocates immediate digital evacuation of uterus without anaesthesia if the general condition is poor.

The role of Hysterectomy as reported by Douglas & Beckman (1966).

In their series of 50 cases of septic abortion, there were 19 hysterectomies (ie. 38%) of which 13 were primary. In nearly every instance of hysterectomy, there were multiple circumstances and indications which influenced the decision.

Major indication for hysterectomy.

	No.	Died
Unresponsive septic hypotension, large uterus	11	3
Intrauterine douche with necrosis	5	0
Anuria	3	1
Total:	19	4

Anuria was the indication in 3 cases. In their experience, the management of acute renal failure is enormously complicated by the presence of infection, and necrotic tissue mass in the pelvis. Further, the procedure becomes far more dangerous if done at a later time, in the face of mounting uraemia and the need for anticoagulants in relation to hemodialysis.

In all cases, the major indication for hysterectomy was septic hypotension complicating abortion in a large uterus. Six of these patients had had preliminary curettage without beneficial effect. Here, the major consideration was that effective removal of infected tissue could not be accomplished if the uterus was larger than the size of 12-week gestation. Two of these patients pursued a downhill course in septic shock and a third died of pulmonary complications related to severe asthma:-

Response to curettage

	No.	Died
Gradual improvement and recovery	22	0
Progression to irreversible shock after curettage.	2	2
In shock when curetted	1	1
No response to curettage hysterectomy	6	2

So if the shock state still persists after conservative therapy of antibiotics and curettage, total abdomi-

nal hysterectomy with BSO is carried out immediately. Early total hysterectomy is advocated in cases of toxic acute renal failure, uterine necrosis, pelvic vascular thrombosis secondary to chemical douche or hepatic involvement (jaundice) as a precedure of choice.

IV. Other methods of management:

(1) Hypothermia: It has been used with some benefit.

(2) Hyperbaric oxygen therapy should be of considerable benefit in Cl. welchii infection.

(3) Cardiac glycosides may be of some value in mycocardial depression and are indicated if Pulm. edema supervenes. Their prophylactic use is not necessary or desirable because of uncertainty of their performance when circulation is labile.

(4) Heparinization has been advised to protect against the Schwartzman reaction. Reports suggest that endotoxin induced consumption of clothing factors may result in hemorrhagic tendency and disseminated fibrin deposition. Douglas & Beckman expressed, on the other hand, the feeling that coagulation defects are rare. They are hesistant to use anticoagulants to their regimen for patients who may require major surgical therapy during their hospital stay.

The problem of Septic/Criminal abortions.

Septic/criminal abortions remain a major problem in East Malaysia.

It is interesting to note that in spite of the fact that the majority of Government hospitals in West Malaysia showed a 100% increase in hospital admission for all types of cases from 1961 to 1970, the incidence of septic abortions showed a fall in incidence.

The reasons for this lowered incidence may be the following:-

(a) Since 1961, more private hospitals, nursing homes and clinics have been established, with the result that patients wanting termination of pregnancy are depending less on the services of unqualified abortionists.

(b) With the establishment of the National Family Planning Board services, women are planning their families with the result that there was a fall in the incidence of unwanted pregnancy.

Table VII Septic abortion, admission and deaths in West Malaysia.

	Admission of septic abortion in Govt. Hosp. 1961		Deaths due to septic abortion in Govt. Hosp. 1970	
Perlis	35	11	0	2
Kedah	44	75	2	1
Penang	44	94	0	2
Perak	97	245	7	1
Selangor	173	157	4	1
Negeri Sembilan	64	96	2	0
Malacca	48	24	0	2
Johore	349	63	1	1
Pahang	2	16	0	0
Trengganu	15	22	1	0
Kelantan	11	11	0	0
	882	814	17	10

Table VII shows that in 1961, there were 882 hospital admissions and 17 deaths for septic abortions but ten years later, in 1970, there was a fall to 814 hospital admissions and ten deaths for septic abortion. The States of Perlis, Selangor and Johore showed dramatic reduction in the incidence of hospital admissions for septic abortions.

Since septic/criminal abortion is a serious problem with high morbidity and mortality, the answer to this problem lies in the prevention of unwanted pregnancies by educating the women and wider utilisation of the family planning services.

Acknowledgement

We are grateful to the Director General of Medical Services and J. Martinez of the Ministry of Health for the data for Table VII. We are also grateful to the Registrars, Dr. Thiruchelvam and Dr. Jalamoorthy, and Medical Officers, Dr. Rosli bin Hussein and Dr. D. Nair of Maternity Hospital who took part in this study.

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Prophylactic antibiotics in children

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IT HAS BEEN estimated by some authorities that as much as 90 per cent of antibiotics are prescribed unnecessarily and in themselves cause adverse reactions ranging from trivial to fatal in 21 to 29 per cent of cases (Hobart, Reiman and D'Ambola 1966). One of the main reasons for wastage of antimicrobials is unnecessary prophylactic use.

The term prophylactic antibiotics refers to the administration of antibiotics to uninfected individuals who, for some reason or other, are in danger of acquiring a bacterial infection. The paediatrician has to decide whether to prescribe or withhold antibiotics in these cases, and it is unfortunate that in many instances, there are inadequate data on which to base a firm decision.

It is the purpose of this paper to study critically the evidence for and against prophylactic antibiotics and suggest an approach that seems rational for specific situations in which clear guidelines are not available. In this paper, antibiotic prophylaxis in the foetus and newborn, infancy and childhood and in paediatric surgery will be reviewed.

Antibiotic Prophylaxis in the Foetus and Newborn

Antepartum infection and prolonged rupture of foetal membranes

Smith, Jennison and Langley (1956) gave streptomycin and oxytetracycline to mothers with presumed intra-partum infection, while they were either in labour or after their membranes had ruptured, and claimed this reduced the perinatal mortality by preventing infection of the foetus. The number of cases they studied was small and birth weight and gestation were not mentioned. In a later communication, Langley & Smith (1959) were unable to show that perinatal mortality was reduced.

Eastman (1958) found that the perinatal mortality rate during a period when penicillin was given to mothers with prolonged rupture of membranes was not different from the rate observed before the advent of penicillin. Lebherz et al. (1963), in a double-blind study involving 1,896 women, found that antibiotics do not alter the perinatal mortality of infants of mothers with premature rupture of membranes.

There is an increased risk of infection in infants born after protracted rupture of the foetal membranes (Pryles et al., 1963) but there is no conclusive evidence that the incidence of infection in the infant is influenced favourably by treatment of the mother. The routine administration of antibiotics to infants born after prolonged membrane rupture has also not been found beneficial nor desirable (Pryles et al. 1963).

Reasonable recommendations for infants who emerge from an apparently infected environment would be to give antibiotics only to those infants who appear ill at birth after swabs are obtained from the nose, throat and umbilicus, and after C.S.F., urine and blood are examined and cultured. The rest should be labelled suspect and observed closely for signs of

possible infection and if this appears, treatment should be started after appropriate culture materials are obtained. In infants of febrile mothers, it may be wiser to collect all culture material before signs appear so this information might then be available, without undue delay, should treatment become necessary.

Prematurity

Small premature infants usually exhibit few clinical signs early in the course of serious infection, and treatment is often not successful. In an attempt to improve survival, antibiotics are prescribed routinely in some nurseries. The effectiveness of this policy has not been established by a critical trial.

The aim should be to prevent infection by keeping the infant's environment as bacteriologically clean as possible by effective handwashing rather than by the widespread use of antibiotics, as this may alter the balance of flora and encourage resistant organisms. Any infant who develops vague non-specific signs which indicate possible infection, particularly after a period of well-being, should be treated after appropriate culture materials have been taken.

Epidemic staphylococcal infections and coliform diarrhoeas in nurseries

Staphylococcal colonisation of the newborn occurs at a high rate but is infrequently associated with disease (Wolinsky, Gonzaga, & Mortimer, 1962). Occasionally, an epidemic strain may appear and cause high rates of major and minor clinical staphylococcal disease, and may be difficult to terminate especially when complete closure of the unit may not be possible. Under these circumstances, mass prophylaxis with appropriate antibiotics to all babies in the nursery and those subsequently admitted to the unit until the infant population has been turned over completely at least twice, has been found usually effective in terminating the epidemic (Mortimer 1968). Mortimer has recommended that any infant shown by culture to have acquired the organism should be treated for at least 10 days in the hope of eradicating the strain.

Outbreaks of epidemic diarrhoea in nurseries are usually due to enteropathogenic E. coli. Effective antibiotic therapy has been shown to be of value in controlled trials (Medical Research Council, 1953) and is useful in the prevention of cross-infection and relapse and stopping epidemics. Effective therapy rapidly reduces the number of enteropathogenic E. coli organisms and decreases the manifestations of clinical illness (Yow 1963). Although the findings of Riley et al. (1964) cast doubt on the advisability of administering antibiotics to every person from whose stool enteropathogenic E. coli is isolated, it is recognised that although many cases of E. coli disease are mild, the course is unpredictable in newborns. Mortimer (1968) recommends closing the unit completely or mass prophylaxis along the lines described for epidemic staphylococcal disease. In both instances, he has emphasised that the institution of mass prophylaxis does not eliminate the need for other control measures, including efforts to identify carriers of the offending organisms.

Respiratory distress and meconium aspiration

There is no clear evidence to support the use of antibiotic prophylaxis in respiratory distress. But in some cases, it may be difficult to distinguish pneumonia from respiratory distress and antibiotics may then be offered as treatment for possible pneumonia and not merely as prophylaxis.

The use of antibiotic prophylaxis in meconium aspiration is controversial as no controlled studies are available. Avery (1968) recommends prophylactic antibiotics as the differential diagnosis between bacterial pneumonia and meconium aspiration is difficult and also because intra-tracheal meconium has been shown to enhance the susceptibility to E. coli infection in rats. Although the reaction in the lungs is a chemical pneumonia, the lungs at autopsy often show evidence of both aspiration and pneumonia.

Antibiotic Prophylaxis in Infancy and Childhood

Rheumatic fever and sub-acute bacterial endocarditis

It is generally accepted that rheumatic fever is casually related to streptococcal throat infections in childhood. There is proof from large scale trials that treatment of streptococcal throats by penicillin reduces the consequent rheumatism (Houser & Eckhard 1952). There is no evidence, however, that rheumatic fever, after a streptoccal infection, can be prevented in all cases by treatment of such patients, and continuous prophylaxis in patients who have experienced one attack is recommended (Cantanzaro et al. 1958). Continuous prophylaxis can be best achieved by benzathine penicillin and oral penicillin, or sulphonamides to a lesser extent, because of failture to take the drug (committee on prevention of rheumatic fever and bacterial endocarditis 1965). Accordingly, all children with rheumatic fever, with or without valvular heart disease, should receive prophylaxis. The duration of prophylaxis is uncertain but it is accepted

that the risk of carditis becomes negligible in adult life.

It has been found that 48 per cent of cases of sub-acute bacterial endocarditis follow dental infection or dental extraction (Cates and Christie 1951). The infection is preceded by a bacteraemia caused by organisms which are nearly always sensitive to penicillin. One injection of penicillin prior to operation should deal with the bacteraemia and prevent the disease. The penicillin umbrella was accepted on theoretical grounds without clinical proof. It is now too late to test the theory as it would be considered unethical to expose patients as controls to such a disease. Penicillin cover is now mandatory during dental procedures in susceptible patients. Patients already on continuous penicillin prophylaxis for rheumatic fever are liable to have penicillin resistant streptococcus viridans or staphylococci in the mouth and should be covered by a different antibiotic, such as erythromycin.

Acute viral respiratory disease

In a double blind study of 60 infants with undifferentiated respiratory disease (i.e. rhinorrhoea, nasal congestion, pharyngeal erythema, cough, rhonchi or noisy breathing but excluding pneumonia, croup, bronchiolitis, exudative tonsillitis, otitis media), antibiotics (penicillin, tetracycline) were found to be of no benefit either in shortening the mean duration of the illness or in preventing secondary complications (Ackerman 1968). Davis and Wedgwood (1965) reviewed the subject of antibacterial prophylaxis in common cold, influenza, measles and other viral respiratory disease. They concluded that antibiotics have no effect on the primary course of viral respiratory disease and thus have no place in their primary treatment. Prophylactic antibiotics have not been shown to prevent bacterial complications and since certain risks are associated with their use, they are contraindicated.

Anatomical abnormalities of urinary tract and recurrent urinary tract infections

Children with obstructive urinary tract lesions are predisposed to pyelonephritis. The routine administration of antibiotics can only be expected to provide resistant flora which is more refractory to treatment. Therapy should be directed at correcting the underlying abnormality and vigorously treating any infections after appropriate bacteriological investigations.

Petersdorf et al. (1957) found that prophylactic antibiotics neither prevented nor ameliorated infection of the bladder in patients with indwelling urethral catheters. They served only to ensure that the infection, when it develops, will be by a highly resistant organism, even more refractory to antibiotics. These data suggest that antibiotic prophylaxis is of no benefit and is distinctly hazardous.

There are no established criteria for determining how long medical treatment should be continued in children with recurrent urinary tract infections. The usual practice is to treat those with an anatomically normal urinary tract who have suffered two or more relapses for a minimum of six months, and if infection recurs after six months, treatment is re-instituted and continued for a year or more. The same regime is also followed in children with chronic infection complicating an inoperable anatomical anomaly. In many cases, it is difficult to control the infection completely but it may be possible to reduce the bacteriuria and control symptoms by continuous antibiotic therapy.

Freeman et al (1967) reported a study concerning the treatment of 225 adult patients with chronic bacteriuria.

Relapses occurred after 13 months in 50, 42, 21 and 87 per cent of patients receiving sulphamethizole, nitrofurantoin, methenamine mandelate and a placebo respectively. This study suggests that significantly better control of infection was achieved using methenamine mandelate than with other compounds. Practitioners will undoubtedly encounter difficulties in giving long-term treatment in Malaysia, but reasonable explanation should win their co-operation.

Kerosene poisoning

There are no controlled studies concerning the effects of prophylactic antibiotics administered to children with kerosene poisoning. It is difficult to differentiate superimposed bacterial infection on kerosene pneumonitis. Mortimer (1968) is of the opinion that the early administration of antibiotics as prophylaxis would do nothing more than alter the flora thereby predisposing to infection with resistant organisms.

Unconscious patients

Petersdorf et al (1957) have shown that the administration of antibiotics to unconscious patients is of no benefit as 45 per cent of prophylactically treated patients developed pulmonary complications whereas pneumonitis occurred in only 15 per cent of the controls. They concluded that antibiotic prophylaxis was

distinctly hazardous owing to the emergence of resistant strains.

Nephrotic syndrome, steroids, haematological disorders, X-radiation and antimetabolic drugs

Children with nephrotic syndrome, those receiving steroids, X-radiation or antimetabolic drugs and those with certain haematological disorders, like leukaemia and agranulocytosis, are extremely vulnerable to bacterial infections because of compromised defences. Continuous antibiotic prophylaxis will not prevent such infection which will instead occur with resistant organisms more refractory to treatment. Antibiotic prophylaxis is, therefore, not recommended; instead careful observation for infection should be conducted and appropriate antibiotic therapy instituted when bacterial infection is recognised.

Local therapeutic measures

Tracheostomies, intravenous canulae and umbilical catheters create portals of entry for infection. Although antibiotics are routinely given to infants in certain centres, the value of this practice is questionable. Bhatt et al (1970), in a recent study of infants with umbilical catheters, found no difference in the incidence of infections in a control group and a group given antibiotics prophylactically. Prophylactic antibiotics can only be expected to produce infection with resistant organisms.

Antibiotic Prophylaxis in Paediatric Surgery

Burns

Parenteral antibiotic prophylaxis has not been efficacious in the treatment of burn patients. But topical application of mafenide (sulphamyion) or 0.5 per cent silver nitrate or gentamycin has been shown to be effective. Teplitz and Moncrief (1964) have shown a reduction in the infection rate (mainly with pseudomonas) from 88 per cent to 22 per cent and also a significant reduction in mortality from 42 per cent to 0 per cent in a 30 to 40 per cent burn and from 59 per cent to 30 per cent in a 40 to 50 per cent burn following the use of sulphamylon.

Cerebrospinal fluid rhinorrhea and otorrhea

This usually follows trauma to the head. Some close spontaneously after a few days or weeks while others persist for months or years and predispose to recurrent attacks of meningitis. Close medical supervision is required in cases where attempts to correct the fistulas are unsuccessful. As the most common cause of meningitis in these cases is the pneumococcus (Whitecar, Reddin & Spink, 1966), it has been considered reasonable to institute continuing penicillin prophylaxis.

Post splenectomy

Horan and Colebatch (1962) reviewed the literature and then followed up with a study of 142 patients on whom splenectomy was performed in childhood. They found the incidence of subsequent serious infection (meningitis, septicaemia, pneumonia, sub-phrenic abscess, etc.) was 12 per cent, and 80 per cent of all serious infections occurred in infants within two years of surgery. The infecting organism is usually pneumococcus and the course of the infection is usually fulminating with high mortality. Following splenectomy, long-term penicillin prophylaxis is considered advisable as almost 75 per cent of recorded infections were due to penicillin sensitive organisms.

Clean surgical operations

Barnes et al (1959) conducted one of the large trials reported. Long-acting penicillin and streptomycin were given post-operatively to 45 per cent of 1,007 cases while the remainder served as controls. The infection rate was 11.4 per cent in those receiving antibiotics and 9.8 per cent in the controls. They concluded that prophylactic antibiotics did not reduce the incidence of post-operative infection. Tachdjian and Compere (1957) reported similar findings.

Potentially infected operations

Johnstone (1963) found the wound infection rate amongst patients who were having potentially infected operations, such as colostomies, was 38.5 per cent in those who had antibiotics and only 17.6 per cent in those who received no prophylactic treatment. But he still recommends selective use of prophylactic penicillin to prevent clostridial infection. McAdams (1960) considers sterilisation of the gut unnecessary as it tends to lead to other organisms, such as pseudomonas and proteus, becoming pathogenic.

Traumatic wounds

Experiments have failed to clarify the effects of antibiotics administered to patients with potentially infected surgical wounds. Burke (1961) has shown that wound sepsis in guinea pigs may be averted by the administration of antibiotics before surgery and to a lesser extent if administered an hour or two later. Penicillin is useful in reducing the danger of infections of wounds by gas gangrene and possibly tetanus

and is therefore used in most cases of accidental wounds in clinical practice (Walker 1966).

Discussion

The dangers of antibiotic therapy have been extensively reviewed (Murdoch 1966). Indiscriminate and widespread use of antimicrobials, especially in hospitals, not only leads to outbreaks of serious hospital-acquired and antibiotic-resistant infections but also increases the incidence of iatrogenic disorders and adds to the cost of medical care.

Prophylactic antibiotics are used for a wide variety of reasons based more often on impression rather than the results of controlled trials. A critical review of the literature reveals that antibiotic prophylaxis is generally not effective in preventing infection, except in a few specific situations. It is useful in patients who have had acute and transient exposure to a specific organism and also in patients who are chronically or recurrently at risk from a specific organism which has continuing sensitivity to an antibiotic of limited spectrum. Patients, whose defences are compromised over prolonged periods and who are susceptible to infection with multiple organisms or organisms known to develop resistance readily, usually do not benefit from prophylaxis.

The situations in which antibiotic prophylaxis is useful are limited. The use of silver nitrate or penicillin in the prevention of gonococcal ophthalmia is well documented (Barsam 1966). Recurrent attacks of rheumatic fever can be prevented by continuous prophylaxis. Penicillin cover during dental extractions is useful in patients susceptible to sub-acute bacterial endocarditis. There is evidence that prophylaxis is useful following splenectomy in infants and in cases of cerebrospinal fluid rhinorrhoea in whom surgery has not been successful. Penicillin can be used in serious accidental wounds to prevent gas gangrene or tetanus, while topical applications of sulphamylon, silver nitrate or gentamycin have a definite place in the management of burns.

In most other instances, there is no clinical evidence to indicate that antibiotic prophylaxis is useful and is generally contra-indicated.

Summary

A critical review of the literature reveals that prophylactic antibiotics are generally not effective in preventing infection except in a few specific situations.

Prophylaxis is useful in preventing:—

1. Recurrent attacks of rheumatic fever.
2. Sub-acute bacterial endocarditis following dental procedures.
3. Gonococcal ophthalmia.
4. Post-splenectomy infections.
5. The spread of staphylococcal infections and coliform diarrhoeas in nurseries.

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The immunisation status of some preschool children in a new village in West Malaysia

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Introduction

IN WEST MALAYSIA, the routine immunisation programme for children includes immunisations against tuberculosis, smallpox, diphtheria, whooping cough and tetanus (Ministry of Health, Malaysia). These immunisations are given free of charge at government hospitals, rural health centres, and municipal health clinics. The usual immunisation schedule followed in the first year of life is as follows:

Soon after birth	—	Intradermal B.C.G. vaccination
Two months	—	First dose of triple antigen (diphtheria, pertussis and tetanus)
Three months	—	Second dose of triple antigen
Four months	—	Third dose of triple antigen
Five months	—	Primary vaccination against smallpox

The purpose of this study is to assess the immunisation status of some preschool children, aged one to five years, in a new village in West Malaysia, and to explore some of the factors relating to the differences, if any, in the rates of different kinds of immunisations.

Study area

The study area, Semenyih new village, is situated near a trunk road in the state of Selangor, West Malaysia. Established nearly 20 years ago, it now has a population of about 1,500, predominantly Chinese, most of whom are rubber tappers, earning generally a low income. The health facilities include a main health centre with a health officer, several staff nurses and midwives, in the village itself; a district hospital with two medical officers, and three private practitioners in Kajang, a small town six miles away.

Procedure

This study was made on households situated east of the main health centre. House-to-house interviews were conducted between 24.2.69 and 7.3.69.

Households that had at least one child between the ages of one and five years at the time of the interview were included in the study. The immunisation status of the younger or youngest child (if there was more

than one child in the stated age group) was first determined through interviews with the parents (only the youngest child within the age group was included in the study as the pre-test showed that the parents could recall more accurately details about the youngest child than those of the older children). The parents' statements were then checked with:

a. The immunisation record on the birth certificate of the child, the child health clinic appointment card issued by the health centre and the child health record card kept in the health centre, as well as
b. Scars on the body of the child consistent with that of B.C.G. vaccination or primary vaccination against smallpox.

There was good cooperation from all the households in the study area.

Results

The results were based on the study of 84 households with at least one child between the ages of one and five. The age and sex distribution of the children included in the study are given in Table I.

Table I.

Number of children by age and sex

Age (years)	Male	Female	Both sexes
1 –	24	29	53
2 –	9	16	25
3 –	4	1	5
4 –	1	0	1
5 – 6	0	0	0
Total	38	46	84

The place of delivery of each child was also determined. (See Table II).

Table II

Place of delivery by the number of children

Place of delivery	No. of children
Nearest district hospital (6 miles away)	69
Other hospitals (20 miles away)	12
At home, in the village	2
At home, in another village	1
Total	84

Thus, most of the children studied were between the ages of one and three and were born in the nearest district hospital, or other hospitals.

Immunisation status

(A) B.C.G. Vaccination: Of the 84 children studied, 77 (or 92%) had evidence of B.C.G. vaccination. The majority were immunised soon after birth. Their place of immunisation is given in Table III. Most of them had their vaccination in the hospitals where the birth took place or in the health centre in the village soon after their return from hospital.

Table III

Number of children who received each kind of immunisation and the place where immunisation was carried out.

Place where immunisation was carried out	B.C.G. vaccination	Vaccination against smallpox	Immunisation* with triple antigen
Nearest district hospital (6 miles away)	46	4	0
Other hospitals (20 miles away)	7	0	0
Health centre in the village	23	31	17
Other health centres	1	1	0
General practitioners	0	6	0
Unknown	0	1	0
Total	77	43	17

* completed 3 doses

(B) Vaccination against smallpox: 43 children (or 51%) had evidence of vaccination against smallpox. Among the vaccinated group, 30 children received it before 1 year, 5 between 1 and 2 years, and 4 during 2 years and above. There were 4 children whose dates of vaccination were unknown. Most of the vaccinations were carried out at the Health Centre in the village (see Table III). A significantly higher rate of vaccination was found in children whose household income was higher (US$100 and above per month)

and whose mothers had received at least four years of primary school education.

(C) Immunisation with Triple Antigen: Only 17 (or 20%) of the children studied had evidence that they had received 3 doses of triple antigen. They all received them before the age of one at the health centre in the village (see Table III). Ten other children received only one dose while 3 others received only two doses of the triple antigen. Again, a significantly higher rate of immunisation was found in children whose household income was US$100 and above per month.

(D) Completed all 3 kinds of immunisation: Only 14 out of the 84 children (i.e. 17%) studied had received all three types of immunisation.

Discussion

The findings indicate that of the 3 kinds of immunisation recommended for children under the age of one, the highest immunisation rate achieved in this group of children was for B.C.G. and the lowest, triple antigen, with the vaccination rate against smallpox in between the two. What factors might have brought about the differences in the immunisation rates? They will be discussed under the following headings:

(a) Awareness of the need.
(b) Time of vaccination.
(c) Perception of the severity of reactions to immunisations.
(d) Number of doses required.

(a) Awareness of the need

In the interviews with the mother, it was found that there was general awareness of the need for the 3 kinds of immunisation for children under the age of one, and that these immunisations were available either in the district hospital 6 miles away or the health centre of the village. With regard to B.C.G. vaccination, several mothers did not know why it was given. They thought that it was meant to protect the infant against all illnesses — a non-specific preventive measure. With regard to vaccination against smallpox, most mothers were not aware that it was a legal requirement to have their children vaccinated before the age of 6 months as stated on the birth certificate of the child. With regard to immunisation with triple antigen, the mothers whose children were not immunised did not know the purpose of getting it.

(b) Time of vaccination

B.C.G. vaccination was generally given soon after birth at the hospital. This was very convenient for the mother. This factor has evidently accounted for the high immunisation rate for B.C.G.

(c) Perception of the severity of reactions to immunisations

B.C.G. immunisation generally produces a very mild local reaction with no general reaction. However, vaccination against smallpox and immunisation with triple antigen usually produce a local reaction, such as ulceration or swelling and a general reaction, such as fever. It appears that most parents had learnt to accept the reactions to vaccination against smallpox as being relatively harmless. On the other hand, most of the parents whose children did not receive the immunisation with triple antigen or whose children did not complete the immunisation with triple antigen stated that their main reason for not starting or completing the immunisation was because of the fever that usually developed after the procedure. A few mothers volunteered the information that the grandparents were against the immunisation, for they (the grandparents) could not bear to see their grandchildren falling "ill" as a result of the immunisation.

(d) Number of doses required

Of the three kinds of immunisation, only immunisation with the triple antigen requires 3 visits to complete the course. However, none of the mothers gave the need for 3 visits as a reason for not starting or completing this immunisation. It appears that this factor played only a minor role in the low immunisation rate for the triple antigen.

Implication for the immunisation programme

How can we raise the immunisation rate of this group of children? In other words, how can we increase the participation of parents in the immunisation programme? Based on the findings, the following measures are suggested:

1. Education of parents: Opportunities for the education of the parents on the need for immunisation exist in antenatal clinics, maternity hospitals, postnatal clinics, child health clinics and general out-

patient clinics. For parents who do not make use of these services, several methods have to be used to reach them, e.g., through the mass media, home visits and community organisations. More attention has to be paid to the lower income and lower education groups, whose participation in the immunisation programmes are generally low. Emphasis in the health education programme should be placed on the kinds of vaccination recommended for children, their purpose, and their side effects. For those parents who are not convinced that diphtheria, pertussis and tetanus are serious diseases, an effective method recommended by Professor Gale is to take the parents to the hospital to see the severe cases of the diseases or if this is not practical, an alternative method is to show the parents photographs of the sick children. This was carried out in Thailand (Professor Gale, 1970). At the same time, the staff should particularly reassure the parents that certain side effects, such as swelling at the site of injection and fever after immunisation with triple antigen, are relatively harmless. An antipyretic should be given together with instructions to the parents on how to use it. For some anxious parents, it may be necessary for the staff to visit their homes at the time the child develops the local and the general reaction to give the parents the necessary assurance and moral support. This also helps in preventing defaultation.

2. Change in the immunisation schedule: If B.C.G. vaccination and vaccination against smallpox are both carried out at the same time soon after birth, the immunisation rate for smallpox could be raised with little additional effort. This is being done at the University Hospital (Dugdale, 1967). This change will decrease by one the number of visits necessary, and thus make it easier for those who live at some distance from an immunisation centre to complete the course.

Summary

A study was made of the immunisation status with respect to immunisation against tuberculosis, smallpox, diphtheria, whooping cough, and tetanus of children between the age of one and six of one section of a new village in West Malaysia. Only one child from each household, i.e. the youngest that falls within the specified age-group, was included in the study. It was found that of the 84 children studied 77 (or 92%) had evidence of B.C.G. vaccination, 43 (or 51%) had vaccination against smallpox, and 17 (or 20%) had received the full course of triple antigen. Only 14 children, i.e. 17% received all the three kinds of immunisation.

Some of the factors relating to the difference in the rates for different immunisations were discussed. It was suggested that certain measures might be used to increase the participation of parents in the immunisation programme: stepping up the education of parents about immunisation through health clinics and hospitals as well as other channels of communication in the community, provision of social support to parents who have brought their children for immunisation through home visits by health personnel, and a change in the immunisation schedule.

Acknowledgement

I would like to thank Professor W. Danaraj for her encouragement, staff of the Main Health Centre, Semenyih, for their assistance, Professor G.W. Gale for his help in drafting this paper and the people of Semenyih New Village for their cooperation in the study.

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Defaulting from a new hypertension clinic in Malaysia

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CONTINUITY OF MANAGEMENT is necessary for the psychological and physical care of a patient with a blood pressure high enough to need continuing treatment. It is wasteful of clinic time if many patients fail to keep their appointments. The sort of person who defaults and why he does so may teach us about the patient's attitude to his illness and how it and the treatment affect his life.

Because of the high rate of defaulting from a newly-opened hypertension clinic in the University Hospital, University of Malaya, we have investigated who defaults and why by studying the rate of defaulting and by comparing a group of defaulters with a group of regular attenders. We were especially interested in the demographic and socio-economic status of the two groups.

There are few published studies on defaulting from clinics and we could find none referrable to a developing country. The University Hospital provides routine medical care for many patients living in the state of Selangor and several specialist facilities for the whole of Malaysia. The ethnic groups of patients treated are predominantly Chinese, Malay and Indian.

Methods

PART I: The attendance records for the first six months of the clinic from July to December 1968 were studied. Appointments were divided into two categories: Those attending the clinic for the first time were called new appointments and those re-attending the clinic or transferred from the special clinic for cardio-vascular diseases were called repeat appointments.

The proportion of each group which defaulted was calculated and the ethnic group distribution of the defaulters was compared with that of the new attenders.

PART 2: The Pair Study. From September 1968, each defaulter who had previously attended the clinic was sent a postcard with a new appointment which most kept. If this second appointment was missed, the patient was selected for special study. Each defaulter was paired with a regular attender matched by first attendance at the clinic within seven days of the first attendance of the defaulter. The first 20 pairs selected in this way and who lived in the state of Selangor were studied.

A medical social worker, assisted by a translator when necessary, visited as many of these patients as possible in their homes in the following nine months. By means of an unstructured interview, she tried to

assess factors contributing to the patient's satisfaction or dissatisfaction with the clinic. The following items were investigated:

Occupation and claimed income.

Past illnesses possibly related to hypertension, such as stroke, angina, myocardial infarction and transient cerebral ischaemic attacks.

Travel to the clinic; was it difficult for the patient? How many miles did he have to travel? Did he travel by bus, car or on foot?

Complaints about the waiting to see the doctor, waiting at the dispensary, dislike of drugs and their side effects.

Factors not covered in the informal conversation were systematically enquired after.

Results

The numbers and percentages of new and repeat appointments kept and missed are shown in Table 1.

Table 1. Appointments at the clinic July to December, 1968

	New appointments		Repeat appointments	
	Attended	Missed	Attended	Missed
Number	60	32	450	181
Percent	65	35	71	29

The difference in the number of new and repeat appointments kept and missed is not significant ($X = 1.539$, $p > 0.2$).

The enthnic group distribution of those defaulting was compared to that of all patients attending for the first time in the first 15 months of clinic. The results are shown in Table 2.

Table 2. Ethnic group distribution of defaulters and first attenders.

Table 2

	Defaulters		All first attenders	
	Number	Percent	Number	Percent
Chinese	127	60	296	64
Malay	23	11	42	9
Indian	58	27	108	23
Other	5	2	16	4
Total	213	100	462	100

The ethnic group difference between defaulters and first attenders is not significant. ($X = 2.367$, $n=3$ $p > 0.3$).

Part 2.

In the pair study, of the 20 defaulters, three could not be interviewed. One was not traceable at the address given, one had moved too far away for interview and one refused to allow the interviewer into her house. Four of the 20 regular attenders could not be interviewed. Two had moved away and become defaulters by the time of the interview. One was not known at the address given and he and a fourth moved away during the civil emergency of May 1969.

Two of the regular attenders were interviewed in hospital because transport to their homes was difficult.

Table 3 compares all the factors looked at in those who were interviewed.

Table 3

	Defaulters	Regular Attenders
Number	17	16
Mean Age	53	46
Male : Female	11 : 6	10 : 6
Chinese : Malay : Indian	7 : 5 : 5	9 : 0 : 7
Occupation *		
Unemployed	5	1
Unskilled, semi-skilled, housewife	10	5
Skilled, women with servants	2	10
Physical Health		
Stroke	5	3
Effort dyspnoea	2	1
Angina pectoris	1	0
Myocardial infarct	0	1
Malignant hypertension	0	1
Transient cerebral ischaemic attacks	0	1
Number physically affected by hypertension	8	7
Travel		
Easy	10	11
Difficult	7	5
Miles to clinic	9	6
Private car	3	7
Bus	12	9

Complaints		
Wait for doctor	3	7
Wait for dispensary	3	6
Seen by different doctors	3	4
Dislike of drugs	2	1
Angry with hospital	1	0
Side effects from drugs**	2	8

* The social class difference between the groups was significant ($X^2 = 9.586$, $n = 2$, $p < 0.01$).

** The difference in incidence of side effects from drugs was significant ($X^2 = 5.699$, $n = 1$, $p < 0.02$).

The most important reason for each defaulter not attending was:	
Now living temporarily or permanently too far away from hospital	6
Preferred to attend other doctor nearer home.	3
Could not manage bus because of stroke.	2
Could not get time off work to attend. (A lorry driver and a cook)	2
Very dissatisfied at waiting too long, lack of explanation about his illness and lack of advice from the doctor	1
Felt that his illness was not serious enough to matter	1
Depressed after death of an only daughter and no longer cared about himself.	1

Drugs

Twelve defaulters and ten regular attenders were taking less than lg. daily of Methyldopa, 2 of each group took 1-2g. and two regular attenders more than 2g. daily. Three of each group were taking Reserpine 0.1 mg. twice daily and all patients were taking Bendrofluazide 5 mg. each morning. It is plain that the drugs used and their doses were similar in two groups.

The side effects of drugs of which the two defaulters complained were giddiness on standing; and those of which the regular attenders complained were giddiness on standing in six, drowsiness in two, and stuffy nose in two.

Five of the defaulters attended again after being interviewed at home and have since attended regularly.

Discussion

Despite its importance, there is little published work on the frequency of or reasons for defaulting from clinics. Knox and Dugdale (1) found that for children it was often the defaulting child who needed most help. They showed, with examples, the importance of visiting the homes of defaulters. In a study of hospitals in Britain (2), 13% failed to keep outpatient appointments but 4% turned up without appointments.

Backett and others (3) found that out of 11,533 new appointments to attend outpatient clinics in N.E. Scotland, 1,217 failed to keep the appointment; however, all but 545 (5% of the total) attended hospital at a later date. Most of those who defaulted had been waiting longer for the appointment than those who attended.

Chamberlain (4) found in two district hospitals in England that 15% in one and 24% in another failed to keep the second appointment. She suggested that defaulting might be because patients knew they could so easily get a further appointment if needed and that if they felt well, they would not bother to attend.

Newill and others (5) studying attendances at a diabetic clinic at Cleveland, Ohio, found that over a 15-year period, 50% of active attenders did not attend for longer than five years. Sussman and others (6) have further studied defaulting from this diabetic clinic. They used a pair technique similar to that reported here but also planted an observer in the waiting area to assess attitudes to the clinic. The most significant difference between regular attenders and defaulters was that defaulters felt that they could look after themselves and did not need to attend the clinic. They found no difference between the groups in the frequency of complaints about seeing different doctors, about fees or transport. Suggestions for improving the clinic were to reduce waiting time and to see the same doctor at each visit. The patients in the present study made the suggestions but could offer no advice on how to achieve these aims.

A study in Dundee, Scotland, on outpatient medical care (7) showed that an important factor in inadequate medical care was the failure to explain the treatment regime to the patient but even with explanation, patients did default when they felt well. Forsyth and Logan (8) found that about 8% of outpatients ceased to attend after six months although it was plain that the consultant expected them to return. The investigators suggested that often the next appointment was not, in fact, given to the patient but that he was told to make his own appointment after certain investigations had been completed.

In our study, the frequency of missed appointments was the same for first visits as for subsequent ones – about 30%. This suggests that the hypertension clinic was not any more deterring to patients than the other hospital clinics. Most of the patients with new appointments had been referred from other other clinics in the hospital and only a very few came direct from wards or doctors elsewhere.

Table 2 shows that ethnic group breakdown of defaulters is the same as that of all those attending for the first time. Whilst it has been suspected that Malays have tended to use Western medicine a little less readily than non-Malays, those who did reach the clinic appeared to value its service.

Table 3 shows that the chief difference between the defaulters and regular attenders was that the defaulters were in a lower socio-economic class as judged by the sophistication of employment. There were more defaulters out of work, more doing unskilled or semi-skilled work, more found travel difficult and had to travel by bus than regular attenders. Caldwell and others (9), studying dropouts from a hypertension clinic in Detroit, found the most important factor associated with a high dropout rate was low socio-economic status.

The regular attenders complained more about the service given and of side-effects of treatment. This was probably because they had selected themselves as a more sophisticated group than the defaulters. Although educational background was not formally recorded, skilled workers and women employing servants would, in Malaysia, normally have had more formal education than unskilled or semi-skilled workers. They would be less prone to accept the clinic and their management uncritically.

They would also have been more able to communicate easily with the doctor about drug side-effects. Regrettably, the personalities of the patients in the two groups were not studied.

The fact that seven defaulters were not living at their original address at the time of appointment was surprising. In May 1969, in the middle of the survey, there was a civil emergency with curfews and other disruptions. This prolonged the study and was responsible for some patients moving home. Work was hard to find for unskilled people and the need to move where work could be found or moving to live with a relative when out of work may have accounted for some of the changes of address.

The Department of Medical Social Work had funds for assisting people with the cost of transport and these were of great help in running the clinic. The fact that one man defaulted for lack of money for transport suggests that we had failed to explain the help available to him. Everyone working with patients knows only too well the type of person who continually demands extra attention: the one man in this study who was intensely dissatisfied was like this. He may have been justified in some of his complaints as patients did sometimes have to wait more than an hour to see the doctor and a similar period to collect their medicine from the dispensary. Similar waiting periods were found in a study in British hospitals (2) in which 11% of patients waited more than an hour to see the doctor in the outpatients.

Nevertheless, in most of the interviews, we were encouraged by the appreciation shown by both the regular attenders and defaulters.

There is no doubt that we failed at times to explain about the illness and advise the patient about an attitude to it. This lack of general advice was likely to have been the cause for defaulting in the man who felt he did not need treatment.

Acknowledgements

We wish to thank the staff and patients of the hypertension clinic who have made it so enjoyable, our colleagues in the Department of Medicine who made the study possible, and Dr. M. Somasundaram and Dr. Ronald Simons for their most helpful advice and encouragement.

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Intrapartum death rates in hospitals

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Introduction

THE INTRAPARTUM MORTALITY RATE, which includes both the stillbirth rate and the neonatal death rate, is accepted as an indicator of the efficiency of maternity services (Lancet, 1967). We have analysed the results of the year 1967 for the Maternity Unit, General Hospital, Kuala Lumpur, and have compared them with the results of the Obstetric Unit, University Hospital, for the years 1968, 1969 and 1970.

Material and Methods

With the permission of Dato (Dr.) Ariffin bin Ngah Marzuki, data were obtained from the case records of the Maternity Unit. The data used were:—

1. The ethnic group of the mother.
2. The social class of the mother:— where the husband's reported occupation was professional, business or tradesman, the mother was considered as "upper class", all others were "lower class".
3. The parity of the mother:— they were divided into para O, para 1—3, para 4—6, and para 6.
4. The sex of the infant.
5. Whether the infant was stillborn, died in the neonatal period, or was discharged alive.
6. The birth weight of the infant. Multiple births were excluded.

Results

There were 11,721 deliveries at the Maternity Unit during 1967. The ethnic group and parities of the mothers are shown in Table 1.

Some of the case records were incomplete. The present study includes 10,175 deliveries, including 427 stillbirths.

Factors affecting death rates

By using a form of multifactorial analysis, it was possible to separate out the effects on the stillbirth and neonatal death rates of the ethnic group, social class and parity of the mother and the sex and birth weight of the infant.

Minor differences in stillbirth and neonatal death rates were associated with the ethnic group, social class and parity of the mother and with the sex of the infant; but none of these reached statistical significance. Only for the birth weight of the infant were there significant changes in the stillbirth and neonatal death rates. It appears that an infant's chances of being stillborn or of dying neonatally at the Maternity Unit, General Hospital, depend only on the birth weight of the infant.

The intrapartum death rates for infants at the General Hospital and the University Hospital are shown in Fig. 1

The death rate falls with increasing birth weight to the 7 lb class, but, after that, the death rate begins to rise again. The death rates have been separated into

Table 1: Total Number of Mothers Admitted (by race and parity of mother)

Parity / Race	0	1	2	3	4	5	6	7	8
Malay	727	357	259	184	187	176	183	138	84
Chinese	2375	713	462	375	305	388	363	283	177
Indian	669	429	337	247	227	204	203	145	121
Other races	51	24	18	16	12	9	7	4	2
TOTAL	3822	1523	2076	822	731	777	756	570	384

Race	9	10	11	12	13	14	Over 14	Unknown	Total
Malay	64	32	28	24	6	4	4	149	2606
Chinese	140	103	50	35	20	5	7	249	6050
Indian	82	39	21	12	5	3	3	165	2912
Other races	1	3	0	0	0	0	1	5	153
TOTAL	287	177	99	71	31	12	15	568	11721

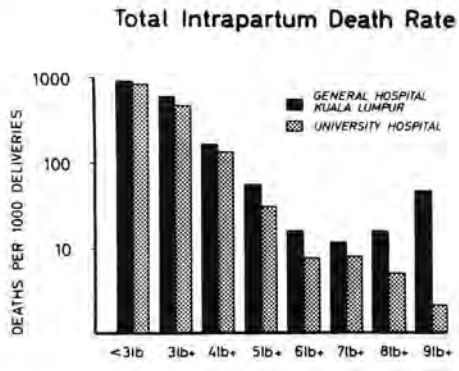

Fig. 1

The intrapartum death rates for infants born at the Maternity Unit, General Hospital, Kuala Lumpur, and at the University Hospital, Petaling Jaya.

stillbirths and neonatal deaths in Fig. 2 and Fig. 3.

For infants under 3 lb birth weight, the death rates are similar for the two hospitals, but for larger infants the death rate is lower in the University Hospital.

If the standards of care of the University Hospital had applied to the Maternity Unit, General Hospital, there would have been fewer intrapartum deaths. The actual reduction in deaths is shown in Table 2.

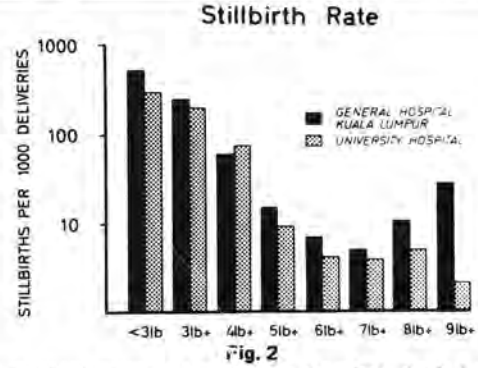

Fig. 2

The stillbirth rates at the General Hospital, Kuala Lumpur, and the University Hospital.

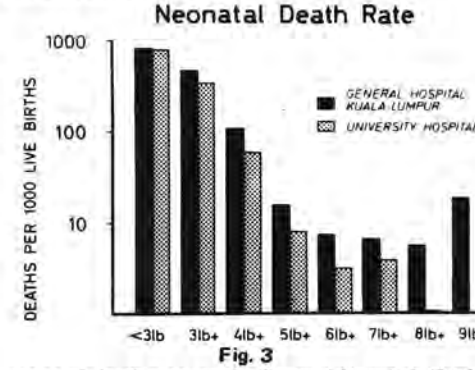

Fig. 3

The neonatal death rates at the General Hospital, Kuala Lumpur, and the University Hospital.

Table 2: The expected reduction in the number of infant deaths at GH achieved by changing the intrapartum death rates.

Birth weight lbs	Total No. of deliveries	Intrapartum deaths	Reduction in number of deaths at GH if		
			UH stillbirth rate	UH neonatal death rate	UH stillbirth & neonatal death rate
3	117	107	5	1	7
3+	149	91	4	16	21
4+	418	68	−6	20	14
5+	1,689	52	10	12	23
6+	3,835	55	10	15	26
7+	2,993	35	3	8	11
8+	867	14	4	5	9
9+	107	5	1	2	3
Totals	10,175	427	31	79	114
Reduction in death rate			7%	19%	27%

It can be seen that improvements in the stillbirth rate would reduce the number of deaths by 31, or 7.3%, improvements in the neonatal death rate would have resulted in 79 fewer deaths or 18.5% less, while improvement in both stillbirth and neonatal death rates would give 114 fewer deaths, or a reduction of 26%. The reduction of numbers of each improvement separately does not necessarily add to the total reduction when both are improved simultaneously, because improved neonatal care can be given only to liveborn infants.

Discussion

It is difficult to compare intrapartum death rates between developing and Western countries. In many developing countries, the only reliable data on intrapartum deaths is from hospitals. These data are biassed, as many women come to a hospital for delivery only if there is a complication of pregnancy or labour (Thomson, Chun & Baird, 1963). However, comparisons between the General Hospital, Kuala Lumpur, and the University Hospital are justified as both serve similar communities and we have shown that differences in ethnic group, social class and parity of the mother do not significantly affect the death rates. With the single exception of infants between 4 lb and 5 lb, the stillbirth and neonatal death rates are lower in the University Hospital.

Because of its special role in undergraduate and post-graduate teaching and in research, the University Hospital is more heavily staffed and better equipped than most of the Ministry hospitals, and these facts probably account for the differences in the death rates. Undoubtedly, the Ministry hospitals will be staffed and equipped at the same standards as the University Hospital in due course, and their standards of care will rise to the same level. However, improvements cost money, which is never plentiful, and it is important that the priority for improvements be arranged so that the maximum benefit is obtained as quickly as possible. From this study, it is possible to make some suggestions for the order of priorities.

1. The special care of small premature infants is expensive in staff and equipment. It seems that the number of lives saved by these special facilities will be small. Although one or two Special Care Nurseries should be available for experimental and educational purposes, the widespread provision of these facilities should be low in the list of priorities.
2. From the data presented in this paper, it appears that improvement in the neonatal death rate would be more effective than lowering the stillbirth rate. But many neonatal deaths occur in infants who have suffered birth injury, and occur in the first few hours of life (Dugdale 1967). Improvement in the care of mother during labour and of the infant in the immediate postnatal period would probably be the most effective way of reducing both the stillbirth and the neonatal death rates. This would involve co-operation of the

obstetrician and the paediatrician in the delivery room. In difficult deliveries, both the mother and infant need special care. The obstetrician is often fully occupied with the care of the mother; the paediatrician should be present to look after the infant. Both obstetric and paediatric trainees should be experienced in the care of neonates, and the care of mother and child should be a joint responsibility. This type of care would do more to reduce death and disability among neonates than the most elaborate of special care nurseries, and at a fraction of the cost.

3. It has been shown that the most important single factor in the survival of neonates is the birth weight. Average birth weights are lower here than in Western countries, and this probably reflects poor maternal nutrition (Richard & Lowe 1966). Our long-term aim should, therefore, be to improve maternal nutrition so that heavier infants with a greater chance of survival are born.

Acknowledgements

We thank Tan Sri (Dr.) Mohammed Din bin Ahmad, Director General of Health, for permission to publish the data from the Maternity Unit, General Hospital, Kuala Lumpur; and Mr. Terlochan Singh, Administrator, University Hospital, for access to the medical records. We also thank the Department of Medical Illustration, Faculty of Medicine, for the diagrams, Mr. Chua Lip Chiow, laboratory technician in the Department of Obstetrics & Gynaecology, University of Malaya, for assistance in obtaining and processing the data and Mrs. M.T. Ng for typing the manuscript.

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Hydrops foetalis due to alpha-thalassaemia: A case report

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Introductory Review

THE THALASSAEMIAS ARISE through genetically-determined reduction in the rate of synthesis of the polypeptide chains required for globin, and hence haemoglobin, formation (Itano, 1957, 1965; Ingram and Stretton, 1959; Weatherall, Clegg and Naughton, 1965). The two principal groups of thalassaemias involve depression of synthesis of alpha-chains or beta-chains respectively of adult Hb–A, but considerable heterogeneity exists within these classes (see Weatherall, 1969). Heterozygous alpha-thalassaemia trait, with partial suppression of alpha-polypeptide chains, is mild in its manifestations but of widespread geographical occurrence, and tends to occur wherever the general incidence of thalassaemia is high (see Motulsky, 1964; Weatherall, 1965; Huehns, 1965). The occurrence of Hb–H disease in such populations has long been recognised (see Huehns, 1965; Weatherall, 1969), and there is some evidence that individuals with this condition show the interaction to two different alpha-thalassaemia genes, 1 and 2 (Wasi, Na-NaKorn and Suingdumrong, 1964; Huehns, 1965). The occurrence and significance of the alpha1 – and alpha2–thalassaemia genes in Thailand has been discussed extensively by Wasi et al. (1969) and Pootrakul et al. (1970).

The pure homozygous form of alpha-thalassaemia is associated with severe hydrops foetalis, anaemia and erythroblastosis foetalis, and is incompatible with life (Lie-Injo and Jo, 1960 a, b; Lie-Injo, 1962, 1964; Lie-Injo et al., 1962). Lie-Injo and colleagues first described the condition in Chinese in Indonesia, and later found it to the extent of 1.6 per 1,000 Chinese newborns and 3.4% of stillbirths, but not in Malays or Indians in Malaysia (Lopez and Lie-Injo, 1960). Besides the occurrence in the Chinese in Singapore (Wong, 1965) and Hongkong (Banwell, 1964; Todd, Lai and Braga, 1967), this form of hydrops has been reported as quite common in Northern Thais (Bhoonsri et al., 1968) and rarely in Greek Cypriots (Diamond, Cotgrove and Parker, 1965) and Filipinos (Pearson, Shanklin and Brodine, 1965). The pathological features of the hydropic infants have been extensively reported in the above papers by Lie-Injo, Lopez and Dutt (1968). The anaemia and predominance of Hb-Bart's (Hb-gamma$_4$) in the red cells of these infants is stressed in all reports (ca. 75–90%). The remaining haemoglobin appears to be characterised by a combination of gamma-chains with unique chains similar to or identical with chains of Hb-Portland, normal Hb–A, A_2 and F being absent (Weatherall, Clegg and Wong, 1970; Todd et al., 1970). The complete suppression of alpha-chain pro-

duction seems to characterise the homozygous alpha$_1$-thalassaemia state (Weatherall, Clegg and Wong, 1970). The known high affinity of Hb-Bart's for oxygen has been stressed as a probable contributory factor to the severe effects on the foetus in alpha-thalassaemic hydrops (Wasi et al., 1969). Weatherall (1969) reviews the genetic and biochemical considerations at nuclear and cytoplasmic levels in the origin of alpha-thalassaemias.

Recognition of the heterozygous alpha-thalassaemia trait condition is difficult (see Huehns, 1965; Weatherall, 1969), and it is not easy to identify matings at risk for the production of hydropic infants. Although low levels of Hb-Bart's (5–10 and 1–2% range) occur at birth, this disappears in infancy. In the adult individuals Hb–A$_2$ levels are normal or low, not raised as in many beta-thalassaemia traits and persistence of Hb–F is unusual. Traces of Hb–H, detectable by electrophoresis of the red cell haemolysate or in the red cell incubation reticulocyte preparation, are variable and inconstant. Thalassaemic red cell morphological abnormalities may be present, mild or absent and the haemoglobin level slightly reduced or normal. Demonstration of increased osmotic resistance of the red cells to saline haemolysis in addition to their morphological abnormalities is valuable in the detection of all forms of thalassaemia trait (Beaven et al., 1964; Beaven, Dixon and White, 1966; White, Lau and Beaven, 1968), and Pearson, Shanklin and Brodine (1965) utilised this to characterise the parents of a Filipino hydropic infant. In the present report, similar methods were used in investigating the parents of a hydropic infant with high proportion of Hb-Bart's in the cord red blood cells, and dying shortly after delivery.

Case Report

A. Patient

W.K.B., a 27-year-old Chinese primigravid female, who had been married for a year, was admitted as an unbooked emergency with a history of swelling of legs and passage of only small amounts of urine for ten days and headache. She was 28 weeks gravid by dates.

On examination, she was pale and had gross ankle oedema and puffiness of face. Her blood pressure was 170/100 mm Hg. She had a grade 2/6 – cardiac systolic murmur over the praecordium. Uterine size was 34 weeks – larger than dates – and the foetus was a longitudinal lie, with a cephalic presentation in the left occipito-anterior position. Foetal heart was heard and regular. Liquor was not excessive. A diagnosis of severe pre-eclamptic toxaemia with possible hydrops foetalis was entertained.

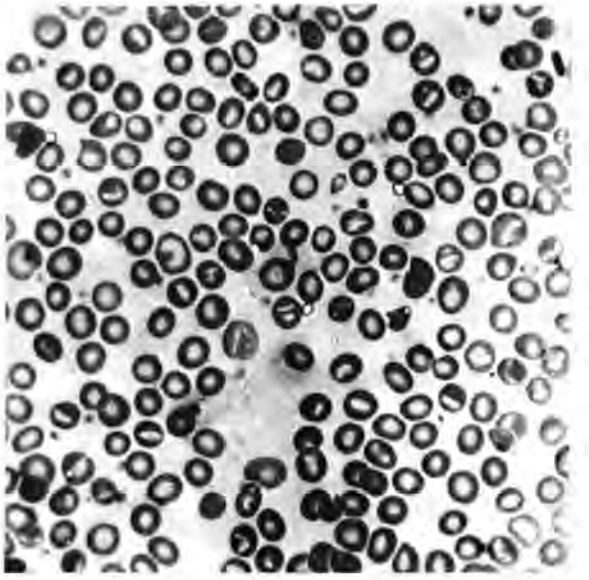

Fig. 1

Peripheral blood film of mother, showing mild red cell abnormalities. (May-Grunwald-Giemsa stain, x 600)

Investigations

Haematological investigations were by standard methods (Dacie and Lewis, 1968), and methods particularly indicated for thalassaemia were also used (Beaven, et al., 1964; Beaven, Dixon, White, 1966). Haemoglobin was 8.0 g/100 ml; PCV 30 per cent; MCV 105.7 cu.u; MCHC 26.8 per cent; blood urea 23 mg/100 ml; serum electrolytes:– Na+ – 130 mEq/1., K+ – 3.8 mEq/1., C1– 106 mEq/1. Blood group O Rhesus positive; no antibodies. ESR – 46 mm/hr.

Serum assays showed a serum iron of 96 µg/100 ml (UIBC, 284, TIBC 380ug/100 ml) and a serum folate of 3.7 ng/ml, vitamin B_{12} – 1171 pg/ml. Blood film morphology showed slight anisocytosis and anisochromasia of the red cells with some microcytosis and overall hypochromasia, and occasional elliptical, small and irregular and poikilocytic cells (Fig. 1). Osmotic fragility of the red cells was markedly decreased before and after sterile incu-

bation at 37°C for 24 hours (Fig. 2), with Median Corpuscular Fragility of 0.275 (g per 100 ml of NaCl) in both instances (normal pregnant means 0.445 and 0.550 respectively, Beaven, Dixon, White 1966). Autohaemolysis normal. Haemoglobin electrophoresis (Fig. 3c) showed Hb–A with normal A_2 (2.6 per cent) and non-haem protein (1.9%); the alkali-resistant haemoglobin fraction was normal at 0.9 per cent, and no Hb–H inclusions present in the incubation reticulocyte preparation.

(b) Urine was cloudy, acid with 2 WBC/μl. No proteinuria; on culture coliform organism were grown with a viable count of 10,000 organisms/μl.

(c) X-ray abdomen – single foetus with maldeveloped upper limbs. Gestational age 34 weeks.

She was therefore considered to be a case of alpha-thalassaemia trait (heterozygous) in addition to having P.E.T. She was treated with sedatives, hypotensive and diuretics.

On 24.1.71 at 30 weeks gestation, she began spontaneous labour and delivered a hydropic female foetus weighing 1600 g, which died soon after delivery. The placenta was large (1060 g), oedamatous, pale and friable.

B. Infant

Haematological Studies

The cord red blood cells taken at delivery were of group O Rhesus positive, no antibodies present (identical with the mother); Direct Coombs' test negative. Electrophoretic examination of the infant's red cell haemolysate showed that Hb Bart's was the major haemoglobin present (Fig. 3b, e).

The Hb-Bart's amounted to 74 per cent of the total haemoglobin. Most of the remaining haemoglobin gave a discreet band in a position similar to Hb–A, using zone electrophoresis in a discontinuous pH 8.9 tris-EDTA-borate, pH 8.6 barbital buffer system on cellulose acetate (but see recent papers by Weatherall, Clegg and Wong Hock Boon, 1970 and Todd et al., 1970 for information on the non-alpha$_2$ beta$_2$ nature of this fraction in alpha-thalassaemic hydrops). Mere traces of non-haem protein in the usual position and of a fast Hb (?Hb–H) were also present.

Alkali-resistant Hb formed 80 per cent by the ¾ minute denaturation method (Beaven, Ellis and White, 1960–61), but by determination of the rate of alkaline-denaturation, this fraction had curvilinear and faster denaturation rate than normal Hb–F, as

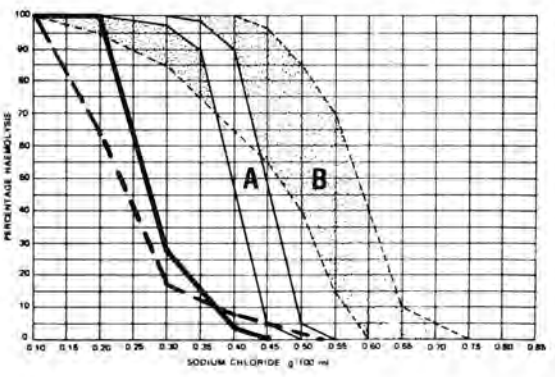

Fig. 2

Osmotic fragility of red cells of mother

—— before incubation.

— — after sterile incubation at 37°C for 24 hrs.

A normal range before incubation.

B normal range after incubation.

Fig. 3

Cellulose acetate electrophoresis at pH 8.6 of haemolysates of family with alpha-thalassaemia

a. Hb-H disease control.
b. Hydropic infant.
c. Mother of hydropic infant.
d. Father of hydropic infant.
e. Hydropic infant.
f. Normal cord blood control
*** NHP, non-haem protein.**
**** Hb fraction in hydropic infant haemolysate in position of Hb–A under these conditions.**

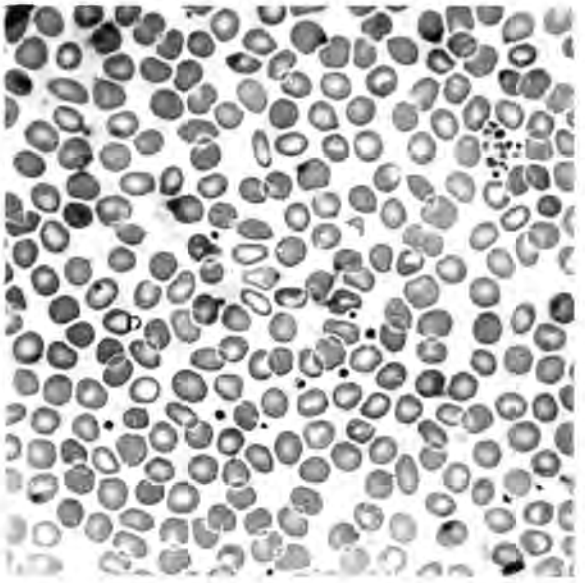

Fig. 4

Peripheral blood of father, showing mild red cell abnormalities and occasional elliptical cells. May-Grunwald-Giemsa stain, x 600.

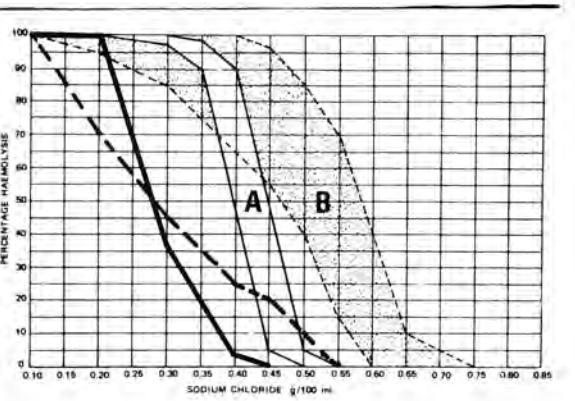

Fig. 5

Osmotic fragility of red cells of father:—

——— before incubation.

— — after sterile incubation at 37° C for 24 hrs.

A normal range before incubation.

B normal range after incubation.

found by Ager and Lehmann (1958) for Hb-Bart's.

Post-Mortem Examination

Revealed ascites, an enlarged congested liver and spleen, with numerous foci of erythropoiesis in both. The cause of death was considered to be hydrops foetalis and erythroblastosis.

Puerperium

Routine abdominal examination revealed bilateral cystic masses in both iliac fossae which, on laparotomy, were confirmed to be bilateral ovarian serous cystomas. Bilateral ovarian cystectomy was carried out.

Since discharge and at post-natal follow-up, she has remained well.

Haematological examination four months after delivery showed Hb 12.2 g/100 ml, PCV 42, MCHC 29 per cent. Red cell characteristics as before; no Hb—H inclusion bodies detected, and red cells containing Hb—F 0.2 per cent (more than might be expected). Electrophoretic composition of the haemolysate unchanged. Serum assays have shown iron varying from 52 µg/100 ml post-delivery to 114 µg/100 ml 2½ months later. Folate levels were satisfactory (18.8 ng/ml) two months after a course of oral folic acid therapy.

C. Haematological Examination of Husband

The husband's blood was examined after the wife's delivery. The haemoglobin was 14.5 g/100 ml, PCV 45, MCHC 32.2 per cent. The blood film showed mild morphological abnormalities, with slight anisocytosis, anisochromasia, hypochromasia and occasional elliptical and elongated cells (Fig. 4). The osmotic resistance of the red cells was markedly increased with MCF of 0.270 before incubation and 0.230 (g/100 ml of NaCl) after incubation (Fig. 5). Autohaemolysis normal. Serum assays, iron 126 µg/100 ml (UIBC, 141, TIBC 267 µg/100 ml).

Haemoglobin electrophoresis showed Hb—A as the major component (Fig. 3d), with normal Hb—A_2 (2.1 per cent) and non-haem protein (1.4 per cent); alkali-resistant Hb normal at 0.8 per cent, and no Hb—H inclusions detected in the incubation reticulocyte preparation.

The findings were considered compatible with the

presence of the alpha-thalassaemia trait. As both parents carry the same abnormal trait, it is possible for the hydropic infant to be homozygous for this condition.

Discussion

Clinical and Pathological Considerations

Hydrops foetalis can result from a number of causes, e.g. haemolytic disease associated with (1) Rhesus or less commonly ABO group incompatibility (see Mollison, 1967; Weiner, 1968), (2) congenital syphilis, (3) severe congenital heart disease (Donald, 1969), (4) homozygous alpha-thalassaemia. In much of S.E. Asia, and in Malaysia particularly, Rh incompatibility is rare apart from the Indian population, though ABO incompatibility is not uncommon. Amongst the Chinese particularly, the occurrence of homozygous alpha-thalassaemia must be considered. The finding of a very large proportion of Hb-Bart's (Hb – gamma$_4$) in the red cells of infants is highly suggestive. Such infants are usually born dead at 28–34 weeks, or die shortly after delivery, and have generalised hydrops, ascites and hepatosplenomegaly with erythroblastaemic anaemia and marked extramedullary haemopoiesis. Further confirmation is obtained if the heterozygous alpha-thalassaemia trait can be demonstrated in the blood of both parents (see Weatherall, 1965, and references in Introductory Review).

The finding of Hb-Bart's in the infant's red cells is not unique to this form of hydrops; it is the very high proportion which is significant (ca. 75–90%). Smaller amounts are common in cord blood cells, particularly in populations where thalassaemia is common (Hendrickse, 1965; Weatherall, 1965; Beaven, Dixon and White, 1966), but the proportions are far lower (<1–2% and 5–10%), and disappear together with the decline in Hb–F during the first six months of life (Ager and Lehmann, 1958). Some such infants will subsequently be found to be healthy but carry the alpha-thalassaemia trait, whilst in others a higher proportion of Hb-Bart's is replaced wholly or partly by Hb–H in the presence of Hb–H disease (see Huehns, 1965; Weatherall, 1969).

The identification of the mother-at-risk in advance and her expectant management depends upon recognition of the alpha-thalassaemia trait. The generally agreed difficulty in doing this has been commented upon above. The general characteristics of the thalassaemia-trait blood picture are (Beaven, Dixon and White, 1966):–

(a) abnormalities of red cells, including microcytosis.
(b) reduced mean corpuscular haemoglobin concentration (MCHC).
(c) reduced osmotic fragility of the red cells before and after incubation.
(d) presence of iron (often increased) in storage reticulum cells and erythroblasts of the bone marrow.
(e) significant proportions of foetal haemoglobin.
(f) marginally or significantly elevated Hb–A_2 levels.

Abnormalities (e) and (f) apply particular to the beta-thalassaemia traits, and not to the alpha-type.

Both alpha- and beta-thalassaemia traits are not uncommon in Malaysia. Morphological changes in the red cells are of very frequent occurrence in Asian populations, and are often attributable to nutritional deficiencies, particularly iron deficiency. Even where this can be excluded with the help of serum assays, etc., the abnormalities are not always readily assignable to any definite genetic trait (White, Lau and Beaven, 1968). In the alpha-thalassaemia trait, the haemoglobin level may be normal or only slightly reduced, Hb–A_2 levels are not raised as is common in the beta-trait, Hb–F is not usually raised and presence of traces of Hb–H is inconstant. The determination of red cell osmotic fragility before and after incubation of the cells is valuable in that the resistance is often markedly increased, but the test is time consuming. Danon (1963) has described a rapid micro method for recording red cell osmotic fragility by continuous decrease of salt concentration which could extend the scope of this investigation, though requiring special apparatus.

Genetic Counselling

It will usually come about that hydrops foetalis due to homozygous alpha-thalassaemia is detected only after birth of an affected child, which may be a first child as in the case reported. The wider question of recognising matings-at-risk in advance depends upon widespread application of techniques for the often difficult detection of the alpha-trait state in the parents-to-be.

In either event, the Mendelian segregation of the abnormal gene indicates that for every severely affected child, two children with the same mild heterozygous trait as the parents may be expected to be born,

and one completely free of the trait. Nonetheless, although this is the expected overall distribution, the order is not necessarily conformed to, and repeated pregnancies may result in further affected infants, as in the three successive cases described by Banwell and Strickland (1964).

Summary

1. A case of hydrops foetalis is described in a female Chinese infant dying shortly after spontaneous birth at 30 weeks of gestation. There was severe anaemia (3.6 g/100 ml), and the red cell haemolysate contained ca. 74 per cent of Hb-Bart's.
2. The alpha-thalassaemia trait was recognised in both parents by the occurrence of minor red cell abnormalities but markedly increased osmotic resistance in the presence of normal proportions of Hb–A, Hb–A_2 and Hb–F in the haemolysate; there was no reduction in serum iron levels.
3. The clinical, pathological and genetic features of the homozygous condition are discussed, and also the problem of recognising the mild, heterozygous alpha-thalassaemia trait.
4. The importance is stressed of recognising homozygous alpha-thalassaemia as a cause of hydrops foetalis in S.E. Asia, among Chinese populations particularly. The parents may be advised that normal and minimally-affected trait carriers may also be expected among their progeny.

Acknowledgements

We are grateful to Professors D. Chan and K.S. Lau. Also to Mr. Yee Kwok Hoi, Enche Mohammed Maidin and the staff of the Nutritional Anaemia Research Laboratory for technical assistance, and the Department of Medical Illustration. This work was supported in part by funds from the U.S. Public Health Service Asia Grant No. AM11048–01. One of us (J.C.W.) is in receipt of a Special Commonwealth Award.

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Foetal blood sampling in clinical foetal distress

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THE PATIENT IN labour who develops clinical signs of foetal distress poses problems in management because, amongst other things, signs such as abnormal foetal heart rate and meconium-stained liquor do not correlate well with the infant's condition at birth (Wood and Pinkerton, 1961; Day et al, 1968). A more precise method for detecting foetal acidosis is by foetal scalp blood sampling introduced by Saling (1965). We have recently performed foetal blood sampling in cases of clinical foetal distress in order to confirm or exclude the presence of foetal anoxia, and to assess its use in the management of these patients.

Technique and Results

The essential steps are similar to those described by Beard and Morris (1965) and Beard (1970). Under sterile conditions, an amnioscope is introduced through the cervix to rest against the foetal scalp. The scalp area is cleaned with small gauze swabs, sprayed with ethychloride, and finally painted with silicone or liquid paraffin. A small incision is made on the scalp with the blade. A droplet of blood forms at the puncture site and a capillary blood sample is obtained through the amnioscope. The instruments used in this procedure are shown in Figure 1. The acid-base status of the foetal blood is determined with the Astrup micro-pH meter.

Foetal blood sampling during labour is indicated in clinical foetal distress in high risk conditions, including cases of intrauterine growth retardation and in patients who had low urinary oestriol excretion during pregnancy (Fliegner et al, 1970). Repeat sampling is carried out if necessary during labour until delivery is completed. The results of 12 patients who had foetal blood sampling done and the foetal outcome are shown in Table I.

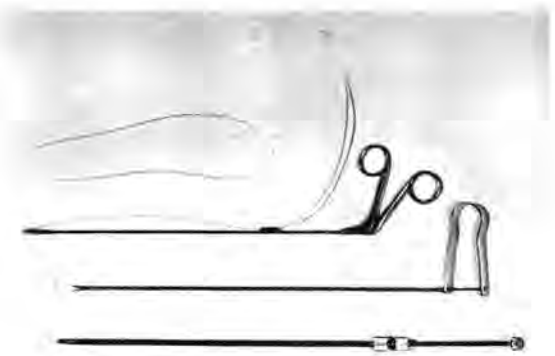

Fig. 1
Instruments for foetal scalp blood sampling

TABLE I

CASES WITH CLINICAL FOETAL DISTRESS SHOWING THE FOETAL pH AND APGAR SCORE AT BIRTH

Case	Foetal Heart Rate	Liquor* Amnii	Foetal pH	Cervical Dilatation (cm.)	Apgar Score at 1, 5 mins.
1.	>160	M	7.24	4	3
2.	Normal	M	(7.32	4)	8, 10
			(7.24	8)	
3.	Irregular	M	7.35	4	10, 10
4.	Irregular	M	7.36	4	9, 10
5.	Normal	M	7.44	4	9, 10
6.	Irregular	M	7.37	6	10, 10
7.	>160	M	7.35	3	7, 10
8.	Irregular	M	7.36	4	8, 10
9.	>160	M	7.34	2	9, 10
10.	>160	M	7.41	3	10, 10
11.	>160	M	7.38	6	9,10
12.	>160	C	7.37	4	6,10

*M — Meconium-stained

C — Clear

Discussion

All the 12 patients showed evidence of clinical foetal distress. Of these, only Cases 1 and 2 have a low pH. Caesarean section was done in Case 1 and the Apgar score of the baby was 3. In Case 2, the foetal blood pH was 7.32 at 4 cm. cervical dilatation but was 7.24 at 8 cm. dilatation. Ventouse delivery was performed immediately and the baby's Apgar was 8 at 1 minute. In all the other patients, the foetal blood pH was normal, and labour was allowed to progress. They all delivered vaginally except for Cases 10 and 11 where Caesarean section was subsequently done for failure of progress of labour. Case 12 had Caesarean section for prolonged labour and intrapartum maternal pyrexia. In all cases, where the foetal blood pH was normal, the foetal condition at birth was good with a high Apgar score. In clinical practice, when there is a combination of foetal heart irregularity, tachycardia or bradycardia coupled with meconium-stained liquor, this calls for some operative procedure to deliver the foetus as soon as possible. Caesarean section would be done if the cervix is not fully dilated. If foetal scalp blood sampling was not done, all these patients might have had Caesarean section performed for clinical foetal distress. Similar findings have been reported by other workers. Due to the more precise diagnosis of intrapartum foetal hypoxia by pH, Beard (1968) has reported a reduction in the Caesarean section rate for foetal distress by over 50 per cent at Queen Charlotte's Hospital in London.

The management of patients with foetal distress has been well documented by Coltart et al (1969). If the pH was normal (greater than 7.25), labour was allowed to continue. If the pH was between 7.25 and 7.20, a further sample was collected within 30 minutes. If the pH was below 7.20, operative delivery was undertaken. Beard and Morris (1969), reporting on perinatal mortality among babies weighing more than 1,500 gms., showed that in the five years following the introduction of foetal blood sampling, the perinatal death underwent a significant fall compared with the previous years.

Lumley and Wood (1969), and Fliegner et al (1970) have shown that foetal blood sampling is a useful technique for detecting foetal acidosis in the first stage of labour. Fliegner et al (1970) have demonstrated its usefulness at the time of amniotomy (A.R.M.) in high risk cases, and the importance of serial estimations during labour for management of cases with clinical foetal distress. It has been shown that there is significant correlation between the foetal pH and baby's condition at birth (Beard et al, 1966). Greater accuracy in the detection of intrapartum foe-

tal anoxia by foetal blood sampling compared to clinical diagnostic criteria has been shown in cases with foetal distress and also in cases with hypertension and proteinuria (Wood et al, 1968; Wood, 1969).

Summary

The technique of foetal blood sampling during labour is described. This is a useful diagnostic aid for the detection of foetal acidosis (chemical foetal distress) in cases of clinical foetal distress and high risk pregnancies, with special reference to placental insufficiency syndrome.

When foetal anoxia is confirmed, operative delivery should be performed quickly to avoid perinatal deaths; when there is no biochemical confirmation of foetal anoxia, unnecessary Caesarean sections can be avoided.

Acknowledgement

We would like to thank Professor Donald P.C. Chan and Dr. T.A. Sinnathuray for their encouragement in this study and for permission to publish.

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Chronic vasomotor rhinitis in the tropics

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CHRONIC VASOMOTOR RHINITIS poses a formidable problem to the rhinologist in the tropics. The patients complain of distressing nasal obstruction, especially at night, with episodes of sneezing and profuse watery rhinorrhoea. They are unduly sensitive to changes in the atmospheric temperature and humidity. Such changes affect the dynamics of nasal circulation. Because of its highly specialised function of purifying, humidifying and warming, the nasal mucosa is endowed with a rich vasculature, controlled by an equally rich autonomic nervous system and local axon reflex. (Ritter 1970 Cuana 1970). Such a specialised functional unit could over react to minor changes, in some patients, causing the above symptom complex commonly known as Vasomotor Rhinitis. In this condition, the nasal airway is totally or partially obstructed. Such obstruction is intermittent and alternates from one to the other side.

There are several methods to relieve this type of obstruction. Almost all of them are empirical since the exact aetiology is unknown. They include:—

(a) Local application of vaso-constrictor drugs. These give only temporary relief.
(b) Long acting antihistamines. They act on the capillaries and mucous secreting glands.
(c) Surface cautery of inferior turbinates with corrosive agents or hot point.
(d) Submucous resection of the inferior turbinate bone (Odeneal 1930) or partial resection of the turbinates. This provides a bigger nasal airway.
(e) Vidian nerve neurectomy
(f) Submucous injection of sclerosing agents such as sodium morrhuate with the hope that they contract the mucosa without injuring the cilia.
(g) Submucous diathermy of the inferior turbinates.

Here an attempt is made to evaluate this last form of treatment. A special effect is made to correlate the result with the clinical picture.

Material and Method

A total of 200 patients, subjected to submucous diathermy between October 1967 – September 1969, were included in this study. A detailed history and their main presenting symptoms were tabulated. (Table I). The complaint of nasal congestion and obstruction was of an alternating type especially present at night. It was aggravated in almost all cases by cold and rainy weather, and changes in atmospheric temperature as when entering an air-conditioned room. The nasal discharge was watery and profuse, associated with sneezing episodes, present mainly in the morning. The headaches varied in their location from frontal, bitemperal to parietal regions; intermittent and severe during attacks. The nasal pain was confined to the nasal cavity. The symptoms in the upper respiratory tract were confined to the post-nasal, oropharyngeal and hypopharyngeal region and varied from discomfort to pain, secondary to infection. The history of allergy was confined to dust and seafood. All these data are tabulated under the major ethnic groups. (Tables I and II).

TABLE I

Presenting Symptoms according to Ethnic Groups

Symptoms	Frequency according to ethnic groups				
	Chinese	Indian	Malay	Others	Total
Nasal congestion and intermittent obst.	122	37	6	3	168
Watery nasal discharge	99	24	7	3	133
Sneezing episodes	62	20	7	0	89
Headache	17	8	0	1	26
Ear complaints	11	–	1	0	12
Nasal pain	1	–	0	0	1
U.R.T. irritation	52	14	2	2	70
Allergy	13	5	2	0	20

TABLE II

Duration of Symptoms – Total 200 cases

Race	0 – 5 months	6 – 12 months	1 – 2 years	2 – 3 years	3 – 4 years	4 – 5 years	5 + years	Total
Chinese	7	6	23	23	11	24	54	148
Indians	2	1	8	6	5	6	12	40
Malays	0	0	2	2	0	1	4	9
Others	0	1	1	0	1	0	0	3

Birtcher Hyfregator was used for this form of treatment. This is a simple device creating, by use of a spark-gap condenser circuit, a very high frequency damped current of relative high voltage, but of a low amperage. Such a current produces electro dessication of tissue around the electrode, causing rupture of cell capsules with transformation into a dry mass. This electrode consists of a fine needle insulated except for one inch at the end. The naked end was inserted submucosally into the inferior turbinate. A current of sufficient intensity between 25 – 50 as shown on the dial of the Hyfrecator was activated for 15 – 20 seconds.

The process was commenced posteriorly and repeated from behind forward (Fig. 1). The nasal mucosa was previously anaesthetised by painting the surface with 5% cocaine in 1:1000 adrenaline. This not only gave an effective anaesthesia but also enabled determination of whether the mucosal swelling was due to oedematous enlargement, in which case it shrank considerably, or to hypertrophy. This confirmed the previous clinical finding by probing. After diathermy, each patient was given long acting antihistamines for varying periods of time. This helped to reduce post-diathermy reaction and edema.

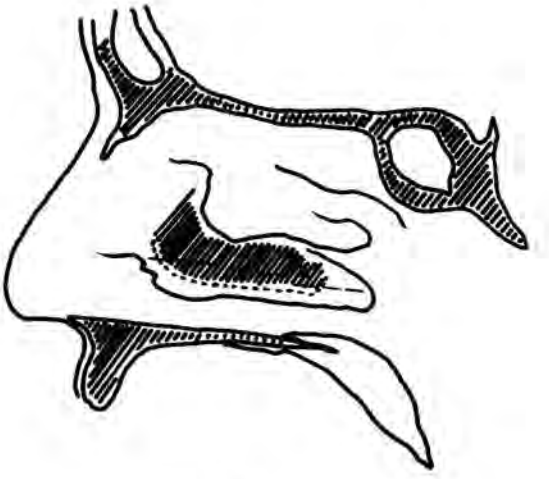

Fig. 1

Diagram showing sites of insertion of electrode along the inferior turbinates

TABLE III

Response to Diathermy according to Clinical and Radiological Finding

Clinical and X-ray Finding	Duration of Systematic Improvement			No
	Immediate 0 – 3 months	Improvement Temporary 3 – 6 months	Permanent 6 months and over	
1. Odematous Nasal Mucosa with Normal Sinus X-ray	15	45	70	2
2. Odematous Nasal Mucosa with +ve Sinuses X-ray Diathermy with Antral washout	2	16	11	–
3. Hypertrophic Nasal Mucosa with Normal Sinus X-ray	12	1	0	10
4. Hypertrophied Nasal Mucosa with +ve Sinus X-rays. Diathermy combined with Antral washout	3	1	0	12

Result

The patients were followed up at intervals of about three months and response to treatment recorded. They were asked whether this treatment gave them relief and if so, the extent and duration. The bulk of these patients were followed up for periods ranging from 12 – 18 months. The response to diathermy was tabulated against the clinical and radiological finding. (Table III). The patients were divided into two main groups:–

(i) Those with engorged and edematous mucosa that pitted easily.

(ii) Those with nasal mucosa that were more turgid and hypertrophied with minimal pitting.

The groups were subdivided according to the radiological findings of the para nasal sinus. Those with positive findings were given appropriate treatment with antral washout, antihistamines and prophylactic antibiotics. Most of them turned out to be mucosal swellings, but those few with frank infection were excluded from this series. The cases with favourable response were divided into three groups:–

Immediate, relief of up to three months

Temporary, relief from three to six months

Permanent, relief over six months.

The failure cases were advised alternative treatment, like partial resection of inferior turbinates with sub-mucous resection of septum if found deviated.

Discussion

The symptoms of nasal obstruction, sneezing and watery rhinorrhoea, in the absence of definite aetiological factors, are distressing to the patients. When the normal airway is obstructed, they experience great respiratory difficulty. The inspired air passing through the nasal cavity has to be humidified and warmed. The relative humidity of alveolar air is 90%, and 70% of this humidity is accounted for by the nasal cavity (Proetz 1963). Similarly, the temperature has to be raised from that of the atmosphere to 35° – 37°C. All this is done in one second – the average time the inspired air takes to pass through the nasal cavity (Ritter 1970). In order to accomplish this, the nasal mucosa not only has to have a rich vascular supply but also an elaborate naso-angio-architectural arrangement. Microscopically, there is a functional arrangement of these vessels in the nasal cavity, especially the turbinates. The minute vessels comprising arterioles, capillaries, sinusoids, venules, have well developed smooth muscles. They run in parallel rows in a posterior – anterior direction and are arranged in three distinct levels in relation to the surface epithelium.

(a) Superficial level lying under the mucosa supplying respiratory epithelium.

(b) Second deeper level in association with the mucous and serous glands, surrounded by loose connective tissue. Sinusoids

are prominent in this layer.

(c) Deeper level adjacent to the osseous supporting framework (Ritter 1970).

These vessels are controlled by:—

(i) autonomic nervous system – sympathetic and parasympathetic

(ii) local axon reflex

(iii) chemical substances carried to the mucosa via the bloodstream (Cuana 1970).

The aim in the above form of treatment is to destroy by dessication the middle vascular layer thereby promoting fibrosis and reduction of the vascular bed. The advantage of this method is that it preserves the respiratory epithelium. Although no histological study was made in this series, clinical observation, as evidenced by the absence of dryness and crusting of the mucosa, seemed to agree with the histo-pathological studies of Uede (1962). He found that low-grade high-frequency electrical current apparently caused vaso-constriction and to some extent occlusion of the vascular network with fibrosis of the submucosal tissue. On the other hand, due to the low-grade current, no injury was caused to the surface epithelium.

The area and depth of tissue dessicated and destroyed with one application in the electrode is directly proportional to:

(a) the current intensity

(b) the surface area of the electrode

(c) duration of current flowing through the electrode

(d) the density and moisture content of the tissue (Birtcher Corp: 1963).

Factor a – c, being constant, the only variable was (d), i.e., the individual variation in the cellular and fluid content. Patients with an edematous vascular mucosa (Table III column 1 and 2) showed a good response to this treatment while those with hypertrophic mucosa had a less favourable result. (Table III column 3 and 4).

Analysing the results of Table I, the majority of patients had one or more of the following symptoms of nasal obstruction, discharge and sneezing episodes. These symptoms were a constant feature. Upper respiratory tract symptoms were present in 70 patients. This is understandable since patients with nasal obstruction breathe through the mouth and this causes drying and irritation of the pharynx. Symptoms of allergy to dust and seafood were present in 20 cases (i.e. 10%), and was controlled with antihistamines. Table III shows the result of submucous diathermy of the inferior turbinates.

Of the 200 cases under review, 176 or 88% had symptomatic relief and 24 or 12% were failures with no relief.

Of the 24 failures, 22 belonged to the hypertrophic group.

Of these improved, 159 or 79.5% were in the odematous group and 17 or 8.5% were in the hypertrophic group.

Of the odematous group, 81 or 40.5% showed prolonged relief, 61 or 30.5% showed temporary relief of up to six months and 17 or 8.5% showed immediate relief up to three months.

Of the hypertrophic group, none showed prolonged relief of symptoms, 2 or 1% showed temporary relief of up to six months and 15 or 7.5% showed immediate relief of up to three months.

Summarising the successful cases, 176 or 88% had beneficial effect, of which 81 or 40.5% had prolonged relief, 63 or 31.5% had temporary relief and 32 or 16% had immediate relief.

Conclusion

Submucous diathermy, as a form of conservative treatment of vasomotor rhinitis, gives satisfactory result in persons who, otherwise, undergo great discomfort. Persons who benefit most from this type of treatment are those in whom symptoms and signs point to a vascular instability resulting in engorged and odematous mucosa. Allergy complicating this condition does not constitute a contra-indication provided it is treated as well. Presence of infection in the nasal or paranasal sinuses is a contra-indication. Long history seems to be the rule (Table II) in most cases under review but my impression is that the shorter the history the better the result of diathermy.

Acknowledgement

The author is grateful to Dr. R. Werner, head, and Dr. U. Prasad for their help and comments and to Miss Yap for assistance in preparing this paper.

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Surgical management of patients with advanced buccal pouch cancer

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Introduction

IN WEST MALAYSIA, buccal pouch cancer is a problem second only to cancer of the cervix. This is in keeping with the fact that the incidence of intra-oral cancer is highest in Southeast Asia.[1] Betel-nut and tobacco chewing is a strong initiator and promoter of cancer of the cheek.[2-4]

Most patients seek treatment only when the primary lesion is in an advanced stage. However, fortunately, apart from involvement of the lymph nodes in the immediate vicinity, distant metastasis is rare.[5] Radiotherapy alone is not the answer to this problem.[10]

Material and Method and Discussion

Between August 1969 and July, 1970, 18 patients were surgically treated in the University Hospital. This is a documentation of our experiences in the surgical management of two groups of patients with advanced intra-oral cancers – (i) Patients with no preoperative radiotherapy, and (ii) Patients who have had a full course of radiation in an attempt to cure. Few comprehensive reports have been made of patients treated surgically following attempts at curative radiotherapy, and the problem encountered.[5,6]

Table 1 shows total number of patients treated, average age, sex ratio, racial distribution and betel-nut chewing habit, and the ratio of patients with and without radiotherapy. The predominance of the Indians over other races is very striking.

In Table II, the reasons for subjecting patients to surgery subsequent to radiotherapy are tabulated. Nine of the ten patients in this group were subjected to surgery because they did not respond to curative radiotherapy. The initial "good response" to radiation is usually not sustained.[10]

The type of excisional surgery carried out is summarised in Table III. Radical neck dissection was done only when there were obvious clinical lymph nodes involvement or when, at surgery, frozen section showed tumour in the neck glands.

A transverse skin crease lip-splitting incision is made. If radical neck dissection is to be carried out, another lower transverse incision is made. These incisions are adequate for radical surgery. Wound healing is much better than in the more commonly used vertical incision. Complete surgical extirpation of the diseases with adequate functional and aesthetic reconstruction and the rehabilitation of the patients in the shortest possible time, is easier managed with these incisions.

At the time of surgery, one gets the impression of cutting into solid tissue in the post-irradiated areas. There is almost total avascularity!

Table IV shows the type of reconstruction done. Primary closure was effected when there was adequate soft tissue left over, both lining and coverage, after excisional surgery. This should leave the patient with no serious functional or aesthetic deformity.

(This paper was presented in part at the 5th Singapore/Malaysia Congress).

TABLE I

Patients treated in University Hospital, Kuala Lumpur, between August 1969 and July 1970

Total number	18		
Average age	58 years		
Sex ratio	M : F = 11:7		
Ethnic groups	Indians	Malays	Chinese
		10	6
Betel nut	10	6	–
Radiotherapy	No	Yes	
		8	10

TABLE II

Irradiated Patients – ten

Reasons for Surgical Treatment:

1. Failed radiotherapy	4
2. Local recurrence with radionecrosis of mandible	5
3. Radionecrosis of mandible	1
	10

TABLE III

Excisional Surgery

	Non-irradiated cases	Irradiated cases	Total
A. Monoblock suprahyoid dissection with wide local excision, including the appropriate segment of the mandible	4	7	11
B. Radical neck dissection on the same side and as in above	4	3	7
C. Bilateral radical neck dissection and as in above	–	–	–
	8	10	18

All excisional surgery was carried out under frozen section control

One flap only was used for the intra-oral lining in seven patients. This was always a temporal flap, based on the superficial temporal vessels.

When there was both inadequate skin and lining coverage, two flaps were used, temporal for lining and deltopectoral for coverage.[11-14] This was done in three of the irradiated patients.

In Tables V and VI, the complications, morbidity and mortality in the two groups of patients are enumerated. It is obvious that surgery following attempts at conventional curative irradiation is fraught with serious drawbacks. When compared with Table IV, it is clear that the type of reconstructive surgery carried out was almost identical and equal in number in the respective groups except in the two-flap technique. The only significant difference is the almost total avascularity in the post-radiation cases. Wound infection and breakdown were major problems. These occured in seven of the ten irradiated patients and resulted in major catastrophes. In comparison, only two in the non-irradiated group developed wound infection and these were of a minor nature. Carotid bulb blow out was a problem in two patients and caused their death. Both were from the irradiated group. This is a definite and serious hazard in patients subjected to surgery following radiotherapy. It is not clear how this can be prevented, except perhaps by not undertaking surgery following curative irradiation or by modification of previous methods of administering irradiation.

Table VI shows interesting figures with regards to number of surgical procedures and average hospital stay of patients. As compared to the non-irradiated group, the duration of hospitalisation and the number of procedures is doubled in the irradiated group and this is because of the complications that are enumerated in Table V, the most prominent being infection and wound breakdown, fistula formation and flap necrosis.

Delaying of pedicle flap was carried out whenever thought necessary.

TABLE IV

Reconstruction

	Non-irradiated cases	Irradiated cases	Total
A. Primary closure	4	4	8
B. One flap (for intra-oral lining)	4	3	7
C. Two flaps (for intra-oral lining and skin cover)	–	3	3
D. Bone graft	1	–	–
	8	10	18

Flap used: 1. Temporal flap
2. Deltopectoral flap

TABLE V

Complications and Mortality

	Non-Irradiated Cases – 8	Irradiated Cases – 10
1. Wound infection and breakdown	2	7
2. Fistula	–	4
3. Flap necrosis	1	3
4. Carotid bleeding	–	2
5. Septicaemia	1	–
6. Recurrence	–	1
. Death	1	1
	Coronary thrombosis	Haemorrhage from carotid artery 3rd post-op week.

TABLE VI

Surgical Procedures and Average Hospital Stay Per Patient

Non-irradiated cases			Irradiated cases		
No. of patients	–	8	No. of patients	–	10
Total no. of surgical procedures	–	14	Total no. of surgical procedures	–	42
Average no. of procedures per patient	–	2	Average no. of procedures per patient	–	4
Average hospital stay per patient	–	6 Weeks	Average hospital stay per patient	–	12 Weeks

Observations

In the current state of our knowledge and experience, we consider that surgery should be the mainstay in the treatment of these patients with advanced disease, perhaps combined with planned pre-operative low dosage radiation which is followed by immediate surgery to cut down morbidity, mortality and recurrence rate.[6,9]

There should be organised communication between various groups of people interested and involved in prevention and treatment of this disease — dentist, oral surgeons, radiotherapist, medico-social worker, cancer surgeons and reconstructive surgeons.

Summary

This is a documentation of our experience in the surgical management of 18 patients with advanced intra-oral cancer, ten of whom had had a full "cura-

tive" course of radiotherapy pre-operatively. Attention is drawn to the problems of surgery following attempts at curative radiotherapy. It is hoped this initial report will serve as a guide for future planning and management of such cases.

Acknowledgements

I would like to thank Professor N.K. Yong, head of the Department of Surgery, for his encouragement and advice in the writing of this paper.

Addendum

Since preparing this paper, a few patients have now been treated surgically after undergoing controlled preoperative radiation with very encouraging results.

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Female sterilisation by culdoscopy

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THE NATIONAL FAMILY PLANNING BOARD purchased a full laparoscope set and under the supervision of Dato (Dr.) Ariffin, it is being used for female sterilisation operations at the Maternity Hospital. In December 1970, under the auspices of the Ford Foundation, Dr. Alfonso Gutierrez Najar, director of the culdoscopy training course, Hospital de la Mujer, Mexico, visited the Maternity Hospital, Kuala Lumpur, and .gave a lecture cum demonstration of female sterilisation by the culdoscope (vaginal) method. The method used at the Maternity Hospital is a modification by Dato (Dr.) Ariffin and Dr. Johan Thambu (1, 2, 3) of Dr. Najar's method.

Selection of patients

The operation was offered to those requiring female sterilisation as part of the family planning services of the N.F.P.B. and the Maternity Hospital. The operation was done free of charge. The patient was admitted the day before the operation but if she was from Kuala Lumpur, she was admitted on the morning of the operation. The following procedure was carried out:-

(a) Written consent for operation is taken from the patient and her husband.

(b) A full clinical examination, including a vaginal examination, is carried out to exclude any gynaecological tumours, infection and endometriosis.

Pre-operative preparation

A simple enema was given on admission and the vagina prepared by dettol douching. The bladder was emptied before the patient was sent to the operation theatre.

Anaesthesia

The operation was carried out under local anaesthesia and intravenous sedation of pethedine and largactil.

(a) Pre medication: This consisted of intramuscular injection of Atropine gr. 1/150, 50 mgm Pethedine and 50 mgm Largactil given one hour before the operation.

(b) Anaesthesia: This consisted of 50 mgm of Largactil and 50 mgm Pethedine diluted in 10 c.c. of distilled water and given at the time of the operation. For local anaesthesia, 1% Liquocaine was used for infiltration into the posterior fornix of the vagina.

Instruments

(a) The laparoscope (or culdoscope) with the fiber

glass connecting cable to the Downs light source projector.

(b) Long handled Plamer's forceps.

Operative Procedure

The patient was placed on the knee chest position on the operating table with the knee joint at right angles. The perineum was cleansed with dettol solution and the dressing towels applied. The cervix and vault are exposed by a Sims speculum. A volsellum was applied to the cervix and pulled down. Local anaesthesia, Liquocaine 1% was injected into the vault. A trocher was used to puncture the vault and this puncture hole was enlarged to 1 cm. to allow the laparoscope or culdoscope to be inserted into the peritoneal cavity. The laparoscope/culdoscope was attached by the fiber light transmitting cable to the light projector; using a Palmer forceps, the Fallopian tubes were clamped and brought out into the vagina. The tubes are tied with linen or nylon sutures. The opening in the vagina was closed with a figure of 8 catgut suture.

Post-operative care

The patient was conscious during the operative procedure and as such, there are no problems during the post-operative period. The patient was allowed to take food immediately and she was discharged home the next morning. The following advice was given:-

(a) Avoid sexual intercourse for two weeks.

(b) Come up to the Gynae. Clinic in four weeks for follow up.

Conclusion

We have found this method to be simple and very effective. The patients are very pleased with the operation as they have no abdominal scar and are able to go home within 24 hours after the operation. The operative procedure takes only about ten minutes and we have had no complications. The culdoscope method of sterilisation is being offered as part of the family planning services of the National Family Planning Board and the Maternity Hospital.

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Oxygen therapy and pulmonary fibroplasia: A review and case reports

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Introduction

THE ADMINISTRATION and prolonged use of oxygen in inspired tensions above that of air has been employed in various fields, e.g. deep sea-diving, space research, and, in the medical field, in radiotherapy and intensive care of infants and adults.

Oxygen, although essential to life, also seems toxic to all living cells. The toxic effect depends on the partial pressure and individual species sensitivity (Bean, 1965). At very high pressure of over 3 atmospheres (hyperbaric), clinical signs and symptoms of oxygen toxicity usually become apparent initially in the nervous and respiratory systems, although because the basic disturbance is at the cellular level, all systems are affected eventually.

The early signs and symptoms of oxygen poisoning are (1) facial pallor, (2) fibrillation of lips (3) sweating, and (4) bradycardia. (Slacks, 1967). Warning signs and symptoms include visual, acoustic, olfactory, gustatory and respiratory changes. Convulsions may occur. At lower oxygen pressure, the lungs appear to react first.

At atmospheric pressure, administration of 98.5 – 99.5% oxygen to a series of 34 normal subjects continuously for 24 hours resulted in 30 of them suffering from retrosternal soreness which became sharp and severe during inspiration. (Comroe et al, 1945). That the breathing of oxygen in high percentage (more than 80%) for prolonged periods consistently resulted in pulmonary changes and sometimes in retrolental fibroplasia in the newborn has been reported in various centres. These cases are usually newborn infants with respiratory distress syndrome (Hyaline membrane disease) which initially requires a high percentage of inspired oxygen in order to maintain the arterial oxygen tension within the physiological range. These pulmonary changes are usually termed pulmonary fibroplasia by various workers, or pulmonary respiratory syndrome (Lancet, 1967).

The pathological features of hyaline membrane disease are known to change with the duration of the illness, and it is rare to find any membrane after four to five days (Lancet 1: 1969). In contrast, lungs of infants kept alive with artificial ventilation showed slowly healing and persistent membranes for as long as ten days, followed by mucosal metaplasia, histiocytic invasion and fibrosis. Patchy fibrosis, thickening of alveolar wall, and distortion of alveolar architecture have been characteristic findings in lung biopsy specimens and necropsy materials from infants requi-

ring respiratory therapy.

Pulmonary fibroplasia is not confined to cases with respiratory distress syndrome. Cases have been described in which many of the patients have had no respiratory or cardiac disease before the use of the ventilator (Nash et al 1967; Pusey et al 1969). Pusey reported a series of 51 newborn infants with respiratory failure treated with artificial positive pressure ventilation, and 11 of 16 infants ventilated for over six days. Five of the 11 infants had initial clinical and radiographic features different from hyaline membrane disease. Nash et al reported post-mortem examinations of 70 patients who were artificially ventilated and many showed characteristic pulmonary changes. These patients' underlying diseases vary from acute myocardial infarction, bronchopneumonia, emphysema to post-operative cardiac surgery.

Although most of the reports on the occurrence of pulmonary fibroplasia are associated with the use of inspired oxygen of more than 80%, there are also reports of characteristic pathological changes with inspired oxygen of less than 80%. Nash et al, in their series, used inspired oxygen varying from 21 – 100% and Pusey et al, in their series, have three infants with pulmonary changes in which inspired oxygen was below 80%.

We describe below two infants, one with respiratory distress syndrome and the other with neonatal tetanus, who developed pulmonary changes, including fibrosis, in spite of inspired oxygen concentration being below 80%.

Material and Methods

The two infants were admitted to the Intensive Care Unit of the University Hospital, the first a few hours after delivery for respiratory distress and post-operative supportive ventilation, and the second for respiratory distress following neonatal tetanus. Both were treated with intravenous fluid; sodium bicarbonate when necessary, antibiotics according to sensitivity reports of cultures from nasal and tracheal secretions; physiotherapy and tracheo-bronchial toilet as often as necessary; vitamin supplements; and intermittent positive pressure ventilation, using the Engstrom ventilator. The adequacy of ventilation was judged clinically by the infants' colour, by auscultation and chest movement and by correlation with micro-Astrup studies. Chest X-rays were taken when indicated to assess the position of the nasotracheal tube, the progress of any consolidation and the occurrence of any pulmonary atelectasis or pneumothorax. The infants' temperatures were kept to 37°C and humidification was achieved by using ultrasonic nebulizer. The general management was undertaken jointly with the surgeon, the paediatrician and the physiotherapist.

Case I – b/o N.K.L.

The infant, the first of a twin, was vertex delivered on 13.7.70 following spontaneous labour at 36 weeks' gestation, (birth weight of 3.17 kgm). She breathed spontaneously and Apgar score at 1.0 minute was 5. She had macroglossia, facial plethora and an exomphalous measuring 20 cm. in diameter. There was mild grunting with intercostal recession, and her respiratory status progressively deteriorated. She had to be intubated and artificially ventilated. The exomphalous was repaired and post-operatively, she was ventilated in I.C.U. (Engstrom ventilator). The ventilation pressure varied between 15 – 34 cm H_2O, using Jackson Rees portex nasotracheal tube, internal diameter of 3.0 mm. The inspired oxygen concentration was initially at 50%, but gradually decreased to 35% by the 23rd day of ventilation.

Several attempts were made to wean her off the ventilator but failed. She developed spontaneous tension pneumothorax on five occasions during her two admissions to I.C.U., the first occasion being five days after I.P.P.V. On all occasions, the tension pneumothorax was drained. The infant was finally weaned off the ventilator completely, 35 days after I.P.P.V. and continued to have oxygen therapy, using the Isolette incubator.

Six days after weaning off the ventilator, the baby developed respiratory and cardiac arrest in the paediatric ward, necessitating treatment with I.P.P.V. in I.C.U. after resuscitation. Inspired oxygen concentration was never above 48% at this stage. She never recovered respiratory independence and finally succumbed, 56 days after delivery.

Necropsy

At autopsy, the infant was found to have multiple congenital abnormalities, the major ones being an exomphalons (with partial surgical repair) associated with organomegaly (liver 160 gm. with Riedel's lobe and kidneys 52 gm. each), multiple small muscular ventricular defects in the heart and malrotation of intestines.

The right and left lungs weighed 40 gm. and 25 gm. respectively. The apical portions were aerated

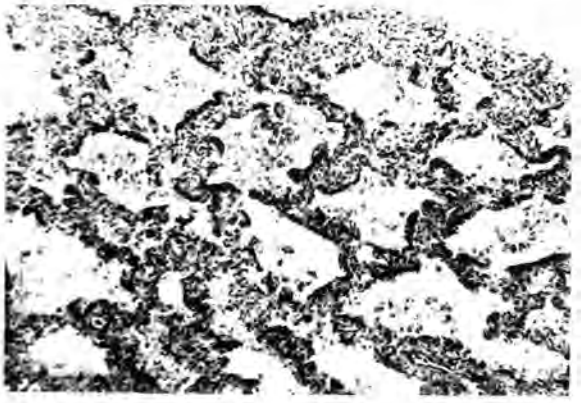


Fig. 1

(Magnification x 150. Van Gieson stain.) This section shows the increased elastic tissue as black in the thickened alveolar walls.

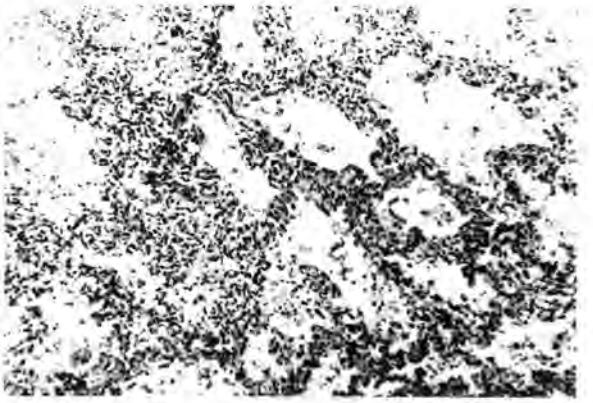


Fig. 2

(Magnification x 150. Haematoxylin/Eozin stain.) Shows the thickened alveolar septae with intra-alveolar macrophages, shed-off septal cells, and initial interstitial fibrosis.

and pink-tan in colour but both basal portions were dark red-purple with small areas of consolidation. There was no evidence of tension pneumothorax or of embolisation.

Microscopically, there was diffuse thickening of the alveolar septae with increase in elastic tissue and fine collagen fibres (Fig. 1). There was also congestion of alveolar capillaries with haemorrhage and some fibrinous material in some alveoli. In other areas, the alveoli were filled by foamy macrophages and shed-off septal cells (Fig. 2). There was squamous metaplasia of the epithelium lining the trachea. No evidence of pneumonia was present.

Case II – T.W.K.

This was a male infant referred to the University Hospital from another hospital at ten days of age with neonatal tetanus. He was home-delivered at full term and the umbilical cord cut with a pair of unclean scissors. Birthweight was unknown, but at ten days old, he weighed 3.17 kgm.

The baby was moderately dehydrated and jaundiced on admission, with severe spasms and respiratory distress. I.P.P.V., using Engstrom ventilator, was immediately instituted. Jackson Rees portex nasotracheal tube (internal diameter 3.0 mm.) was used, the inflation pressure varying between 14 – 32 cm H_2O throughout. Inspired oxygen concentration was 39% initially, tailing to 37% on 11th day of ventilation, but increasing to 42% subsequently due to consolidation of both apices of the lungs on the 14th day of ventilation.

On the 18th day of ventilation (26 days old), the baby suddenly developed bilateral tension pneumothorax with spreading subcutaneous emphysema. Resuscitation was done with drainage, but with supervention of cardiac arrest, resuscitation was unsuccessful.

Necropsy

At autopsy, there was extensive surgical emphysema over the head, shoulders and trunk extending into the upper portion of the thighs. The pericardial sac was distended by frothy clear fluid and two blebs, 2 x 4 mm. in size each, were present over the anterior pericardial surface.

There was bilateral tension penumothorax; about 1 ml. of air was released from each pleural cavity when they were pierced under water. The right lung weighed 33 gm. and the left 30 gm. Both lungs were collapsed, of a red-purple colour and sank in water. There were many blebs of 2 – 4 mm. size in the interlobular fissures of both lungs and larger bullae of 1 – 2.5 cm. diameter were present over the surface of the right lung.

Microscopically, there was atelectasis with prominent perivascular air spaces along major vessels and these spaces extended along interlobular connective tissue to the pleural surface. There was congestion of pulmonary vessels and alveolar capillaries, and the alveoli contained macrophages and shed-off septal cells (Fig. 3). The alveolar septae were thickened. No in-

Fig. 3

(Magnification x 150. Haematoxylin/Eosin stain.) Shows thickened alveolar septae and alveoli containing foamy macrophages and shed-off septal cells.

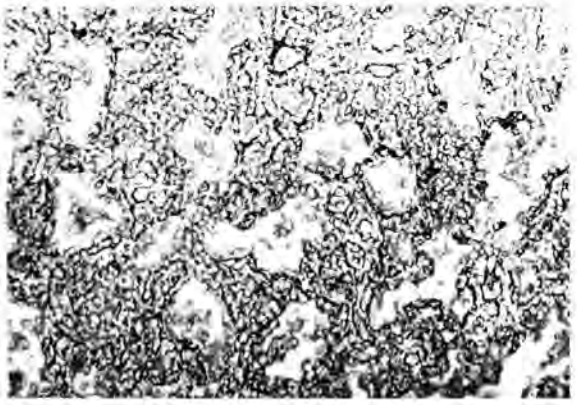


Fig. 4

(Magnification x 150. Reticulin stain.) Demonstrates the increased reticulin in the prominently thickened alveolar walls.

crease of collagen was demonstrable but reticulin was definitely increased (Fig. 4). Some bronchioles showed squamous metaplasia.

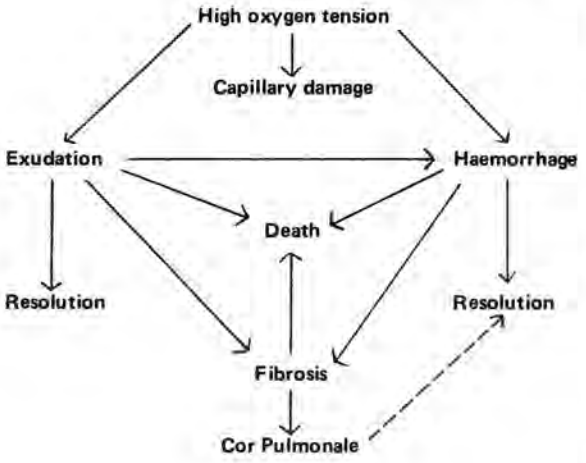
Discussion

That oxygen in high concentration (more than 80%) is toxic to the tissues is well documented by various workers. As early as 1897, Lorrain Smith concluded that oxygen at 41.6% of an atmosphere was well tolerated by mice, and at 70–80%, 50% of mice were dead at the end of one week. Kaplan et al (1969) also documented the oxygen toxicity in their work with monkeys. In man, most of the work on oxygen toxicity was either at increased atmospheric pressure or at ambient pressure with inspired oxygen concentration of more than 80%, and most of these centred around treatment in hyaline membrane disease. Recent reports have shown that pulmonary changes can occur at lower inspired oxygen concentration. Patients requiring respiratory therapy for pulmonary disease other than hyaline membrane disease also showed pulmonary changes, including diffuse interstitial fibrosis.

Northway et al (1967), from their clinical, radiological and pathological observations, have reconstructed the development of the pulmonary sequelae in which four stages were described, the radiological and pathological stages of which may overlap each other slightly. Stage I, within 2 – 3 days, a "period of acute respiratory distress syndrome" with increased pulmonary density and air bronchogram. There is hyaline membrane, atelectasis and metaplasia, and necrosis of bronchiolar mucosa. Stage II (4 – 10 days), a period of regeneration, with necrosis and repair of alveolar epithelium, persisting hyaline membrane, focal capillary basement thickening and bronchiolar eosinophilic deposition. Stage III (10 – 20 days), a transition period, with widespread bronchial mucosal metaplasia, moderate exudation of alveolar macrophages and histiocytes, emphysema, atelectasis and interseptal collagen deposition. Stage IV (more than one month), a period of chronic disease. Emphysema, atelectasis, increased macrophages and histiocytes, perimucosal fibrosis, widespread metaplasia, reticulin, collagen and elastin fibres in septal walls may all be present.

In both our patients, there is pathological evidence of emphysema, atelectasis, macrophagic infiltration and diffuse interstitial fibrosis in one (Figs. 1 and 2), with marked increase in reticulin in the other (Figures 3 and 4), the latter being the initial stage in the formation of fibrosis.

There are several reports in the literature which implicate high oxygen tension and oxygen toxicity, but due to many conflicting views, it is difficult to be certain of the factors which may play a role in the development of diffuse interstitial fibroplasia. Rowland and Newman (1969) have drawn up a scheme showing the effect of high oxygen tension on the lung as follows:



Northway et al postulated several possible mechanisms.

1. It is the result of pulmonary healing in infants with respiratory distress syndrome, who ordinarily do not survive.
2. It is the results from toxic effects of oxygen on the lungs superimposed upon pulmonary healing in infants with severe respiratory distress syndrome.
3. It results from the effects of pulmonary oxygen toxicity, healing severe respiratory distress syndrome, I.P.P.V. and poor bronchial drainage secondary to endotracheal intubation.

Respiratory Distress Syndrome

In the Pusey et al series, five infants, who developed diffuse interstitial fibrosis, did not have an initial diagnosis of respiratory distress syndrome; neither did the first of our cases. Our second infant had normal lungs initially. Nash et al reported cases of interstitial pulmonary fibrosis in patients who had no cardio-respiratory diseases to start off with. Thus the development of diffuse interstitial fibroplasia does not appear to be dependent on a specific pulmonary patho-physiology associated with respiratory distress syndrome.

Prolonged use of high concentration of oxygen.

Oxygen is administered clinically to re-establish a patient's arterial oxygenation tension to a physiologically normal range, usually around 70–90 mmHg. The difference between the PIO2 (inspired oxygen tension) and PaO2 (arterial oxygen tension) is an index of either diffusion or ventilation-perfusion abnormality. Changes in magnitude of PIO2 – PaO2 difference have served as an additional clinical prognostic sign. Harris et al (1968) have closely monitored PIO2 as well as PaO2 in clinical situations where a very high PIO2 was required for 1 – 14 days in order to maintain PaO2 in the normal range. In spite of the necessarily high PIO2, they have not encountered an identifiable case of oxygen toxicity. They found that when employing machines with provisions for accurate oxygen addition, control of PIO2 is simple and reasonably accurate, but with venturi-mix pressure limited machines, PIO2 can vary between 50% to 95%, as Pusey et al found with the Bennett and the Bird Ventilator. Harris et al devised a formula for the dosing of oxygen as follows:

$$\dot{V} \text{ gen/min.} = 1.25\,\dot{V}\,\frac{(PB - PIO2)}{PB} = \text{Litres oxy-}$$

where $\dot{V}$ = minute ventilation of patient,
PB = existing barometric pressure,
PIO2 = Inspired oxygen concentration.

Tunstall et al (1968) reported 90 newborn infants treated by using volume cycled ventilator. None had "respirator lung syndrome" as reported in Lancet 1: 1967. Our two infants were both on volume cycled ventilators but both had pulmonary changes.

Respirator therapy and inspired oxygen concentration of 80–100% were common to all cases of pulmonary fibroplasia so far described, given continuously for at least 2 – 3 days. Much circumstantial evidence incriminates oxygen toxicity apart from its action in causing retrolental fibroplasia. In retrolental fibroplasia, Robertson et al (1968) found two cases in which the retinal PaO2 were more than 160 mmHg, and they arbitrarily fixed the level of PaO2 at 160 mmHg for retrolental fibroplasia to occur.

The implication that pulmonary fibrosis occurs as a result of prolonged use of high oxygen concentration is difficult to evaluate. Various animal studies with 100% oxygen have shown thickening of the alveolar septal walls attributed to capillary proliferation, thickening of capillary endothelium or pulmonary oedema, but interstitial fibroplasia has been demonstrated in only one study of adult monkeys where septal fibrosis was seen 31 days after exposure

to pure oxygen (Robinson et al, 1967), and in rats after exposure to 700 mmHg oxygen for up to ten days (Schaffaer et al. 1967). It is also interesting to know that complications of diffuse interstitial fibroplasia was not seen in pulmonary pathology in infants dying of hyaline membrane disease between 1944 and 1948, a period when 100% oxygen was widely used. And yet, in our two infants, PIO2 was never above 60% in one, and 42% in the other. Morgan (1968) concluded that no toxic threshold for oxygen exists, and that any increase in oxygen of inspired gas mixture is a threat, but when oxygen administration is limited to a few days, percentage of oxygen more than 70% is dangerously high.

Prolonged nasotracheal positive pressure artificial ventilator

This has been known to be associated with squamous metaplasia and, occasionally, necrosis of tracheal epithelium, thus interfering with ciliary activity. Also, positive pressure ventilation may force secretions back into distal air passages. Whether this could eventually cause interstitial pulmonary fibrosis is unknown.

Could the respirator per se be a contributing factor to the development of fibroplasia? It is well known that patients on ventilators have progressive decrease in lung compliance secondary to progressive atelectasis due to the absence of the intermittent "sigh reflex" (Bendixen et al, 1963). Infants ventilated via an endotracheal tube cannot inspire deeply or cry, thus limiting their tidal volume. To avoid this, our infants were hourly hyperinflated via the by-pass in the Engstrom, using modified Ayre's T-piece system after tracheo-bronchial secretions were removed. In the absence of this, could progressive atelectasis end up in diffuse interstitial fibroplasia? This is at present unknown.

Could high inflation pressure used to ventilate the lungs of infants lead to metaplasia and fibroplasia? In prolonged ventilation of newborn infants, Tunstall et al (1968) recommended that the ventilation pressure should not be above 20 cm H_2O and the ideal size of naso-tracheal tube is one that allows a slight audible leak back past the larynx when this pressure is applied. Infants with respiratory distress syndrome necessarily require a higher ventilation pressure. Becher and Koppe (1969), in their series of 14 babies with hyaline membrane disease, had eight fatalities and all these had high ventilation pressure – 50 cm H_2O on the average, with high oxygen concentration. Five of the six babies who survived were treated with relatively low pressures of 35 cm H_2O. In both our infants, the ventilation pressure in one varied from 15 – 34 cm H_2O and in the other 14 – 32 cm H_2O, a pressure considered "low" by Becker and Koppe.

Reduction of surfactant.

Loss or reduction of surfactant secondary to over distension of alveoli may result in atelectasis, but this does not appear to be implicated in the formation of pulmonary fibroplasia. Hawker et al (1967) reported normal surface tension measurements on lungs of five infants dying from diffuse interstitial fibroplasia after prolonged respiratory therapy. They inferred the presence of surfactant from findings of low surface tension of lung extracts. Apparently, the effect of oxygen toxicity on respiratory tract is not mediated through surfactant.

Conclusion

It is apparent from the various reports and conflicting opinions, that the direct factor causing pulmonary changes in patients under treatment with oxygen and I.P.P.V. has not been established, though oxygen itself in high concentration appears to be one of the factors. Even here, some workers do not think that it is causally related to the appearance of diffuse interstitial fibroplasia.

The mechanism of oxygen damage to the lung has not been fully elucidated, and the highest concentration of oxygen without toxic effect in the lungs is not yet known, but what is certain is that the use of 90 to 100% oxygen for a prolonged period is probably hazardous, and that careful monitoring of blood gas tensions is required when high oxygen tension is used (B.M.J. 1968). Pulmonary damage is not confined to patients ventilated with high oxygen concentration as our two infants have shown and reports in the literature have shown that it is possible even in lower concentrations.

The practice of oxygen therapy is to administer oxygen in a concentration that results in an arterial oxygen tension of 70 – 120 mmHg, sufficient to give a 95 to 99% saturation of arterial blood (Nash et al, Harris et al). This treatment often entails the use of a high concentration of inspired oxygen, including 100% oxygen. Nash et al have emphasised that such therapy is not withheld for fear of possible toxic effects on the lungs or other organs. However, the inspired oxygen concentration should be reduced as

soon as is possible, to a level compatible with adequate function of vital organs. Other measures to improve oxygenation of the body, thereby permitting a decrease in the alveolar PO2, such as fastidious tracheal toilet and correction of pulmonary oedema or congestion; treatment of anaemia and acidosis; reduction of fever, should also be utilised (Hyde and Fischer, 1969).

Summary

Oxygen therapy, at atmospheric pressure with inspired concentration above and below 80%, are reviewed. Two cases are reported of infants subjected to I.P.P.V. via Engstrom ventilator, with PIO2 below 80%, and the postmortem finding of pulmonary changes (fibroplasia). These changes, and their causal relationship to oxygen and other factors, are discussed, together with the review of reported series in the literature. It is emphasised that (1) pulmonary changes can occur with PIO2 greater than that of air (21%), and (2) the administration of oxygen as such is not withheld for fear of possible changes in the lungs, but the oxygen concentration should be reduced as soon as is permissible.

Acknowledgement

We wish to thank Dr. A.E. Delilkan for his encouragement and guidance in the preparation of this paper; to Mr. Milton G. Sirimanne for his laboratory investigations; and Miss S. Dawood for secretarial work.

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Outpatient treatment of psychotic patients with a long-acting phenothiazine: Fluphenazine decanoate

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Introduction

SINCE APRIL, 1970 the Department of Psychological Medicine, University Hospital, Kuala Lumpur, Malaysia has been using fluphenazine decanoate, a new, long-acting phenothiazine on selected psychiatric outpatients. This is a report of the first 15-month experience with this intermuscular drug.

A consistent problem in the management of psychiatric outpatients has been their refusal to take oral phenothiazine. This has often led to a relapse of symptoms, which required rehospitalisation. A recent study (Irwin, et al, 1971) which confirms older studies, found 35% of chronic schizophrenic outpatients were not taking minimal amounts of medication. A long-acting injectable phenothiazine overcomes this problem by assuring that the patient receives his medicine. This provides better control of his illness.

A second advantage of the long-acting phenothiazine is lowered accumulative toxicity for chronic patients. Relatively small quantities of the medicine is required as it is effective over several weeks due to its substained release properties. Thus the total accumulative body dose is markedly reduced. No significant delayed or cumulative toxicity, which has been found with other phenothiaziness, have appeared with fluphenazine decanoate (Grozier, 1971).

Oral fluphenathiazine hydrochloride is a major tranquilliser of the piperazinyl group. It has been prepared in two long-acting forms; enanthate, a heptanoic acid ester, and decanoate, a decanoic acid ester. Fluphenazine enanthate has been found to be an effective long-acting anti-psychotic agent (Hsu, et al, 1967; Haider, 1968; Karkalus, 1968; Kinross-Wright et al 1963; Kline, et al 1970).

The decanoate preparation was developed to give a longer duration of action as well as fewer side effects. Studies have found fluphenazine decanoate to be similar to the enanthate form in treating chronic hospitalised schizophrenics (Kurland and Richardson, 1966) and in chronic schizophrenic outpatients (Keskiner, et al, 1969; Bucci, 1970). Further work has supported the value of decanoate in chronic psychosis (Itil and Keskiner, 1970; Grosser, 1970; Neal, 1970; Keskiner et al, 1968). Grozier, in 1971, reporting on the 862 patients treated with fluphenazine decanoate in the combined studies, stated 68% had a satisfactory clinical response, 32% had extra pyramidal reactions but only 0.5% had to discontinue because of the adverse effects.

Patient Population and Method

Between April 1, 1970 and January 31, 1971, a total of 31 patients were given fluphenazine decanoate. The final evaluation of the patients was made in July 1971. Thus patients who continued taking the medication had a minimum of six months drug trial and some had as long as 15 months.

The patients were selected on the basis of chronicity of their illness, a failure to respond to oral medication or a strong suspicion that they were not taking oral medication. All but one (senile psychosis) was diagnosed as schizophrenic, usually chronic undifferentiated type. Ten patients had symptoms for more than four years, including four patients who were ill for more than seven years. The average duration since first onset of symptoms was 4.6 years. All had been on oral phenothiazine previously and most had multiple hospital admissions. Of 31 patients, 15 were males and 16 females. The patients were a mixed racial group comprising 19 Chinese, 3 Malays, 3 Indians, 4 Aborigines (Orang Asli) and 2 Eurasians.

Most patients were started on decanoate as outpatients but some were started during an inpatient admission after the acute symptoms were controlled by oral medication. The starting dosage usually was 25 mgm. intermuscularly given in the upper gluteal region. The dosage and duration were adjusted according to the clinical response. Anti-Parkinsonian medication, Benzhexol 2 mgm. b.i.d. was given to cover potential extra pyramidal effects.

Results

Dosage and duration of action: The dosage for each individual patient was quite variable in the early phases of treatment but a stable pattern for each patient emerged. The dosage ranged from 12.5 mgm. to 37.5 mgm. and the duration of action varied from three to six weeks. For the patients who were continued for six months or more, the great majority (18 of 21) required one injection every four weeks. One required medication every five weeks and two could be maintained for six weeks. The dose was 25 mgm. in 11 cases (52%) and 12.5 mgm. in eight cases (38%). Two cases required 37.5 mgm.

Clinical Response: The patients who were continued on medication were given a global rating of their clinical response at the final evaluation. This was a composite score of:

(1) self-rating of their improvement,
(2) when possible a relative or personal contact's rating of patient's behaviour, and
(3) the psychiatrist rating of the presence of psychopathology.

The following was the criteria for the 5-point scale:-

1) Excellent: Patient has no symptoms nor impairment and is able to function as well as prior to first symptoms.
(2) Much improved: Patients has residual symptoms but is able to function with minimal distress to family and community.
(3) Improved: Patient has a moderate degree of symptoms but is more stable and less disabled than previously.
(4) No change.
(5) Deteriorated: Patient has increased symptoms and more social impairment.

Table 1 shows the results of all the patients who received fluphenazine decanoate. A total of 21 patients, all those who stayed on medicine for six months or more, had at least some improvement. The majority were rated at much improved or excellent. If this total group are considered "satisfactory responses", then the overall improvement rate is 68%.

Seven or 23% dropped out from the treatment. Three stopped within two months and one at three months. Three continued past four months and were reported doing well. One patient showed continued deterioration on the drug and long-term hospitalisation was recommended.

Side Effects: As seen in Table I, two patients had much severe side-effects that further medicine could not be given. Both had received only 12.5 mgm. fluphenazine decanoate on two occasions. One became very restless and agitated for two days following each injection and refused treatment on the third injection. The other patient had severe neck stiffness, drawling, rigidity and an oculogyric crisis after the second injection. Both patients were placed on other phenothiazines but did poorly and had to be hospitalised within six months.

The overall incidence of side-effects are seen in Table II. Most side effects were mild and controlled by an anti-Parkinsonian drug, Benzhexol. Although most patients were started on Benzhexol, it was found to be unnecessary with many patients. However, when patients were urged to try without the anti-Parkinsonian drug, many reported much therapeutic value attributable to the drug and refused to give it up. This implies a strong psychological dependency and placebo-effect from daily use of an anti-Parkinsonian drug.

Table 1

Results of Patients Receiving Fluphenazine Decanoate

		Total	Percentage
Continued medication 6 months or more		21	68%
Excellent	3		
Much improved	13		
Improved	5		
No change	0		
Deteriorated	0		
Dropped out		7	23
Stopped because of side effects		2	6
Deteriorated and required hospitalisation		1	3
		31	100%

TABLE II

Fluphenazine Decanoate Side-Effects

		Total	Percentage
None		13	42%
Patients with extra-pyramidal effects		8	26
* Restless/akathesis	3		
Rigidity	4		
Tumors of hand	3		
Occulagyric crisis	1		
Stiff tongue/mouth protrude	2		
Excessive weight gain		2	6%
Drowsy		1	3
Unable to think clearly — "feel in a daze"		2	6
More withdrawn		1	3
Irritable		1	3
Poor appetite		1	3
Initial hyperactivity reported		1	3
Slightly depressed		1	3

* Many patients reported more than one extra-pyramidal symptom.

No irritation or inflammation developed at the injection site. Interestingly, one patient while on fluphenazine decanoate conceived and delivered a normal infant.

Patient's Acceptance: Seventeen patients were asked regarding their preference for monthly injections or daily oral anti-psychotic medication. Thirteen or 76% preferred the injections, indicating a high degree of acceptance.

Discussion

The results show that fluphenazine decanoate has a long duration of action of about four weeks, and is an effective drug for the maintenance of these difficult, schizophrenic patients. It has significant advantages of convenience, good tolerance and patient acceptability. Like other phenothiazines, fluphenazine decanoate rarely completely relieves all of the schizophrenic symptoms; however, over half of the patients were reported to be much improved or functioning normally. Sixty-eight per cent of our patients on long-term dosage were found to make some improvement. This is identical to Grozier's (1971) report of percentage of satisfactory responses.

Side-effects can be troublesome to some patients on an idiosyncratic basis, especially following the first few injections. Two people (6%) had to be dropped from this study because of their adverse reactions. Extra pyramidal effects were reported by 26% (eight) and some side-effects mentioned by all but 42% of the patients. The tendency to report adverse effects became much less as the drug was taken longer. Extra pyramidal side-effects generally responded to anti-Parkinsonian drugs and even this was found to be less necessary as treatment progressed. Nevertheless, many patients became psychologically dependent upon these drugs, ascribed to them specific therapeutic value, and were reluctant to give them up.

The study indicates a group of special concern — those who respond well to medication but fail to return for further injections. This drop-out group represents nearly one-fourth of the total population. This group responded well and reported few side-effects. It is possible that this group felt so much improved that they felt no need to be continued upon the medication. Considerable research indicates that the relapse rate is very high among schizophrenics who stop medication prematurely (Englehardt, 1967). This high drop-out group emphasises the need for further patient education about their illness and its treatment.

The Aborigine patients, of whom four were included in this study, indicate the unique value of fluphenazine decanoate. These patients often live in remote jungle areas far from medical facilities. Here chronic psychiatric patients are a real challenge to medical management. Fluphenazine decanoate has been used to stabilise these patients at Gombak Aborigine Hospital and then they can be returned to their homes. An Aborigine medical staff gives them their monthly injection in the jungle. They are returned for medical evaluation every three months. This has proved to be an effective therapeutic approach and currently ten patients have been maintained in this manner.

A further consideration is the substantial savings in cost. Currently a 12.5 mgm. ampule of fluphenazine decanoate costs the patient M$4.00. The great majority of patients could be maintained for M$4.00 or M$8.00 per month. Even at M$8.00 a month, the cost would be one-half of a comparable monthly maintenance drug supply of chlorpromazine and one-third the cost of perphenazine.

Summary

This report is about the University Hospital, Malaysia, first 15-month experience with fluphenazine decanoate, a long-acting intermuscular form of phenathiazine; 31 chronic psychiatric patients were started on the drug with a minimum follow-up period of six months. The drug generally could be given in a dose of 12.5 or 25 mgm. every four weeks. Sixty-eight per cent showed some improvement and 18 (58%) had much improvement or excellent response. Seven (23%) dropped out and one deteriorated and required hospitalisation. Although two were discontinued because of adverse effects, the side-effects tended to be mild, became less troublesome with longer use and controllable with anti-Parkinsonian medication. Fluphenazine decanoate has significant advantages in treating chronic psychiatric outpatients because of its long duration, of providing certainty that the patient receives his medication and because of good patient acceptance and lower cost.

Acknowledgements

The fluphenazine decanoate (Modecate) was provided by Squibb (Far East) Limited, Hongkong. The authors are grateful for the assistance of Dr. Chin-Teong Lee and the helpful encouragement of Professor Eng-Seong Tan. Technical assistance was provided by Lay-Lan Chan.

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Short term use of large doses of furosemide in some surgical problems

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FUROSEMIDE (LASIX) has been in use for some time now and its clinical formula, mode of action and its superiority as a diuretic agent has been well documented in numerous clinical trials elsewhere (Verel, Stentiford, Rahman, Saynor 1964, Stokes and Nunn 1964, Timmerman and Springman 1964). Its therapeutic indications has also been reported in numerous articles by various authors in several countries. However, reports of the use of large doses of furosemide in surgical patients have been limited (Fourth International Congress of Nephrologists – Stockholm 1969, McKenzie, Fairley and Baird 1966, Muth 1968). It is the purpose of this article to add some information on short-term use of large doses of furosemide in some surgical patients, who were resistant to normal initial doses.

Material

During the past 18 months, 44 patients were treated with large doses of furosemide. Table I indicates the conditions for which they were used. Four patients developed intractable ascites and oedema following major hepatic resection for malignancy or for benign conditions where extensive resections were performed. Eight patients developed marked ascites and oedema following emergency porta caval shunts for bleeding oesophageal varices due to cirrhosis of the liver. Seven other patients with severe cirrhosis admitted to our units for bleeding and treated conservatively developed marked ascites. In these cases, presence of marked ascites causing respiratory distress necessitated the use of large doses of furosemide to produce quick massive diuresis.

TABLE I

Conditions for which Furosemide was used

	No.
1. Major hepatic resection for malignancy or benign conditions which developed ascites.	4
2. Emergency porta caval shunts which developed ascites.	8
3. Cirrhosis of liver with ascites treated conservatively.	7
4. Severe burns with oliguria or anuria.	8
5. Advanced malignant lesion of alimentary tract with ascites.	10
6. Head injury with cerebral oedema.	7
	44

Eight patients with severe burns between 60 to 70% developed oliguria or anuria. Ten patients had advanced malignant lesions in the alimentary canal and developed severe ascites which caused respiratory

TABLE II

Effect of High Dosage Furosemide in Liver Disease following Hepatic Resection

No.	Initial Serum Electrolytes MEq/1				Urea mg/100	Dosage	Time of full response	Serum Electrolytes at time of full response				Amount of urine passed
	Na	K	Cl	HCo3				Na	K	Cl	HCo3	
1.	129	3.7	94	27	48%	100mg i/v	2nd day	120	2.3	87	24	4¾ litres
2.	138	4.2	108	24	54%	150mg i/v	3rd day	127	2.9	94	19	6 litres
3.	132	5.1	107	22	22%	250mg i/v) and i/m)	4th day	120	2.7	93	17	8¼ litres
4.	127	3.8	102	25	54%	400mg i/v) and i/m)	3rd day	119	2.3	90	18	11 litres

Post Porta Caval Shunt in Cirrhosis of Liver Ascites and Oedema

No.	Initial Serum Electrolytes MEq/1				Urea mg/100	Dosage	Time of full response	Serum Electrolytes at time of full response				Amount of urine passed
	Na	K	Cl	HCo3				Na	K	Cl	HCo3	
1.	127	3.8	93	28	57%	1500mg i/m	2nd day	119	2.3	86	23	8 litres
2.	120	3.1	104	27	67%	2500mg i/m	3rd day	107	2.4	92	25	7½ litres
3.	134	4.3	109	22	42%	3500mg i/m) and i/v)	120	2.7	103	20	12	litres
4.	132	4.7	106	24	53%	400mg i/m) and i/v)	2nd day	124	2.8	99	22	9½ litres
5.	138	3.2	103	24	42%	2500mg i/v	3rd day	130	2.1	100	19	8 litres
6.	131	4.1	106	23	52%	3500mg i/v) and i/m)	2nd day	126	2.7	98	20	12 litres
7.	138	3.2	103	24	48%	5200mg i/v) and i/m)	4th day	124	2.1	97	20	16 litres
8.	126	4.2	107	24	52%	5250mg i/v) and i/m)	5th day	117	2.3	98	22	13¼ litres

Note: i/v and i/m – in divided doses – morning and evening.

distress. Seven patients were treated for cerebral oedema following head injury. They had either extradural or subdural haematoma which were evacuated by trephening.

In all these patients, the normal daily dose of 40 mg. intravenously or intramuscularly was commenced and gradually increased to 400 mg. daily in divided doses. Fluid intake and output were recorded. Serum electrolytes were estimated daily. Where practicable, the patients were weighed daily and blood pressure, pulse rate and central venous pressure were monitored. Blood sugar levels were estimated periodically. If the response to 400 mg. daily was poor or if the patient's condition caused anxiety, the dose of furosemide was increased to 1,000 mg. on the first day with a further increase of 1,000 mg. daily, if necessary. The highest dosage given in this series was 5,250 mg.

Result

Table II shows the detailed analysis of the patients with liver diseases. The ascites responded well to high doses of furosemide. The injections were discontinued within a week and subsequently the patients were given oral maintenance dosage of 40 mg. twice daily. Liver function studies showed no deterioration in the function.

All the eight patients with severe burns showed marked improvement, the urinary output returning to satisfactory levels within three to four days of the commencement of the therapy. The results of the blood urea appeared to be variable but returned to normal within a week.

In ten patients with advanced malignant lesions of the alimentary tract, high doses of furosemide caused immediate response in seven patients as shown by the decrease in the girth of the abdomen and relief of respiratory distress. The remaining three patients showed virtually no response even after a daily dosage of 5,000 mg. However, as soon as the intravenous therapy was discontinued, the ascites in seven patients, who had initial response, recurred. No further response was then obtained after a week's treatment.

The seven patients with cerebral oedema following trephening improved dramatically after administration of high doses of furosemide. A daily dose of 1,000 mg. was given intravenously for 4 – 6 days in all the patients.

Adequate hydration was ensured by monitoring blood and central venous pressures. Electrolytes were supplemented according to the serum electrolyte levels estimated after the first large dose and massive diuresis. No changes in the blood sugar levels were noted.

Discussion

Ascites and oedema rapidly developed following hepatic resection, or porta caval shunts in cirrhosis of the liver, because of hypoproteinaemia and anemia. In most cases, the normal dose of furosemide is adequate to control the ascites and oedema. However, in resistant cases, it was found necessary to give large doses of furosemide to achieve a response. Our experience has been that the parenteral route is the most suitable to achieve quick response, since absorption is unpredictable by oral route. This procedure eliminates the water but conserves proteins. The main disadvantage with higher dosage in hepatic patients is hypo-kalemia (Sherlocks and Shaldon 1963) which should be supplemented, according to serum electrolyte results.

It is our current practice to administer 40 mg. of furosemide for most cases of burns involving more than 30% of the body surface. This enables rapid elimination of overt oedema and preventing the oliguria phase. When, however, oliguria or anuria is present, it is customary to increase the dose of furosemide. In our experience, eight patients required dosage upwards of 1,000 mg. to effect a diuretic phase. No permanent damage to the kidneys were observed.

Although temporary response was obtained in seven out of ten patients with intractable ascites in malignant lesions of the alimentary tract, our findings indicate that furosemide has little to offer to these patients except in the immediate phase. Such patients are probably better treated by abdominal paracentesis.

Our experience has shown that furosemide is extremely effective in head injuries and our findings agree with those of others (Galle and Standacher 1968). In some patients, rapid recovery from the effects of cerebral oedema can be achieved by the use of high doses of furosemide when the recovery is slow.

Our preference for the administration of high doses of furosemide by injection in these 44 patients is that rapid onset of action and precipitation of early massive diuresis prevent accumulation of the drug in the system (McKenzie et at 1966).

These series have shown that apart from the possibility of massive output of urine which may lead to dehydration and electrolyte depletion, especially potassium, no other major side-effects were noticed. The main problem seems that only 20 mg. vials are

available in our country and it is cumbersome to the nursing staff in administering the drug parentally and painful to patients who have to receive such large doses intramuscularly.

Summary

Large doses of furosemide, varying from 1,000 mg. to 5,250 mg. were used in 44 surgical patients. Since they were resistant to normal doses of 40 mg. in the initial stages, higher doses were employed as a short-term therapy to evoke a diuresis.

Twenty-nine patients had marked ascites due to liver diseases or malignancy of the alimentary tract, eight patients had severe burns with oliguria or anuria and seven patients cerebral oedema following head injury.

Although seven out of ten patients with malignancy of alimentary tract responded well initially, the ascites returned soon after withdrawal of therapy and became resistant to subsequent higher doses. For these cases, we feel, use of this regime, probably, is of no value.

Marked diuretic response, absence of side-effects and desired clinical improvement achieved in liver, kidney and head injury cases prove the fact that, with adequate supplementation of electrolytes, large doses can be safely given in resistant cases.

Acknowledgement

We wish to express our gratitude to Dr. Law Gim Teik, F.F.A.R.C.S., for guidance and to the Director-General of Medical Services, Malaysia, for permission to publish this article.

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Idiopathic Addison's disease

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IN PAST YEARS, tuberculosis was the commonest cause of Addison's disease (Guttman, 1930). In Singapore, even though tuberculosis is common, Addison's disease, whether due to tuberculous destruction of the adrenals or idiopathic atrophy, is rare. Most cases of Addison's disease seen in Western countries nowadays is due to idiopathic atrophy of the adrenal glands (Friedman, 1948). In these cases, there is an increased prevalence of antibodies against adrenal gland tissue (Blizzard and Kyle, 1963). These antibodies are in many cases associated with antibodies against other organ-specific antigens, presumably due to the same underlying autoimmune disorder (Irvine et al., 1968). In this paper, we report a case of idiopathic Addison's disease associated with primary amenorrhoea and antibodies against the thyroid gland.

Case Report

The patient, a 45-year-old unmarried woman, was admitted on 9th March, 1971 with a 4-month history of progressive darkening of the skin. She also noticed that she was getting weaker, was mildly anorexic and had lost some weight. The symptoms were worse in the last few days before admission and she felt faint after exerting herself.

Further questioning revealed a history of primary amenorrhoea.

On examination, the patient had generalised hyperpigmentation, especially in the pressure areas. The blood pressure was 100/80, mm. Hg. and the pulse rate 72 beats a minute. Breast tissue was poorly developed; axillary and pubic hair was scanty. The uterus and cervix were normal and the adnexae were not palpable. A buccal smear and chromosomal analysis on a sample of peripheral blood revealed a normal karyotype.

A chest radiogram revealed right lower lobe pneumonia which required a course of tetracycline therapy. An abdominal radiogram revealed no evidence of adrenal calcification. Haemoglobin was 11.9 g% and the total leucocyte count 6,700/c.mm. with 63% polymorphs, 25% lymphocytes, 3% monocytes and 9% eosinophils. No ova or cysts were detected in three stool specimens. Fasting blood sugar was 85 mg%. Plasma cortisol levels at midnight and 8.00 a.m. were both 10 mcg%. A 24-hour urine collection (vol. 1550 ml.) for 17-ketosteroids and 17-OH corticosteroids gave values of 0.5 mg and 1.0 mg, respectively. A 1-hour A.C.T.H. stimulation test (Maynard et al., 1966) was performed. At 9.00 a.m., the plasma cortisol level was 9 mcg%. At 10.00 a.m., 1 hour after 25 units of A.C.T.H. were given intramuscularly, the cortisol level did not rise but remained at 9 mcg%. Soffer's test revealed poor excretion of a water load (170 ml. urine was collected over a 5-hour period after an initial loading dose of 1,500 ml. water). Antithyroid antibodies were positive to a dilution of 1/25.

During the first few days in hospital, the patient felt weak, anorexic and nauseated. She also felt faint on standing up for long periods due to orthostatic hypotension. However, with the clearing up of the pneumonia, together with cortisone replacement therapy, she became asymptomatic.

Discussion

The classical symptoms of Addison's disease are well known. However, in early cases, where symptoms are mild and non-specific, diagnosis is more difficult. Increased pigmentation, as in the present case, is an important sign of primary failure of the adrenal cortex. Other common symptoms and signs include weakness, weight loss, hypotension, anorexia, nausea and emesis. In early adrenal failure, the ability of the adrenal glands to respond to stress is impaired, and the signs and symptoms become more pronounced in periods of stress. The failure of the adrenal cortex to respond to stress forms the basis of the A.C.T.H. stimulation test, an important test in the diagnosis of Addison's disease.

While tuberculosis is fairly common in Singapore, Addison's disease is very rare in these patients, and is usually of the idiopathic variety. The reason for this is obscure.

It is postulated that the primary amenorrhoea in this patient arose on an autoimmune basis with damage and dysfunction of the ovarian tissues before menarche (Irvin et al., 1968).

Summary

A case of idiopathic Addison's disease associated with primary amenorrhoea and antibodies against the thyroid gland is reported. The rarity of Addison's disease inspite of the frequency of tuberculosis is stressed. The frequent association of idiopathic atrophy of the adrenals with other autoimmune disorders is noted. Early diagnosis is important as acute decompensation brought on by stress may be fatal.

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Age variations in the internal radii of human arteries

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Introduction

INTERNAL DIAMETER OR RADIUS is the most important dimension of an artery in the dynamics of the cardiovascular system. (Abramson, 1962 & 1967). An accurate measurement of it by direct method in vivo is not easily obtained. It may be determined from arterial segments of a cadaver after histological sections. Even this is also not easy, because of the changes due to post-mortem contracture of the arterial wall in addition to those produced by histological processing.

Some workers have measured the internal calibre of blood vessels by angiography and established a pressure-radius relationship of the blood vessels. (Luchsinger, et al 1962; Schobinger, et al 1964; and Lerhrer, 1968). Others have done the same by direct method and determined the external diameters of arteries during a surgical operation or otherwise. (Rushmer, 1955; Greenfield, et al 1962; and Reich, et al 1964). Many methods of measuring this dimension are on record in the literature. (Reynold, 1952; Saunders, et al 1954; and Rushmer, 1955; also Turner, 1957; Luchsinger, et al 1968; & Wiederhielm, 1963).

This present study is an endeavour to estimate the internal radii of some specific arteries, both elastic and muscular, by direct method and to observe the variations in them due to ageing. Though these measurements were obtained after death, yet they represent the actual radii of these blood vessels during life. A simple but fairly accurate method has been applied to measure them.

Materials and Method

A random investigation has been made on the arteries of 50 apparently healthy and fresh cadavers of different ages – mostly from accidental deaths. Cross-sections from selected sites of the following arteries, viz; Subclavian, Internal Carotid, Internal Iliac, Renal and Coronary arteries were made and histologically prepared. Slides of these stained sections were projected on a screen to a desired magnification (x 20). The inner margins of these arterial shadows were carefully traced on a paper and then measured with an opisometer (map-measurer). (Turner, 1957; Pallie, et al 1962). The resultant measurements were scaled down to proper lengths and converted into millimeters which represented the true inner circumferences of these arteries. The calculated numbers were then used to find the radii from a mathematical formula, $C = 2\pi r$, where, C = circumference, r = radius and $\pi = 22/7$. These results were put on scatter-graphs according to age and the corresponding measurements. This is shown in the following scatter-graphs. (Figs. 1, 2, 3, 4 & 5).

Results

From the study of these scatter-graphs, it is observed that there is a gradual increase in the internal calibres of these arteries as age advanced. This change is found both in elastic and muscular arteries with a few exceptions. Nevertheless, the mean graph-line on both sides of which the scatters are equally distributed, shows a steady upward inclination indicating

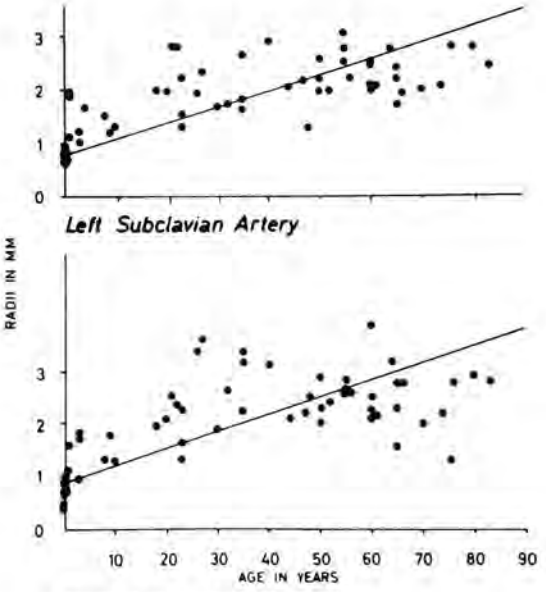

Fig. 1
Right and left subclavian artery.

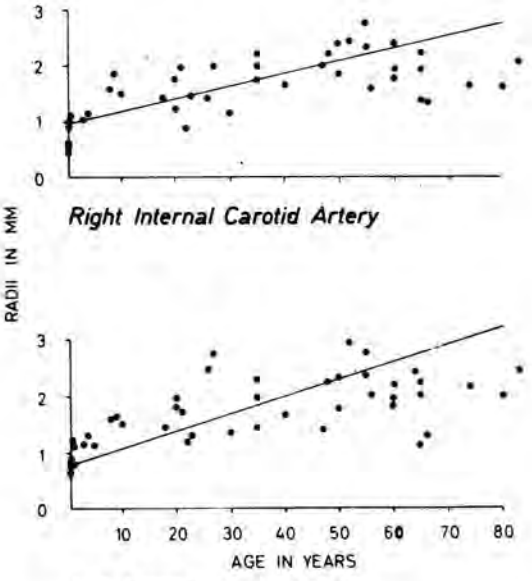

Fig. 2
Right and left internal carotid artery.

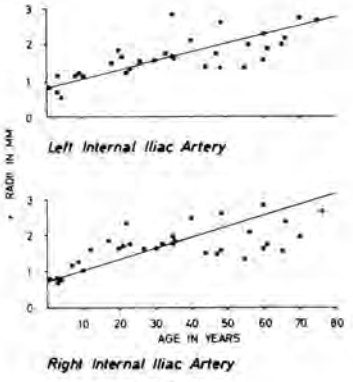

Fig. 3
Right and left internal iliac artery.

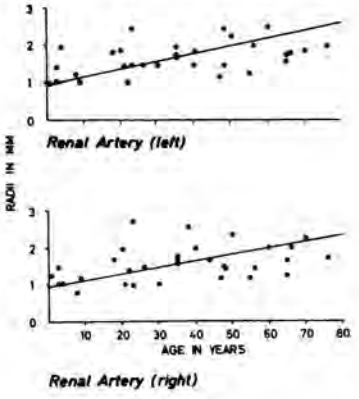

Fig. 4
Right and left renal artery.

that there is a gradual increase in the radii of these arteries with ageing.

Discussions

Some work on the internal radii of arteries has been documented in the literature. Elastic arteries dilate; small muscular arteries and arterioles contract. But nothing much has been recorded about the medium-sized muscular arteries. This study is mainly based on them.

Normally, when not contracted, arteries have a fairly uniform and smooth inner margin. Fig. 6. (Van Citters, et al 1962; Hayes, 1967; and Ham, 1967). But this margin is thrown into wavy folds when they contract. (Fig. 7). If this wavy border can be traced and measured with a suitable instrument after proper magnification, the real circumference and the radius of an artery can be calculated. This will give the true measurement of the arteries when the owners of these arteries were alive, even though

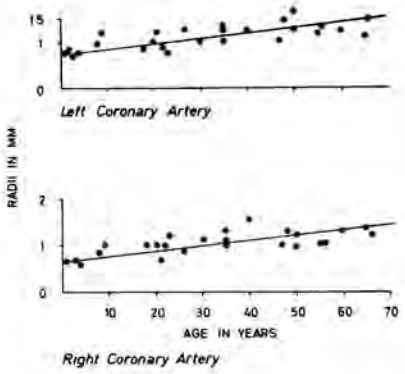

Fig. 5
Right and left coronary artery.

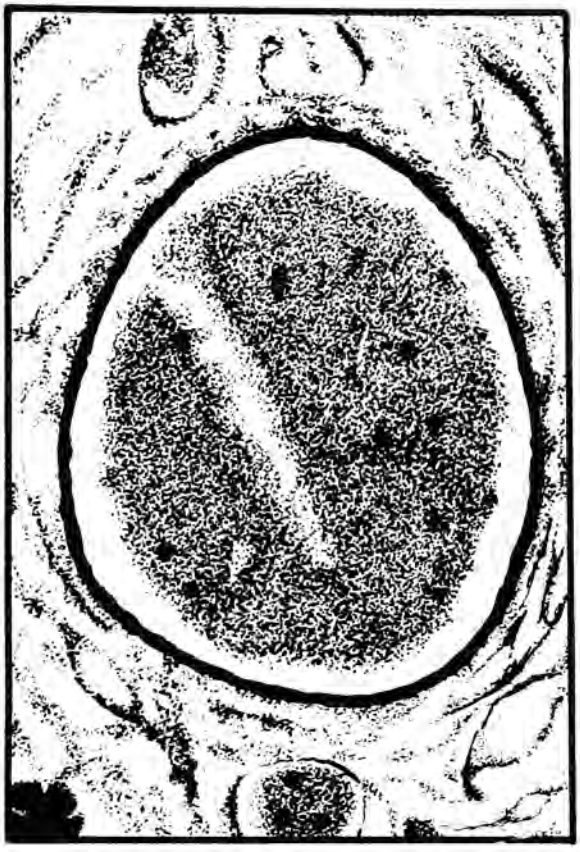

Fig. 6
Diagram showing uniform inner circumferential margin of an artery when not contracted.

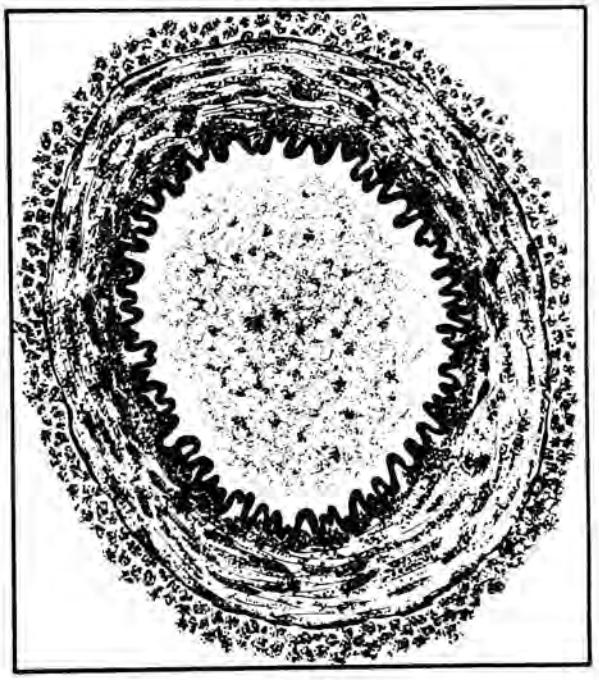

Fig. 7
Diagram showing the wavy inner circumferential margin of an artery when contracted.

these measurements have been obtained from their cadavers. This has already been mentioned in this paper.

Elastic arteries

That the radii of elastic arteries enlarge with age has been universally accepted. In this investigation, a few exceptions are observed, but on the whole, these arteries have shown a gradual enlargement of their internal radii with advancing age. The thirtieth year is considered to be the maximal age of developmental maturity in man. (Blumenthal, 1954 & 1967). This increase in radii is attributed to the following factors, viz; fragmentation of elastic lamina, increased fibrosis of arterial wall, its rigidity with loss of elasticity and the proportional rise of blood pressure during old age. (McDonald, 1960; Bourne, 1961; Bard, 1961; Levine, 1964; Ahmed, 1967; Lansing, 1969). This condition of widening is named "senile ectasia" of arteries according to Aschoff. In this present study, it is confirmed once more.

Muscular arteries (medium-sized)

It has been proved that smaller muscular arteries

and arterioles are narrowed down with age. This is one of the reasons of raised blood pressure in old age and subsequent dilatation of elastic arteries. As regard medium-sized arteries, nothing definite has been proved.

In this investigation, it has been noticed that these arteries also manifest similar widening of their lumen-like elastic arteries. This finding agrees with those found by Dibble (1966) and Abramson (1967), but differs with Roach and Burton (1969) who found narrowing of the lumen of these muscular arteries. All the factors that are responsible for the enlargement of the lumen of elastic arteries in old age are found in the walls of these muscular arteries with ageing. In addition to these changes, there are defects in the neuromuscular junctions in the arterial walls. The general weakness of muscle due to old age may also be considered another additional factor. (Pareira, et al 1953; Lansing, 1959; McDonald, 1960; Comfort, 1965; Lavine, 1964; Learoyd, et al 1966; Ahmed, 1967; and Robins, 1967).

From the above explanations, it is quite reasonable to conclude that the radii of these arteries should also have identical changes like those of elastic arteries. We found it in our present observations.

An analogy may be drawn between the consistency of an arterial wall and that of an India-rubber tube. In a new piece of such tube, if inflated, the pressure inside it will distend its wall and make its calibre bigger. When the pressure is released its wall will recoil and regain its original calibre. But the same thing when "old" and stiff will not do so even after the withdrawal of the distending force. (Bard, 1961). A comparable phenomenon takes place in an arterial segment. Though an artery is not an inert structure like India-rubber yet with advancing age, physical and biochemical changes in the elastic and muscular tissues of its wall will make it firm and rigid with loss of elasticity.

Arterial calibres are controlled by various factors. Everything remaining normal, there is always a longitudinal and lateral expansion of the arterial walls during a cardiac systole. (Gould, 1968). As age advances, the changes produced in the arterial walls (already mentioned) will produce a compensatory rise in blood pressure. During this phase of life, the expansion of the arterial walls with each cardiac systole, however negligible it may be, will never recoil back to its pre-existing shape. This being continued, there is every reason to believe that the radii of these arteries will increase in size. The medium-sized arteries should not be an exception.

Acknowledgement

Thanks are due to the staff of the Department of Anatomy and the Department of Medical Illustrations, Faculty of Medicine, University of Malaya, for their co-operation.

Summary

An investigation on the arteries of 50 cadavers of different ages has been done to compare the variations of their internal radii with ageing. A gradual increase in them is observed in both elastic and muscular arteries. A simple method for measuring the radii of these arteries has been described and the author's opinion is submitted.

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Reviews

LECTURE NOTES ON HAEMATOLOGY by N.C. Hughes Jones. Blackwell Sci. Publ., Oxford & Edin. 1970.
p.p. 144.8 plates £1.50 nett.

SPECIALLY WRITTEN for the medical student, these lecture notes provide a basic knowledge of clinical and laboratory aspects of haematology required to pass examinations. It is broadly similar to that of the course given to medical students at St. Mary's Hospital Medical School.

The normal physiological and biochemical principles of the haemopoietic system are presented and signs, symptoms and pathological changes are discussed in the light of the normal mechanism. Chapters are devoted to iron metabolism, the anaemias, haemostasis, blood transfusion, haemolytic diseases of the newborn and haematological techniques. There is an index.

It is up-to-date and authoritative and should also be useful to the busy practitioners of medicine.

A SHORT TEXTBOOK OF HAEMATOLOGY
by R.B. Thompson 3rd Edn. 1969.
English Language Book Society and Pitman Med & Sc. Publ. Co. Lond Paperback pp384 12s.

THIS LOW–PRICED text presents a readable and yet informative account of the disorders of blood and blood-forming organs. Thus it fills the gap between the unwieldy major textbooks of haematology and the textbooks on medicine which fail to supply enough detailed information to be of real value. Thus it is of special value to the general physician and the senior medical student.

The emphasis throughout is clinical but a discussion of basic physiology or pathology is included in each sector. The references at the end of each chapter have been selected because they are likely to be easily obtainable, informative and contain adequate key references. There is an adequate index.

TEAMWORK FOR WORLD HEALTH
Edited by Gordon Wolstenholme and Maeve O'Connor J. & A. Churchill, London. 1971 pp. 242 £3.00.

THIS VOLUME RECORDS the proceedings of the Cuba Foundation Symposium on Health of Mankind in 1970 at Istanbul. Money and manpower are scarce in health services everywhere. Poor countries lose doctors and nurses to richer ones; in richer nations, new diseases appear and greater demands are made on overburdened medical services.

Can fresh sources of manpower be found? Will new methods of training and management increase efficiency? Is the quality of care changing? How can remote areas attract and keep the health workers they need? What can teamwork achieve – but first what is a team and how does it work?

These and many other questions were discussed by twenty-six delegates and eighteen observers at the symposium and are recorded in this volume. It should be of benefit to all health workers and those interested in medical care, psychology and sociology.

Correspondence

The Editor,
Prof. A.A. Sandosham,
Medical Journal of Malaya.

Dear Sir,

In our paper (Bisseru and Abdul Aziz, 1970) we reported our findings on the intestinal parasitic infections of school-children in the various communities. We did not then recommend a drug for mass therapy.

Subsequently, I have used Pyrantel pamoate in the form of 'Combantrin' (Pfizer) for the treatment of multiple parasitic infections over the last few months in children and adults in rural areas in Selangor State, Malaysia. I have found my results extremely encouraging, 'Combantrin' being highly effective against **Ascaris lumbricoides** (roundworm), hookworms (**Necator americanus** is the predominant species in Malaysia), and **Enterobius vermicularis** (pinworms or threadworms).

Field studies at the Montfort Boys' Home, Batu Tiga, Selangor have shown 84.5% (49 out of a total of 58) boys examined were found to carry one or more intestinal helminth. Of these 49, 33 were available for treatment with 'Combantrin' at a single dose of four tablets each of 125 mg. active base. A repeat stool test was carried out two weeks after the treatment.

In ten of the 11 boys with Ascaris infection, no eggs of the parasite were seen in the stool post-treatment, i.e., a "cure-rate" of the patent infection of 90.9%. Similarly, of the 11 boys with hookworm, no ova of this parasite were seen in the stool of ten boys, i.e., again a "cure-rate" of the present patent infection of 90.9%. Stool tests revealed three cases of **Enterobius** infection and the post-treatment picture should show a cure of this patent infection.

In 21 boys with scanty **Trichuris** infection (eggs less than 200/grm faeces) which was the commonest parasite seen, no eggs were detected in the stools of 12 (57%). While there was very significant egg reduction in the remainder (43%), all these being boys harboured very scanty infections, namely less than 80 eggs per gram of faeces.

Further outpatient field trials in progress on about 300 children and adults on two rubber and oil palm estates have been extremely encouraging. Similar results have been found on in-patients at the Gombak Hospital, Selangor. I have so far found no side-effects following the use of this drug and it could therefore be used where no medical personnel are available for supervision. It is suitable for mass therapy as it is a single dose treatment; an elixir is available for paediatric use.

Work has been carried out with 'Combantrin' in Taiwan (Hsieh and Chen, 1970) with equally promising results and insignificant side-effects.

Yours sincerely,

(Professor B. Bisseru)
Head
Department of Parasitology

Reference

1. Bisseru, B. and Abdul Aziz bin Ahmad (1970). Intestinal parasites, eosinophilia, haemoglobin and gamma globulin of Malay, Chinese and Indian schoolchildren. *Med. J. Malaya, 25,* 29.
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