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Editorial

Affiliations and Memberships of the Malaysian Medical Association

by A. A. Sandosham

IN ADDITION TO being affiliated to the British Medical Association, the Australian Medical Association, the Medical Association of New Zealand and the Singapore Medical Association, the Malaysian Medical Association is a member of the Commonwealth Medical Association and the Confederation of the Medical Associations of Asia and Oceania. Such association with medical organisations of other countries is of great value to us in that it helps to broaden our outlook and perspective and to solve some of our medical problems as a result of the experiences gained by our colleagues elsewhere. It fosters international understanding and fellowship among the medical fraternity and results in easy exchange of information for our mutual benefit.

The Commonwealth Medical Association

The C.M.A. had its origin some 20 years ago when the first conference of national medical associations of the Commonwealth countries was held in Canada. Subsequent conferences have been organised at irregular intervals until the C.M.A. was formally established in 1962 with provisions for a meeting of its Council every two years. In 1970 Malaysia and Singapore were the joint hosts to the fifth council meeting under the joint presidentship of Dr. Gwee Ah Leng and myself.

At this meeting, it was decided to deny membership of the C.M.A. to South Africa and Rhodesia as their governments' policies of apartheid and segregation were thoroughly inconsistent with our constitution. It was felt that the two-year interval between council meetings was too long and that the Executive Committee should meet during the interim period and that provision should be made for regionalisation of the Commonwealth countries with representation in the executive. Accordingly, Canada and the Caribbean Council were entrusted with the responsibility of drafting a new Constitution.

Problems of medical ethics in Malaysia was one of the subjects discussed at the fifth council meeting and it was felt that similar problems were being confronted in some of the other Commonwealth countries. Malaysia and Singapore were entrusted with the responsibility of getting in touch with the other countries and draft a set of rules for the consideration of a future meeting of the C.M.A. Council.

At the meeting of the C.M.A. executive in Jamaica in 1971, the draft Constitution was dis-

cussed in detail and the amended version was to be tabled for confirmation at the sixth C.M.A. council meeting. Coincident with the meeting of the C.M.A. executive was the first Caribbean Medical Conference.

At the sixth C.M.A. council meeting, Malaysia was represented by Dr. Pius Martin, the M.M.A. nominee, and myself as Joint President.

The draft Constitution was formally approved and came into force immediately. Provision was made for the Commonwealth countries to be subdivided into six regions, each to be represented on the executive by an individual elected by the representative from the countries of that region who would become one of the vice-presidents of C.M.A. for the following two years. The Southeast Asian region would comprise Malaysia, Singapore, Australia, New Zealand and Fiji, and Dr. Gwee Ah Leng was elected as its representative.

The finances of the C.M.A. were discussed at length. It was decided to recommend a new quota of subscription based on the total membership of the national associations, and to facilitate the financing of regional meetings, it was decided to discontinue expenditure on the Commonwealth Travelling Fellow. It was decided that the seventh council meeting of the C.M.A. would be held in the West Indies in 1974.

Confederation of Medical Associations in Asia and Oceania

This organisation came into being largely as the result of the initiative taken by the Philippines Medical Association and the efforts of the first secretary-treasurer, the late Dr. Victorino S. de Dios. Though the idea was mooted as early as 1950, the Constitution and by-laws were only approved at a meeting in Manila in 1956. Subsequently, meetings have been held at two-year intervals in Japan, the Philippines, Japan, Australia, Japan, Taiwan and South Korea, the national medical associations acting as hosts. The respective governments of the host countries have given considerable moral and financial support to these congresses which have been a great success from the point of view of attendance and the quality of the papers presented.

The eighth C.M.A.A.O. congress is scheduled to be held in Kuala Lumpur to coincide with the M.M.A. annual general meeting next year. This is a suitable opportunity, therefore, to acquaint our members of the activities of the C.M.A.A.O. and our responsibilities as hosts in 1973. The main objectives of the organisation are the promotion of closer ties among the national medical associations in the countries of Asia and Oceania and the study of problems related to medicine and the exchange of information leading to the attainment of the highest possible level of health in the region.

Among the problems are the insufficiency of funds for travel of delegates to attend meetings and the inadequacy of a knowledge of English (the official language of the Confederation) on the part of some of the delegates. The M.M.A. has been represented at the biennial meetings by Datuk Dr. Lim Kee Jin, Datuk Dr. Keshmahinder Singh and myself. I have served in the past as a Councillor and was elected President last year while Datuk Dr. Keshmahinder Singh is the Vice-President. Now that our M.M.A. house is ready, it is to be hoped that we will be able to equal, if not better, the arrangements we made for the C.M.A. council meeting in 1970.

Malay customs in relation to childbirth

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THE ART AND SCIENCE of obstetrics have been practiced in this country for decades. It is surprising that no effort has been made to look into the customs and traditions of the local population. This is typical of the British colonial attitude. An art developed in and tailored to the needs of the British population has been infused into our population without regard for the differences in religion, customs and traditions which obviously exist. On the other hand, Malaysian obstetricians have not given the matter much thought either — certainly there has been no report on the subject.

This paper deals with customs and practices of the Malays in relation to childbirth. There are 3 distinct phases, viz, pregnancy, labour and puerperium, including the newborn.

Material

As mentioned, there is a great scarcity of reference work on the subject. The few Malay customs reference books available carry very brief mention of this aspect of Malay customs.

The sources of material for this paper are:—

1. Malay patients who have been under my care.
2. Malay doctors who have so kindly read my manuscripts and given advice and comments.

One point worth noting is that these practices differ from state to state and even from district to district within the same state. Many of the practices are no longer followed and others are practised by the kampong Malays only. However, even in urban practice, either in a hospital or in a private nursing home, one still comes across these practices occasionally. When questioned, many of these patients are either too shy or not very conversant with the practices to go into detailed discussion. Some even admit that they are ignorant of the significance of the practices but carry out the requirements as instructed by their elders.

On the other hand, many of the older Malay midwives are able to give rather concise accounts

of the customs. The setback is that, to the uninitiated like myself, facts become very mixed up and controversial. Each midwife is equally adamant that hers is the true version. The point is that the story of the customs and practices depends entirely on which area the narrator has been brought up in.

The Malaysian doctors, many of whom are too ingrained in Western education and training, are not very conversant with Malay customs. The other reason may be that almost all from whom I have sought information are male doctors and are not conversant with customs relating to childbirth.

Results

I Customs related to the pregnant woman

Beliefs affecting the pregnancy

1. Bathing in the evening may cause hydramnios.
2. Ill-treatment of a bird or fish the month before conception may lead to congenital defects.
3. If the woman is "bitten" by a crab, the infant may be born with hare-lips.
4. "Kenan": this infers that if the pregnant woman sustains any fright, the infant runs the risk of being born with certain abnormalities.
5. Throughout pregnancy, the woman defends herself against attacks by evil spirits. One of these is the "langsayar" — belived to be the spirit of a woman who died in childbirth. It consists of a head and entrails only.
6. The following ceremony is performed on all primiparous women at the 7th month of pregnancy. The aim is to clear all evil spirits so that the woman will have a normal delivery.

"Melingang Perut" or "Mandi Tian", in which the midwife examines the abdomen of the pregnant woman and then places 7 pieces of coloured cloth on the floor. The woman then lies on these. The midwife waves the edges of these pieces of cloth and after chanting some prayer removes the pieces of cloth. A few days later, the woman is bathed by the midwife. The latter then sprinkles rice powder mixed with water (tepong tawar), yellow rice (beras kunyit) and burns incense over the pregnant woman.

Beliefs affecting labour

1. Prolonged and difficult labours may result from:
   (i) Sitting on the doorstep.
   (ii) Crossing over a line or a pole.
   (iii) Sleeping in the afternoon.
2. Non-separation and retention of placenta may result from:
   (i) Sitting on the ground, crossing a line or a pole.
   (ii) Eating creeping vegetables, e.g. pumpkin.
   (iii) Not cleaning a starch-container thoroughly after starching clothes.
3. Normal separation of placenta is encouraged by eating lady's fingers.
4. At the onset of labour pain, a "bomoh" is called to the house to choose a place for the delivery. He is given a parang or an axe. This is thrown on the floor at random; wherever the instrument lands on is the spot chosen for delivery. A hole is dug beneath the house directly under where the instrument fell. Thorny leaves, such as pineapple leaves and mengkuang leaves, are put around the hole. The tail of a rayfish, spider's web, an old fishing net and a kind of bitter grass are thrown into this hole. The belief is that this will guard the mother against evil spirits during childbirth. Sometimes a coconut with holes in it is hung from the floor for the same purpose.

All unlocked cupboards and drawers are opened so that the woman can deliver normally. If the delivery tends to be delayed, the husband is summoned. He then steps over his labouring wife once. This is supposed to hasten the labour.

The placenta is usually buried without any ceremony. However, it is very important that the placenta must be buried. Should there be a stillborn, this is also buried.

II Beliefs affecting the Puerperium

After delivery, the mother must remain indoors for 44 days. In the old days, she used to stay and sleep by the fireplace. She puts on old clothing and does not bother about her appearance so as to be not too attractive to her husband during this period. She does her hair into a tight bun so as to "support the uterus", and to delay involution. It is encouraged that involution should be delayed. Early involution is believed to lead to prolapse of the uterus.

Her food consists of a plate of rice with salt and pepper only. A second serving of food is not allowed as this may cause early involution of the uterus. Vegetables and fruits should not be eaten as they are cooling and may cause weakness. Water is restricted because if too much is taken, it may cause distension and watery discharge. Fresh milk and fruits, if eaten, may result in haemorrhage.

Early bowel motion leads to frequent pregnancies. Hence, purgatives are not given in the

puerperium. In the puerperium, the mother usually wears an iron nail in her hair. Alternatively she carries with her a knife, a pair of scissors or a small penknife. It is believed that birth spirits fly away at the sight of iron and sharp objects.

After a bath, the "tungku" (a stone pounder), a piece of stone or iron bar, is heated and wrapped with a certain kind of leaves and cloth. This is then applied to the abdomen to reduce the "swollen nerves" which follows delivery. It also ensures good contraction of the uterus. Thereafter a tight abdominal binder is applied to help the abdomen regain its shape.

For 3 days after delivery, the midwife massages the mother to encourage the flow of milk and to "bring the nerves back into position". The mother is then given a bath with hot water containing all kinds of leaves.

On the 44th day, the midwife performs the ceremony of disposal of the fireplace. She also wishes the mother well. The mother then puts on new clothes and is allowed to join the family and friends for a feast. The puerperium is then officially over and this is referred to as the "Lepas Pantang".

III Beliefs with regards the newborn

1. Neonatal thrush is believed to be the result of a woman wearing flowers in her head during the ante-natal period.
2. After birth the baby is bathed, dressed and then put on a rice tray covered with seven pieces of sarong. The father whispers prayers from the Koran into the child's ears. The midwife takes a little betel juice from her mouth and gently spits on the baby to protect him from disease. The baby's tongue or lips are touched with a gold ring for power and with honey to induce sweetness of disposition.
3. If the baby is a male and resembles the father very much, it is believed that either will die soon; therefore the child's ear is pierced immediately by the widwife to avert this.
4. After the "lepas pantang", if the baby is to be taken out of the house, the forehead is marked with soot from the "kuali" in three directions. This is done to scare away evil spirits that may want to attack the baby.
5. On the seventh day, after the child is lifted from the rice tray, his head is shaven except for a lock; rice powder is put on his face. This is said to prevent any evil spirit from attacking the child. The rice from the tray is cooked into porridge and distributed amongst other children. The baby is fed on baked banana with a little salt, and sometimes a little rice is mixed with it.
6. The umbilical cord of the infant is dressed with ash obtained from burning old rags or from the stove. Occasionally sireh leaves are applied. This is held in position with a small abdominal binder. When the umbilical cord drops, it is wrapped in cloth with some spices and this is heated over "kamiyan" (incense) and applied to the baby's umbilicus. This prevents "wind" from entering the abdomen.
7. Another ceremony is performed on the child when he is six months old. The "Turun Tanah" is the ceremony when the child is allowed to touch the ground for the first time. This takes place at 5.30 a.m. before the morning prayers. In this ceremony, a tray containing rice, gold ornaments, pencil, needle and the Koran is placed in front of the child. The child is held with its feet touching the ground and facing the tray.
8. The mother breast-feeds her baby "on demand". The neonate is fed on the right breast first because this is supposed to contain food. The left breast is supposed to contain water and hence is seldom offered to the infant.
9. The weaning diet consists of rice and sauce with a little salt fish and, occasionally, vegetables. Biscuits are given in between meals.

Comments

This is not a true scientific paper in as much as the materials are mainly hearsay evidence. A few of the practices have been witnessed by the author. However, in view of the scarcity of reference work on this topic, it is felt that the materials collected ought to be recorded in a medical journal.

As expected, many of the practices are mere mythological and superstitious beliefs. Most of them are inocent and harmless. They seek to find an explanation for complications that happen. In a way, a very similar practice exists in western medicine as practiced in the United Kingdom as well as in Malaysia; women have been told that they have a "twisted womb" or a "tilted womb" to explain various conditions. Even today, a "tilted womb" is used by doctors to explain infertility, backache, dyspareunia and a host of other things.

In studying the matter, one is impressed by the frequent association of ideas; for instance, the water used in bathing may give rise to hydramnios; the "bite" of a crab may cause hare-lip, and so forth. It is noticed that retained placenta is something undestirable and eating lady's fingers is said to help separation of the placenta. Could it be that

the slimy nature of this bean will "lubricate" the delivery of the placenta?

One practice that is consistent and almost always carried out is the disposal of the placenta. Even so, the author has met with a few young Malay couples who have refused to take the placenta home for disposal.

It is interesting to note that in the puerperium, the post-natal woman is not to make herself too attractive to the husband. Perhaps the idea is to put off sexual intercourse for the 44 days' confinement. Again, some Malay couples have started sexual intercourse before the "lepas pantang".

Early involution of the uterus is discouraged as this leads to prolapse of the womb. The author is unable to elicit an explanation for this. Even before the family planning board came into existence, frequent pregnancies are discouraged. To this end, purgatives are not given to the patient!

On the whole, as revealed by this study, most of the practices in relation to pregnancy and childbirth, as practised by the Malays, do not appear to be medically harmful.

Acknowledgement

The author would like to thank all the patients, nurses and medical students who contributed ideas to this paper.

Growth charts based on measurements of Malay pre-schoolchildren

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Introduction

GROWTH IS A USEFUL indicator of the well-being of children, particularly in the toddler and pre-school age group where normal growth is rapid and malnutrition and disease are common. A child's growth achievement and nutritional status can most easily be assessed by comparing several body measurements with norms derived from a relatively healthy, well-nourished population of genetically similar children (Jelliffe, 1966).

Dugdale (1969) and Chen and Dugdale (1970) have published such norms in the form of growth charts for Malaysian infants and schoolchildren respectively, but similar information for children in the intermediate age range has been lacking. We, therefore, are presenting charts derived from our measurements of a group of some 660 Malay children below school age.

Material and Methods

The subjects were all of the Malay ethnic group, the children of soldiers in the Malaysian Army who were stationed in the Kuala Lumpur area.

All children were examined by physicians, and any with gross physical defects were excluded from the study. We also excluded those whose exact ages could not be determined from birth certificates or maternal recall.

Measurements were made by a specially-trained team of technicians in January 1968, following the methods suggested by Jelliffe (1966). All measurements except weight were made in triplicate, as follows:

1. *Weight*, with shorts only, taken on an Avery beam balance accurate to ¼ ounce.
2. *Length*, taken with the child held supine on a measuring board accurate to 0.1 cm.
3. *Head circumference*, taken to the nearest 0.1 cm. with a steel tape in the horizontal plane of greatest dimension just above the eyes.
4. *Triceps skinfold thickness*, measured with Lange calipers held horizontally at the measured posterior midpoint between the acromion and the olecranon of the left arm, held in relaxed 90° flexion.
5. *Mid-arm circumference*, measured to the nearest 0.1 cm. at the same position as the skinfold thickness.
6. *Mid-arm muscle circumference*, calculated by the formula: muscle circumference = mid-arm circumference — (3.14 x triceps skinfold thickness).

The number of individual measurements available were: weight, 648; length, 653; head circumference, 655; triceps skinfold thickness, 665; mid-arm circumference, 654; and mid-arm muscle circumference, 654.

Data were punched on 80-column cards, which were then arranged in order of age. For each measurement, the total group was then divided by age into nine equal subgroups (the oldest subgroup sometimes having one or more extra cards). Within each subgroup, the cards were arranged in ascending order of the measurement considered and the 90th, 10th and 50th (median) percentile values extracted. Curves were then fitted to these percentile values with a minimum of visual smoothing, and charts were constructed.

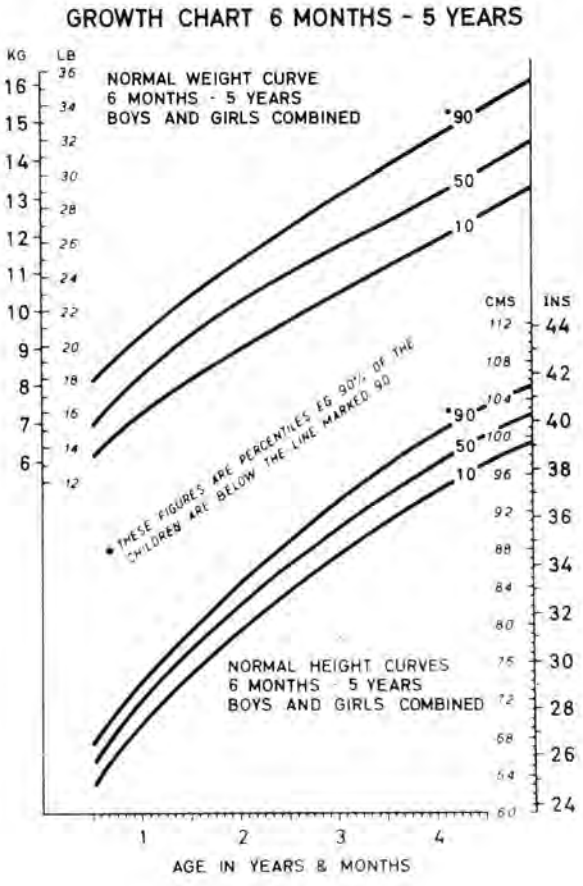
Results

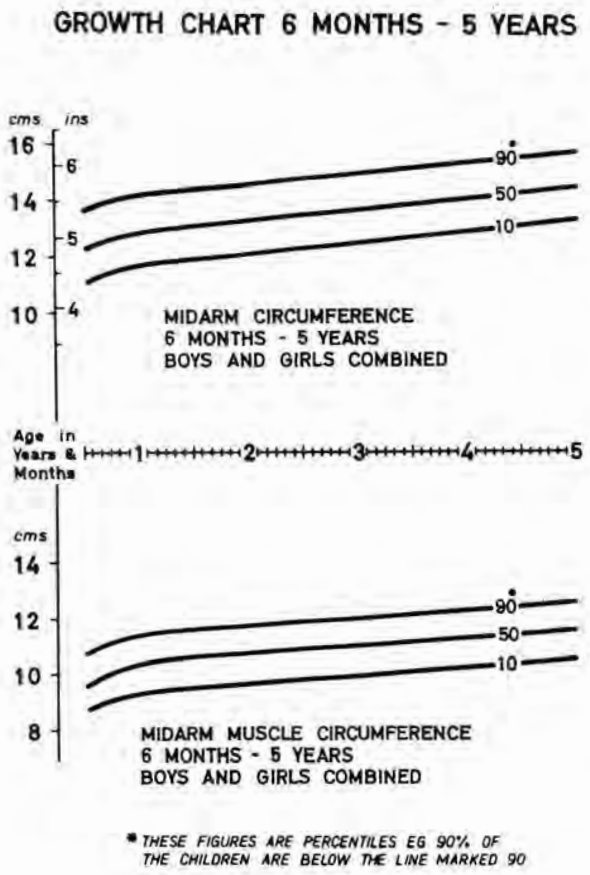
The resulting charts are shown in figures 1, 2, and 3. The data for the nine subgroup points on which each percentile curve is based may be obtained from any of the authors.

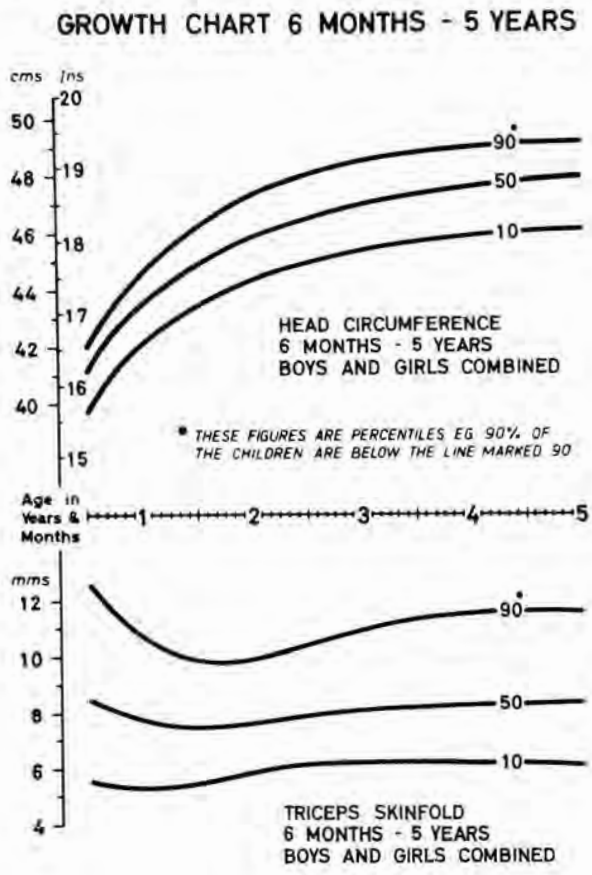
Discussion

We have presented elsewhere (McKay, et al. 1971) more detailed analysis of these data in comparison with other groups of children, of the relative usefulness of the different measurements used, and of the appropriateness of using these norms as "standards" in assessing the health of children in this country.

The most useful measurements for routine nutritional assessment appear to be weight, length (or height), and mid-arm circumference. Mid-arm circumference is the least affected by age uncertainty and is easy to use in field surveys (Jelliffe and Jelliffe, 1969). The measurement of skinfold thickness and the calculation of mid-arm muscle circumference may indicate the relative adequacy of protein versus total calories in the diet (Dugdale et al., 1970). Head circumference is related mainly to brain size and is used mostly as an index of general development in the first three years of life







rather than as an indicator of malnutrition (Jelliffe, 1966).

We suggest plotting a child's measurements on these charts as a practical aid to assessing growth and health. Our experience indicates that children with measurements below the tenth percentile on these charts should be considered a risk of significant malnutrition or other growth-retarding pathology, even though by definition 10% of the reference population of Army dependents falls into this range. Values plotted between the tenth and fiftieth percentiles indicate "below average" growth, and children consistently in this intermediate range may be experiencing marginal malnutrition. Children whose measurements are above the fiftieth percentile are unlikely to be in nutritional difficulty.

Copies of these charts in a form suitable for clinic use are available from the Department of Paediatrics, Faculty of Medicine, University of Malaya.

Acknowledgements

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Smallpox vaccination: Complications and present role

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Introduction:

EVER SINCE JENNERIAN vaccination was widely adopted in the control of smallpox in many endemic countries, attention had been focussed on its complications. With the virtual eradication of smallpox in many Western countries, these complications have raised major controversies about the very usefulness of vaccination in controlling outbreaks of smallpox. We have now sufficient knowledge of smallpox from many epidemiological studies to justify a proper assessment of the exact place of vaccination.

Malaysia has been free from smallpox since the last outbreak in Kedah in 1946-47 when 599 cases were reported with 293 deaths. In the middle of September 1971, a suspected case of smallpox seen in the University Hospital, Petaling Jaya, aroused the fear of imported smallpox in Klang, followed by a mass vaccination campaign. This paper presents the results of a study of the complications seen following the mass vaccination, and reviews the present role of vaccination.

Materials and Methods

Between 15th and 19th September 1971, 186,329 people of all ages were vaccinated in Klang. All doctors in the hospital and in private practice were asked to look for complications and to refer patients to the hospital for this study. Forty cases were studied in detail. Where necessary, patients were treated as in-patients.

Results

The following complications were seen during the study.

1.	Generalised vaccinia	12
2.	Toxic erythema	12
3.	Auto-inoculation	4
4.	Erythema exudativum	2
5.	Local necrosis	1
6.	Miliary eruption	1
7.	Herpes zoster	1
8.	Angio-neurotic edema	1
9.	Steven-Johnson syndrome	1

10. Eczema vaccinatum	1
11. Encephalomyelitis	3
12. Vaccinia in newborn	1

Discussion

Complications of smallpox vaccination may be broadly classified into three types:

1. Cutaneous complications
2. Neurological complications
3. Miscellaneous complications.

Cutaneous Complications:

1. *Secondary Bacterial Infections*: These are quite common, especially in children. Being a minor complication, few were referred to the hospital. Local application of an antibiotic cream, such as achromycine, usually heals most lesions.

2. *Local Necrosis*: This can occur as a result of severe secondary bacterial infection or severe pustulation itself. In the case seen in this study, severe necrosis in a Malay male, aged 27, was accompanied by brawny edema of the whole upper limb.

3. *Auto-inoculation*: This follows scratching and transfer of the vaccine material to other parts of the body or to another person in close contact with the vaccinated person. This usually occurs during the first 9 days after vaccination.

Case 1. A 38-year-old Chinese female developed typical vesicles over the upper and lower eyelid with edema of the surrounding area, on the fifth day after vaccination. Recovery was uneventful.

Case 2. A recently vaccinated mother brought her 8-month-old child with typical vesicles over the back of the child's neck, due to auto-inoculation while carrying the child on her left arm.

4. *Toxic Eruptions*: These were the commonest cutaneous complication seen, accounting for 15 cases.

(a) *Miliarial eruptions*: One patient presented with miliarial eruptions along the lymph channels leading from the site of vesiculation.

(b) *Erythema Multiforme*: This is a very common complication, occurring usually 7 to 10 days after vaccination, sometimes up to the 14th day. The eruptions may be localised or generalised, cause little constitutional disturbance and clear in 3-5 days. Sarkany and Caron (1962) described toxic erythema, erythema nodosum, pityriasis rosea, eczema and granuloma annulare after vaccination. Of these, toxic erythema was the commonest type seen in the present study.

(c) *Erythema exudativum*: This is a more severe form of toxic erythema with generalised bullous formation, fever and protracted course, often described in dermatological literature. Three of our patients had this complication.

Case 1: A Malay female, aged 60, had localised bullous eruptions over the deltoid with echymotic areas.

Case 2: A 9-year-old Malay girl was admitted to the hospital, 8 days after vaccination, with high fever and vomiting. She had developed generalised erythematous eruptions, affecting the whole body, including the soles and palms, with multiple bullae all over, which left large raw areas, on rupture. Healing was satisfactory at the end of 2 weeks. She was very ill on admission, and the fever subsided after 7 days. Treatment included Prednisolone, Marboran 3 GM b.d. for a day, and oral achromycine. These toxic eruptions are probably due to some form of allergy to the vaccine.

4. *Allergic Reactions*: A case of angino-neurotic edema with urticarial eruptions over the trunk was seen. The edema affected the right eyelid and both lips. Another patient had mild Steven-Johnson syndrome.

5. *Eczema Vaccinatum*: This has been reported often since Kaposi originally described the 'varicelliform' eruption named after him. This description is now known to be a misnomer, as the lesion is not caused by varicella at all, and is usually vacciniform or varioliform. Kaposi's eruptions are pox exanthems on a previously damaged skin, usually by chronic eczema. Both vaccinia, herpes simplex and other agents may produce acute pock rash in these cases. Copeman and Wallace (1964) reported 185 cases of eczema vaccinatum during the smallpox outbreak in England and Wales, with 11 deaths. During the outbreak, 3¼ million people were given primary vaccination and an equal number revaccinated.

Eczema vaccinatum usually occurs 5-14 days after vaccination in an individual with eczema or accidental inoculation by contact with a vaccinated person. Severe forms are marked by toxicity and high fever. The lesions are always more localised to the areas of eczema, and asymmetrical. It generalised, the lesions may closely simulate smallpox. The palms and soles are spared.

Case 1: A 7-year-old Chinese boy was refused vaccination during the campaign, on account of flexural eczema of 3-4 years duration. However, he was in close contact with 9 other recently vaccinated persons at home. He was admitted with extensive eczema vaccinatum on 15.10.71, with a temperature of 103° F. He had developed profuse confluent eruptions over the areas of eczema over

Table 1

	Generalised Vaccinia	Smallpox	Chicken-pox
1. Prodromal Period	None. More likely with skin disease	Constant even in benign cases Uniform composition and period	None.
2. Distribution of Lesions	No constant pattern	Centrifugal	Centripetal.
3. Lesions on palms, soles	None	Present except in scanty lesions	Absent.
4. Restriction to some areas	Common	Widespread even in scanty lesions	Widespread.
5. Lesions with skin disease	Restricted to diseased skin	Also numerous over diseased skin but distribution elsewhere unaltered	
6. Symmetrical distribution	May be asymmetrical	Always symmetrically bilateral	
7. Confluence of pocks	Unilateral	Bilateral	Bilateral.

the neck, axillae and flexural areas over the trunk, 10 days prior to the date of admission. The general practitioner who saw this boy sent him as a suspected case of smallpox. The fever subsided after 7 days in the hospital. Oral achromycine and Prednisolone 5 mg. t.d.s. for a week enabled a complete recovery.

Winston Turner et al (1962) found Marboran effective in treating eczema vaccinatum, though gamma-globulin was ineffective.

6. *Generalised Vaccinia*: Brown (1965) doubts the existence of this type of lesions and is of the opinion that varicella or other causes are responsible for the lesions. However, most authors with wide experience of smallpox agree that these lesions have distinct characteristics. Jubb (1943) has best pointed out these features:

(a) Auto-inoculation is to be excluded.

(b) The eruptions do not appear earlier than the 4th day and seldom earlier than the 9th day after vaccination.

(c) The eruptions are away from the site of vaccination.

(d) Vesicular stage must be present.

Jubb estimated the incidence of these eruptions as 1 in 100,000 vaccinations. Lawrence et al (1952) found them in 1 in 25,000 vaccinations in children in the first year of life.

The distinguishing features of generalised vaccinia, smallpox and chicken-pox are summarised in the following table.

During the mass vaccination campaign, many cases of chicken-pox were seen. However, it was not difficult to diagnose the 12 cases of generalised vaccinia seen. Of these, 2 had fever for two days before they were vaccinated. Three others, including a child who had primary vaccination, had fever with the eruptions. One child had boils on the scalp, while an adult had chronic acne. A labourer who works under the sun daily had the generalised vaccinia localised to the areas exposed to the sun.

Marboran was given for most of these cases with satisfactory results.

7. *Vaccinia in the newborn*: It is now widely accepted that smallpox vaccination is contra-indicated in pregnancy. Both variola and vaccinia can cause abortion and intra-uterine death of the foetus. Abortion can occur even when exposed after the ninth week of pregnancy (S. M. Tucker and D. E. Sibson, 1962). The foetus is at risk even at mid-term (Entwistle et al, 1962). The foetus can develop generalised vaccinia. Pre-natal vaccinia can occur even when the mother is unvaccinated, probably due to airborne vaccinial infection, as report-

ed by Wielenga et al (1961). Eighteen fatal cases of generalised vaccinia in the foetus have been reported so far in the literature. MacArthur reported 10 abortions in 34 women vaccinated in the second and third months of pregnancy. In Poland, the abortion rate in women vaccinated before the 16th week of pregnancy was found to be three times that among controls.

In South Wales in 1962, 2 foetal vaccinia cases were seen among 242 cutaneous complications. One of them survived.

In our study, an Indian boy born on 2.11.71, about a month after the mother had been vaccinated, was found at birth to have generalised vaccina, of an abortive type, with little vesiculation.

8. *Herpes Zoster Intercostalis*: This may arise in a recently vaccinated person, presumably due to re-activation. One of our patients had this complication. A similar case was reported before from Singapore (1964).

9. *Progressive Generalised Vaccinia*: Here the initial vaccinial lesion fails to heal and spreads to the adjacent skin with necrosis. Metastatic lesions develop in skin, bones and viscera. This rare and fatal complication is associated with hypo- or a-gammaglobulinaemia.

II. Neurological Complications

These have become important as one of the major complications of vaccination in many countries, notably Holland and Britain. In South Wales in 1962, 39 neurological complications were seen after 800,000 vaccinations, out of which 30 involved the C.N.S., with 11 cases of encephalomyelitis. Spillane and Wells have reviewed these complications.

(a) *Post-vaccinial Encephalomyelitis*: This occurs only after the vaccination of the non-immune (primary or re-vaccination), usually after an incubation period of 8-15 days. Fever, headache, vomiting, meningitic signs, paralyses, drowsiness and coma or convulsions are the main clinical features. The C.S.F. shows an increase in cells, mainly lymphocytes, and in protein. E.E.G. shows high voltage slow waves. This complication occurs usually in older children and adults and does not occur in children below 2 years. Recovery is complete.

In the acute stage, mutism, dysarthria and involuntary movements are common. Sometimes the spinal cord is involved with the sequelae of spastic weakness of the lower limbs. Amnesia for the illness is permanent though recovery is complete.

C.S.F. shows an increase in cells, mainly lymphocytes, and in protein. E.E.G. shows high voltage slow waves.

Encephalomyelitis does not occur below the age of 2 years, and is usually seen in adults and older children .

In Spillane's series, steroids produced dramatic improvement in 3 cases.

Case 1.: A 13-year-old Chinese schoolgirl (K.K.E.) was admitted on 27.9.71 with history of inability to walk, a week after vaccination. She had a well-formed vesicle. She walked with an unsteady gait, looked dazed and withdrawn and exhibited mutism and marked slowness in executing voluntary movements. The cranial nerves were normal. There was slight neck rigidity and spasticity of the left leg. Reflexes were brisk. Plantar was extensor on the right side. Fundi were normal. On admission she had a fever of 101.4°F.

Lumbar puncture was unsuccessful. She was treated with Marboran 3 GM b.d. for a day, and Prednisolone 20 mg. t.d.s. for five days, the dose being tapered off. Penbritin 250 gm. every 6 hours was also given. Her temperature touched normal after three days and she made a slow recovery, regaining her speech. Amnesia for her recent illness was noted. She was discharged on 4.10.71.

Case 2.: A 39-year-old Chinese male (C.C.W.) was re-vaccinated on 18.9.71. He complained of headache for a week after the vaccination and was admitted on 26.9.71 with inability to walk for two days, with difficulties in speech. He had a temp. of 102°F. He was aphasic and had marked spasticity of all limbs, with opisthotonus. Reflexes were brisk, with bilateral extensor plantar response. B.P. was 150/100.

Lumbar puncture showed C.S.F. under pressure, with 71 cells mostly polymorphs, with sugar 28 mg. %, chlorides 606 mg. %, protein 108 mg. %, and globulin. He was treated with Marboran, A.C.T.H., and antibiotics. His condition did not improve and he died on 1.10.71.

In this case, post-vaccinial encephalomyelitis is the most probable cause of the illness.

Case 3.: A 13-year-old Malay girl (R.b.O.) was vaccinated on 18.9.71. A week after the vaccination, she developed fever and an unsteady gait, and some eruptions on her trunk and lower extremities. On admission on 6.10.71, she was very ill and occasionally delirious. Temp. was 101°F. There was neck rigidity. She was anaemic and also dehydrated. She had lesions of erythema exudativum on her sacrum, and left knee. C.S.F. was turbid, with sugar 216 mg. %, chlorides 704 mg. %, protein 21 mg. %, globulin negative.

Table 2.
Neurological Complications of Vaccination

	Encephalomyelitis	Encephalopathy
1. Age group of victims	More than 2 yrs.	Infancy and childhood.
2. Incubation period	8-15 days	20 to 18 days.
3. Clinical features	Fever, vomiting, headache, drowsiness, coma, convulsions, mutism, paralyses	Abrupt fever Convulsions Hemiplegia Aphasia
4. C.S.F.	Protein raised Cells raised	Protein may be raised or normal Cells normal
5. E.E.G.	High voltage slow waves	Slow asymmetrical focal activity
6. Pathology	Peri-venous microglial proliferation	Cerebral edema and vascular lesions
7. Involvement of spinal cord	Present	Absent
8. Recovery	Complete Amnesia common	CNS signs may persist No amnesia

In spite of treatment with parenteral fluids, Penbritin and Prednisolone, her temperature did not touch normal except for a day. She developed jaundice and died of septicaemia on 11.10.71.

The clinical picture and the close relationship in time of the illness in the above two cases, to recent vaccination, strongly suggested that these two patients were suffering from post-vaccinial encephalomyelitis.

(b) Encephalopathy: Here, after an incubation period of 2-18 days, usually 8 days, abrupt onset of high fever is followed by convulsions, aphasia and hemiplegia. The spinal cord is not involved. C.S.F. is normal, with some increase in protein in some cases. E.E.G. shows asymmetrical, slow focal activity. Amnesia is uncommon. In some, residual C.N.S. signs may persist. Encephalopathy usually affects children below 2 years.

Table 2 summarises the clinical features of encephalomyelitis and encephalopathy after vaccination.

Meningism, polyneuritis and facial palsy have been reported after vaccination but are rare.

Wynne Griffith has reviewed the neurological complications of vaccination in the United Kingdom since 1896. He found the incidence of encephalitis highest in the first year of life, 15.8 per million (mortality 8.7 per million). It was lowest in those between 1-4 years, 2.1 per million with no deaths. After the age of 15 years, the incidence was 28.7 per million with 2.9 deaths per million.

III. Miscellaneous Complications: Thrombocytopenic purpura (8 cases in literature), osteomyelitis, hyperostosis of bones and cardiac complications, such as angina with E.C.G. changes, pericarditis, arrhythmias and acute focal myocarditis have been reported as complications of vaccination.

Present role of Vaccination:

The present study has focussed attention on the complications of vaccination. There is no doubt the 40 cases seen were a small proportion of the actual number affected, as many patients are unwilling to go to hospital unless the complications are very severe. There is a large amount of morbidity following vaccination, causing a lot of personal inconvenience and suffering, with consequent absence from work. It may be relevant therefore in this context to review the current thinking on the value and place of vaccination.

Dixon has pointed out the limitations of vaccination. According to him, universal infant vaccination will produce immune infants, partially immune older children and generally susceptible adults. Prof. Dick has emphasised that mass vaccination in response to public demand has little effect in controlling the spread of infection. Recent studies by the W.H.O. in African countries has shown that smallpox is not a disease that can spread like wildfire, and contrary to lay opinion, its transmission is slow and limited to the immediate environment of the patient.

Epidemiological control of outbreaks is done on the "ring vaccination" plan (Dixon). The basis of such control is to isolate the case, seek out and vaccinate every contact and keep them under effective surveillance. Thus, vaccination is done "only to protect the right people at the right place at the right time" (Dick). That mass vaccination has seldom any value in the control of a smallpox outbreak has been amply borne out in the outbreak in England and Wales between December 1961 and April 1962. The report by the Ministry of Health

pointed out that indiscriminate mass vaccination did nothing to control the outbreak. Only when the well-tried epidemiological procedures of case-finding, contact tracing and control appear to be failing should vaccination of the whole community be considered, and at first it should be limited to the area where the outbreak exists. (Leader, B.M.J., (1964), II, 1148). "Mass vaccination during a smallpox outbreak is a panic measure and as such is of little preventive value and is to be condemned". (B.M.J. 1964, II, 1348).

Between 1951 and 1970, there were 100 deaths due to vaccination in England and Wales, half of them due to neurological complications. During the same period, 13 imported cases of smallpox gave rise to 103 cases with 37 deaths. (George Dick, 1971) In Canada in the last 20 years, only one fatal case of smallpox occurred compared to 21 deaths due to vaccination. No wonder that countries like the U.S.A. and Great Britain no longer insist, from 1971, on travellers to these countries having valid smallpox vaccination certificates, unless they come from an area where there is a recent outbreak of the disease.

Of course, in many of the African and some of the Asian and South American countries, where smallpox is still prevalent every year, control measures will be based on an effective programme of infant vaccination and selective re-vaccination of contacts to control outbreaks as and when they occur. The World Health Organisation is carrying out very effective smallpox eradication campaigns in all these countries and the day is not far off when the disease will be eradicated on a global level.

Summary

Forty cases of complications following a mass vaccination campaign to prevent an outbreak of smallpox in Klang are presented. There were two deaths due to encephalomyelitis. Common compications of smallpox vaccination are reviewed. The limited place of vaccination in the effective control of smallpox outbreaks is emphasised. Mass vaccination is rarely indicated.

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The epidemiological approach to atherosclerosis

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Summary

ATHEROSCLEROSIS HAS NOT as yet been fully understood through particulate and highly specialised types of investigation. Epidemiology offers means of exploring heart disease and other afflictions on the organismic level, and provides the basis of relating ecological, geographical, social, ethnic and many other factors to the incidence of man's diseases.

Epidemiology seeks to demonstrate relationships and associations of factors rather than expecting to achieve cause-and-effect results on initial investigation, a logical failing of many scientific endeavors.

Correlational statistical analysis provides a useful way of studying relationships among diseases and other variables on the populational sub-level. A matrix of correlation coefficients demonstrated statistically significant relationships between arteriosclerosis and socio-economic variables such as number of telephones. Senility correlated negatively and significantly with arteriosclerosis. A significant negative association between suicide and natality indicates that population density rather than increase in natality per se may be an implicated stress in suicide rates.

A crucial need of epidemiology is definition of uncomplicated yet reliable traits or factors that can be linked with disease incidence. The number of telephones and the amount of deep facial wrinkling may seem an odd couple to form a troika with coronary heart disease but the study of arteriosclerosis and other human afflictions probably has even greater surprises in store for us.

Introduction

"Act I, Scene II

Celia: Peradventure this is not fortune's work neither, but nature's, who perceiveth our natural wits too dull to reason of such goddesses, and hath sent this natural for our whetstone: for always the dullness of the fool is the whetstone of the wits. — How now, wit? wither wander you?

Act V, Scene IV

Jaques: Is not this a rare fellow, my lord? he's as good as anything, and yet a fool.

Duke S.: He uses his folly like a stalking-horse, and under the presentation of that he shoots his wit.

As You Like It

In this classical excerpt from Shakespeare, we see two levels of awareness — the one by the play's characters who described their companion as a whetstone and the other directly by the author who named him Touchstone[1]. Clearly the Bard intended the audience to consider his "Clown" simultaneously from both perspectives.

It is interesting to note that a common property of both the touchstone and the whetstone is to remain relatively unchanged after evoking the reaction in other substances and in this sense the function of Shakespeare's Touchstone is similar to that of a catalyst in chemistry.

The early history of medical science is interwoven with the genesis of modern chemistry in the practice of the Medieval alchemists who attempted to turn "baser" metals into gold, prolong life, and perfect a *panacea* or cure-all for the diseases of man, in their search for the philosopher's stone (Reichen 1963). At the same time, the common man sought the key to the mysteries of life by indulging his impatience among the paraphernalia of the clairvoyant including the fortune-telling Tarot, T. S. Eliot's "wicked pack of cards" which has, as was pointed out in *"The Waste Land"* (1932), persisted to this day.

This Faustian urge for either a natural or mystical embodiment of the *elixir vitae* is based on the assumption, as stated in Celia's dialogue, that there is a purpose and not randomness in certain natural associations.

The association of sickle cell anaemia with malaria, of blood groups, dermatoglyphics, voice prints, PTC tasting, color blindness and anthropometric formulae with various abnormal conditions, of such objects as fava beans with favism and G6PD deficiency (Stern 1960, McKusick 1969), and of dietary changes with Familial Mediterranean Fever (FMF) (McKusick and Elliot, in preparation) are all examples of the use of apparently simple, naturally observable things to indicate the presence, experimentally increase the penetrance (as in the glucose tolerance test) and therapeutically affect the prognosis of certain medical afflictions.

Genetic linkage has proved a useful tool of not only the hospital-bound specialist but also of the epidemiologist. Epidemiology has been variously defined but can be briefly considered "——— as the study of health and disease of populations and of groups in relation to their environment and ways of living" (Morris 1957, p.16).

It is too expensive and often impossible in epidemiological application to carry methods of detailed clinical investigation into field situations and in terms of global comparisons, there would never be enough time to complete such investigations. Therefore in atherosclerosis research such variables as serum lipids (especially cholesterol), subcutaneous fat deposits (Damon, Bleibtreu, Elliot and Giles 1962, Keys et al. 1966), deep facial wrinkling (Elliot, in preparation), number of telephones in the population (Jolliffe and Archer 1959), and other apparently simplistic, basic, and in some cases supposedly farfetched topics, form the paraphernalia of the epidemiologist who seldom anticipates cause and effect results but looks for associations, whether they make logical sense or not, between serious medical conditions, such as atherosclerosis, and easily measured traits of supposedly reproducible nature.

Epidemiologists hope that consistent associations that are statistically significant may act as keys to our understanding of basic underlying disease processes that until now are hidden from our view.

The employment of large-scale survey methods of social and other local environmental factors is particularly pertinent to investigation of ischemic heart disease which is apparently subject to alteration by many environmental stresses.

Causal relationships are therefore out and associative relationships are in, as far as the epidemiologist is concerned. Multifactoral approaches combining constitutional, cultural and geographical studies will, predictably, provide us with not just one but several touchstones on which to test the statistical purity of the approaches used in the diagnosis and prognosis of coronary heart disease (CHD).

In the following discussion, it should be remembered that many of the factors concerned are guilty by association only in the investigation of CHD and that although they may be unwilling accomplices

1
According to Webster (1951, p.2677) Touchstone is 1) a mineral "used to test the purity of gold and silver by the streak left on the stone when rubbed by the metal" and 2) "—— any test or criterion by which to try a thing's qualities." 'Whetstone is defined (Webster 1951, p.2911) as: "A stone, natural or artificial, for whetting edge tools." and, 2) "To make sharp, keen or eager, excite, stimulate, as to whet the appetite" (Webster 1960, p.974).

we may, by persistent cross-examination, force them to reveal evidence that will help clinicians to track down the real offenders in the complex case of coronary illness.

Study at the Organismic Level

The epidemiological approach concerns itself with matters arising beyond genetics, such as environment, habitat, ecological niche and social groups. Large functional units are now as eagerly investigated as are molecular matters. Geneticists are as aware of this as anyone else, for, according to Dobzhansky (1963):

> "——— biology, must, however, deal not with one but with several levels of biological integration. Living matter is integrated on the molecular, chromosomal, cellular, individual, populational and biotic-community levels. It is convenient to divide these levels into two classes — the molecular and the organismic.
>
> The reductionistic faith, that if we knew a lot about the lower-most level than all the phenomena of the highest integration levels would somehow explain themselves, is still the religion of some scientists, but it is really contrary to the aim and method of science. The organismic phenomena have to be studied as such, not deduced from the molecular phenomena. Man is an organism, not a molecule, although some diseases which afflict his flesh are molecular diseases."

Populational Sublevel

Populations may be taken as units and valuable information can be gathered from averages derived from such data. Population may be defined as a group of interacting organisms or individuals of the same species in a common spatial arrangement and is unique in that it has important group characteristics shared neither by individuals in the population nor by the biome or community, the community being all the animal and plant populations in a given area (Hanson 1962)[2].

Epidemiology gives the appearance of covering limitless fields of inquiry and of being all things to all people. The basic purpose, however, of epidemiological investigation is to define and describe populations or social, ethnic and geographical groups that show a high incidence of certain diseases and to isolate the variables that effectively separate these disease-prone groups from other groups which are apparently free from the afflictions under study. Multivariate analysis using electronic computers has been particularly useful in such endeavours (Gertler et al. 1959, Damon et al. 1962).

According to Dawber and Kannel (1958):

> "The major endeavor of an epidemiological study is the identification and measurement of the various factors which are acting on the subject and which may be playing a role in the development of disease. For the successful outcome of such a study, it is necessary that there be sufficient variability in the factors studied and that the variability be measurable."

Alternate approaches to measurement of this variability include study of cardiovascular disease according to the dimension of time, as witnessed by the Framingham longitudinal heart study (ibid), or, conversely, to do cross-sectional clinical and vital statistical comparisons from country to country and among sub-regions of these countries.

International comparisons, based mainly on clinical diagnosis and vital statistics, have not only singled out atherosclerosis as first among causes of death in Europe and America but also as having a much lower incidence in some other regions of the world. Several environmental factors, such as diet, drinking water, stress, life style, climate and trace elements, differ geographically and have been shown to have statistically significant correlations with the incidence of heart disease (Yudkin 1957, Masironi 1969).

Caloric intake has been frequently related to cardiovascular complaints (Yudkin, op. cit.), one of the most dramatic relationships cited being the very significant positive correlation of saturated fats as contrasted to the negative correlation of unsaturated fats with the death rate due to arteriosclerotic and degenerative heart disease (Jolliffe and Archer 1959).

A wide variety of variables have been employed. Yudkin (op. cit.), for example, found high correlations between trends in coronary mortality and income, occupation and the number of radio and television licences as well as the abundance of registered motor vehicles. Jolliffe and Archer (op. cit.), in "illustrating the intercorrelations of the supposedly independent variables and their conco-

[2] Some investigators are satisfied with the explanation that the population represents "—— the individuals of a given species which exists in a given area at any one time" (Benton and Werner 1966) although other scientists prefer Boulding's (as quoted in Bates 1960, p.106) characterisation of population as: "—— an aggregation of similar items enclosed by a picket fence of definition, with an entrance by way of birth and an exit by way of death."

Table I

Arteriosclerotic Heart Disease and Other Vital Statistics — International Comparisons

Country		Variables (a) 1	2	3	4	5	6	7	8	9	10	11	12
United States	A	704.7	319.7	35.8	21.6	9.6	25.2	18.2	1.2	23.1	30.3	11.0	4.9
Finland	B	621.7	255.6	11.3	18.1	9.2	18.2	13.7	1.2	20.5	36.3	19.2	2.4
Canada	C	588.3	241.5	27.6	24.6	7.8	26.3	18.1	0.8	23.6	30.7	7.6	1.3
Australia	D	577.4	273.0	18.5	21.6	8.7	19.5	14.3	0.7	24.5	24.6	15.7	1.5
New Zealand	E	525.7	255.8	25.6	25.4	8.8	19.6	12.8	0.5	16.5	28.1	9.6	0.6
United Kingdom (b)	F	427.5	333.7	14.0	18.5	12.2	21.7	14.6	1.1	13.5	26.7	11.7	0.7
German Federation	G	313.7	210.5	8.3	18.3	11.7	27.0	19.9	5.9	24.8	33.2	19.3	1.2
Denmark	H	294.8	263.2	20.5	17.6	9.8	19.1	14.8	1.3	17.9	31.1	19.1	0.8
Sweden	I	294.6	298.0	31.5	14.8	10.1	15.4	12.3	1.2	16.7	27.2	18.5	0.8
Austria	J	293.9	230.5	7.7	18.8	12.8	31.3	21.5	4.0	24.4	42.0	21.7	0.9
Switzerland	K	273.0	246.8	25.5	19.1	9.9	20.5	15.6	1.6	22.7	41.7	17.1	0.7
Chile	L	267.3	56.2	2.2	33.7	12.0	—	—	7.5	12.3	63.9	6.9	6.0
Belgium	M	250.1	133.5	10.6	17.1	12.6	27.2	17.6	7.3	18.5	36.1	14.0	0.7
Norway	N	248.8	263.5	17.8	17.3	10.1	16.9	11.9	6.3	11.0	40.0	8.0	0.7
Italy	O	226.8	205.4	5.4	19.0	10.2	40.1	23.3	4.3	22.2	27.3	5.3	1.1
Japan	P	122.5	51.6	3.8	17.3	7.0	23.2	13.8	9.2	15.7	25.5	16.1	1.6
France	Q	109.9	84.7	7.6	18.2	11.7	25.4	16.7	14.2	20.8	46.3	15.5	0.8
Portugal	R	107.7	116.0	3.2	23.4	10.8	73.1	26.4	14.5	11.4	29.5	9.5	1.0
Ceylon (c)	S	103.4	23.1	0.3	—	—	—	—	24.4	2.8	27.1	11.6	3.2
Yugoslavia	T	68.2	116.3	1.0	21.4	8.9	—	—	24.7	—	53.9	—	—
Mean		321.0	198.9	13.9	20.3	10.2	26.5	16.8	6.6	18.0	35.1	13.3	1.6
S. E. Mn. (d)		±54.7	±20.8	±2.4	±0.9	±0.4	±3.2	±1.0	±1.6	±1.3	±2.3	±1.2	±0.3
N		20	20	20	19	19	17	17	20	19	20	19	19

(a) Variables 2,4-12 are based on 1963 data from WHO Reports (1966).

(b) This represents the mean average for the United Kingdom as a whole since WHO made separate listings for England and Wales; Northern Ireland; and Scotland. In this case averages are derived after the separate figures have been adjusted for population size based on the World Almanac (Long 1968).

(c) 1962 only.

(d) S.E. Mn. = Standard Error of the Mean.

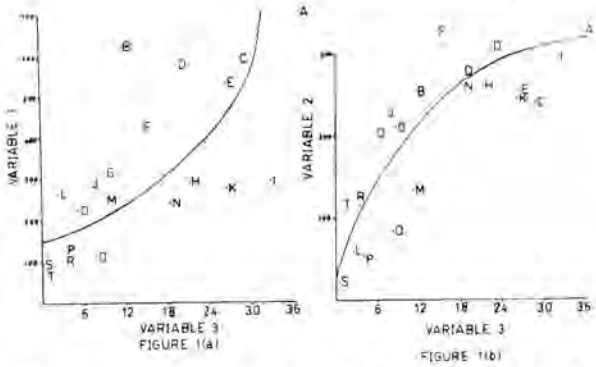

FIGURE 1(a) FIGURE 1(b)

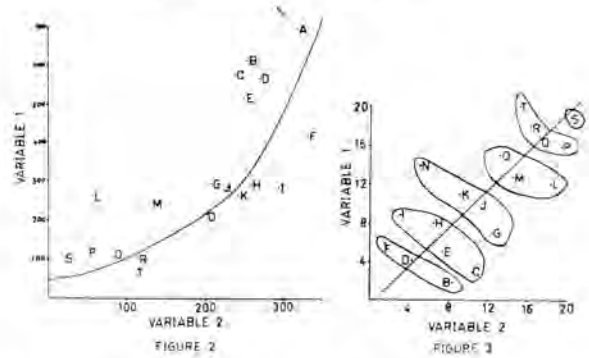

FIGURE 2 FIGURE 3

mitant indirect actions," cite the dramatic parallelisms between the number of telephones per 100 population and the cardiac death rate. We are reminded of an earlier occasion when polling of telephone owners before an American presidential election incorrectly predicted the outcome because of failure to sample voters who could not afford telephones. In the same way that we find more frequent diagnosis of coronary disease in cities with large medical centers and among the wealthier and better educated, it is also possible that this association between telephones and cardiac death is explained on the basis of medical accessibility. Other factors are undoubtedly involved and may illustrate more basic ethnic and geographical determinants of cardiac disease incidence.

It is doubtless true that we can prove nearly anything we wish to through the use of statistics. Vital statistics of death rates and other populational phenomena among countries have nevertheless provided useful clues to many disease problems and indicate that if we keep our minds open, we can only gain from the process.

Epidemiological reports from the World Health Organisation (1966) provide information on death rates and other vital statistics on a country-to-country basis and these may be compared to the cardiac death rate in the same way as Yudkin (1957) and Jolliffe and Archer (1959) studied dietary factors.

Variables

1. Arteriosclerotic and degenerative heart disease death rate per 100,000 for men aged 55 to 59 years. From Jolliffe and Archer (1959).
2. Arteriosclerotic and degenerative heart disease death rate (total population) per 100,000 (ISC category B-26).
3. Telephones per 100 population. From Jolliffe and Archer (*op. cit.*).
4. Natality per 1,000 population.
5. General mortality per 1,000 population.
6. Infant mortality per 1,000 live born.
7. Neonatal mortality per 1,000 live born.

Death Rates per 100,000 Population

8. Senility without mention of psychosis, ill-defined and unknown causes (ISC category B-45).
9. Motor vehicle accidents (ISC category BE-47).
10. All other accidents (ISC category BE-48).
11. Suicide and self-inflicted injury (ISC category BE-49).
12. Homicide and operations of war (ISC category BE-50).

Table 1 lists international figures for natality, general mortality and death rates due to atherosclerosis and various other causes along with two variables from Jolliffe and Archer's study. These figures are, of course, not completely comparable since they represent nations of differing size, sex and age composition and great variability in gene mixture. Some countries are relatively consistent as to ethnic groups. Others are political unions of very diverse genetic groups.

Scatter diagrams of the various relationships among the variables yielded non-linear regression lines in many instances as shown by Figure 1. In comparing the atherosclerosis death rates for men aged 55 to 59 years (Variable 1) to the general atherosclerosis death rates (Variable 2) a curvilinear relationship is likewise demonstrated (Figure 2). Various procedures may be employed to adjust such data to show more linear regression lines. Jolliffe and Archer (op. cit.) for example, used logarithmic transformations. In this instance, rank-order comparisons of the various countries have reduced the polynomial to greater rectilinearity and demonstrated some interesting clusters among nations on the atherosclerosis scale (Figure 3). Both atherosclerosis variables (1,2) varied likewise from linearity in their relationships with the other variables whose scatter plots are not shown here. Senility, for example, showed a J shaped curve of regression with the atherosclerosis variables (Figure 4). For these reasons, all the variables were transferred to rank orders and their relationships with the two athero-

Table II
Rank Order Intercorrelations of Vital Statistics Variables

1	2	3	4	5	6	7	8	9	10	11	12	Variables
——	.747	.779	.189	-.281	-.368	-.203	-.913	.532	-.194	.216	.123	1
		.839	-.081	-.146	-.529	-.461	-.814	.221	-.254	.149	-.293	2
			-.039	-.328	-.586	-.409	-.838	.372	-.134	.130	-.316	3
				-.177	.348	.409	-.203	.139	.090	-.501	.286	4
					.452	.426	.342	-.110	.377	.030	-.290	5
						.914	.444	.289	.115	-.235	.157	6
							.267	.456	.181	-.113	.292	7
								-.446	.354	-.093	.133	8
									.145	.404	.114	9
										.098	-.144	10
											-.032	11
												12

Levels of Statistical Significance of r_s

.01	.05
$r_{s1.2}$	$r_{s1.9}$
$r_{s1.3}$	$r_{s2.6}$
$r_{s1.8}$	$r_{s3.6}$
$r_{s2.3}$	$r_{s4.11}$
$r_{s2.8}$	
$r_{s3.8}$	
$r_{s6.7}$	

sclerosis variables were then demonstrated on scatter diagrams as in the examples presented in Figures 5-7.

Pearson — Product Moment Correlation Coefficients (Snedecor 1956) — calculated on the raw data yielded an r of .5944 (significant at $<$ .01 level) between the two atherosclerosis variable (1,2). Variable 1 showed an r of .5254 (significant at $<$ .05 level) with number of telephones (Variable 3) while the correlation of Variable 2 with telephones was .7637 (significant at $<$ .01 level). An increase in linearity led to more consistent covariation as shown in the calculation of rank order correlations for the semi matrix presented in Table 2, according to the procedure in Walker and Lev (1953).

Certain caveats are in order here in addition to questions regarding advisability of rank order correlations which do, however, have statistical justification (Walker and Lev, op. cit.). It is true that in one out of twenty times, we expect a significant r by chance alone. In addition, all countries were given equal weight in the calculations despite population differences in size and age composition.

It is well to keep these objections in mind while interpreting the figures in Table 2 while not overlooking the clues they may give us for plotting further research projects. One of the most interesting relationships was the negative one shown between the atherosclerosis variables and the number of telephones on the one hand and senility (Variable 8) on the other. Sociological influences, including varying techniques of health records, as well as ethnic factors, are probably indicated here and well worth further investigation.

The intercorrelations of Table 2 were examined further in a factor analysis carried out as described in Harman (1967). When the proper matrix calculations were completed, two factors were demonstrated (Table 3).

Factor I may be referred to as a "brevity of longevity" factor whereas Factor II is basically sociological which illustrates the point that many medical factors are basically social ones. General atherosclerosis (Variable 2) formed part of an additional factor, relatively minor for this analysis which, of course, depends on the number as well as type of variables plugged into the system. Another small factor singled out the country of Austria

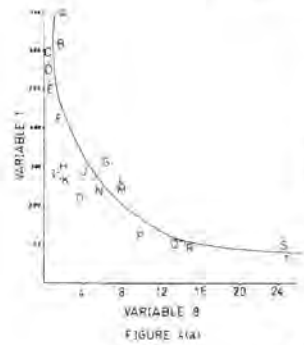

FIGURE 4(a)

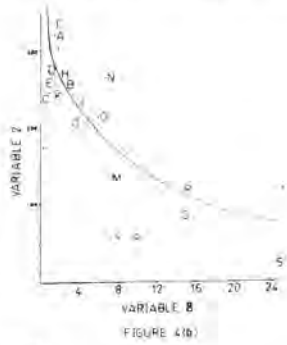

FIGURE 4(b)

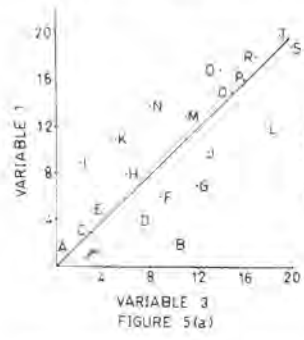

FIGURE 5(a)

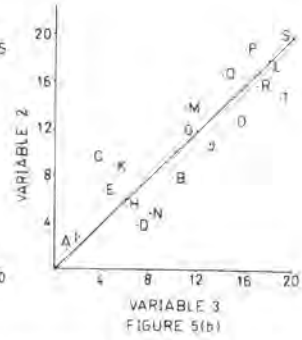

FIGURE 5(b)

Table III

Factor Loadings

(a) Factor I

Neonatal mortality	7	.775
Motor vehicle accidents	9	.768
Infant mortality	6	.555
Arteriosclerosis, men aged 55 to 59 years*	1	.447
All other accidents	10	.293
Natality	4	.279
General mortality	5	.217
Suicide	11	.161
Telephones*	3	.119
Homicide and war	12	.100
General arteriosclerosis	2	.064
Senility	8	-.248

(b) Factor II

Telephones*	3	.339
Motor vehicle accidents	9	.233
Neonatal mortality	7	.171
Infant mortality	6	.152
Other accidents	10	.107
Arteriosclerosis, men aged 55 to 59 years*	1	.105
General mortality	5	.083
Suicide	11	.069
Homicide and war	12	.067
General arteriosclerosis	2	.035
Natality	4	-.033
Senility	8	-.132

*From Jolliffe and Archer (1959). All other variable from WHO Reports (1966).

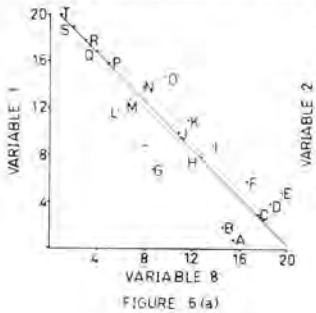

FIGURE 6(a)

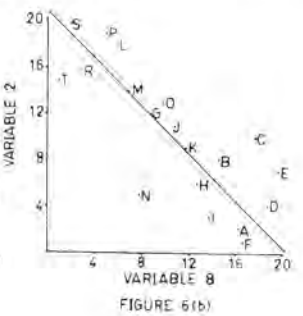

FIGURE 6(b)

and appeared to be best decribed as a stress factor which is fraught with possible interpretations as Austria was, interestingly enough, the home of Freud and psychoanalysis.

The two atherosclerosis variables are not, of course, perfectly correlated with each other and may therefore be entered into together in analysis of this type. This factor analysis is presented here mainly for illustrative purposes and the resulting factors should be regarded likewise. There are many effects that can alter the outcome of any type of analysis on data of vital statistics, epidemiological surveys and even clinical investigation. As stated by Ciocco (1957):

"——we have yet to develope analytical procedures for long-term studies that will allow us to make adjustments for possible interactions between the incidence of the disease on the one hand and refusals, migration and morbidity and mortality from other disease conditions on the other; and thus allow us to estimate the true incidence of a disease condition.

The development of such procedures is the task which the statistician faces — until this development is accomplished, comparison of incidence rates from place to place or interpretations of relationships between incidence rate and possible etiological factors will have to be accepted with several grains of salt."

Perhaps in the case of heart disease, we can

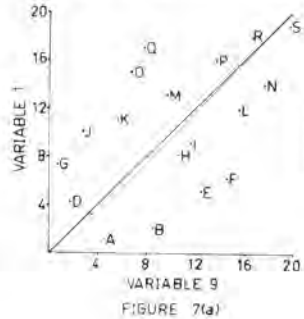

FIGURE 7(a)

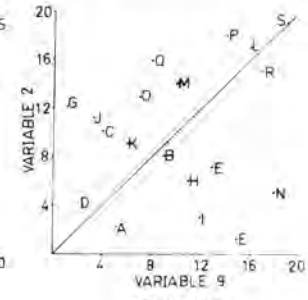

FIGURE 7(a)

literally very well do without the salt while digesting it figuratively. On the other hand, the various authors of epidemiological studies (Yudkin 1957, Jolliffe and Archer 1959, Groom 1961) have likewise noted these qualifications while pointing out the value of their comparisons as clues for further investigation rather than as end products in themselves.

Conclusion

The epidemiological approach to atherosclerosis research offers an excellent opportunity while at the same time presenting challenges in the way of statistical and logical nuances, some of which have been discussed above. Crossfertilisation between the organismic level and the particulate level may hopefully yield not only viable but fertile lines of investigation.

In this consideration of stones, several epidemiological avenues of study have been explored. Concretions come in many sizes and shapes and although analysis of atherosclerosis and certain calculi may invariably reveal cholesterol, another type of stone may serve as catalyst for our thoughts.

Rather than repeating in modern science the same lines of thinking of the alchemists and the readers of Tarot, we may resign ourselves to settling for touchstones and whetstones rather than the philosopher's stone. Our methods of analysis can be sharpened and refined by the whetstone of modern electronic computers whose output can encourage further efforts. This can enable adequate testing of concepts and techniques through use of the touchstone of multivariate statistical analyses of regression and genetic linkage.

The etiology of atherosclerosis and other afflictions indicates the final solution for a disease will rest on not one but several philosopher's stones derived from organismic as well as molecular strata.

Acknowledgement

I wish to thank Mr. Wong who drew the figures.

Final Note

"1941 The alchemists' dream is realised with the artificial production of gold from mercury by Sherr, Bainbridge and Anderson."

(Reichen 1963, p.110)

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The problem of cervical incompetence in Malaysian women

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Introduction

THERE IS NOW general acceptance that cervical incompetence associated with recurrent mid-trimester abortions is a distinct, but uncommon, clinical entity. Even so, there is no lack of controversy about its precise aetiology. The diagnosis, too, is difficult to verify, depending, as it does, more on the clinical history than on any scientific determination of the competency of the cervix. In the circumstance, it is not surprising that its incidence, and the results of treatment, seem so variable.

We believe that a reappraisal of the problem of cervical incompetence is best served by analysing our own clinical experience with the condition.

Incidence

In the period, April 1968 to April 1972, a total of 20 cerclage operations was performed on 16 patients during pregnancy, at the University Hospital, Kuala Lumpur. Four had the procedure done twice; in two of these, the first operation failed. The group consisted of 9 Chinese, 5 Indians and 2 Malays. Their ages ranged from 18 to 38 years. During the same period, there were 9,033 deliveries, giving a ratio of 1 cerclage procedure for every 451 deliveries. When compared with other series (Weingold[10] 1 in 933; Barter[2] 1 in 1842; Nishijima[9] 1 in 953), this figure appears rather high, but can be explained by the fact that 7 of

the 16 patients were referred from other parts of the country.

Previous Abortions

There were 40 previous abortions amongst the 16 patients. Except for 1 patient, all had 2 or more abortions each. The one exception concerned a patient in her first pregnancy with a cervix dilated to 3 cm. at 22 weeks' gestation. She aborted before a cervical ligature could be inserted. Of the 40 abortions, only 2 occured before the 12th week of gestation; 18 occured between the 13th. and 15th. week of gestation, and the remaining 20 abortions took place between the 16th. and 28th. week of gestation. Table 1 shows the number of abortions per patient before treatment.

Table 1
Number of Abortions Per Patient Before Treatment

No. of Patients	No. of Previous Abortions	Total
1	1	1
5	2	10
7	3	21
2	4	8
		40

Previous Livebirths and Premature Births

There were 9 previous livebirths with gestation of 36 weeks or more amongst the 16 patients. These were infants born to mothers in their first pregnancies. In addition, 5 premature infants were born between the 29th. and 33rd. week of gestation; but all died in the neonatal period.

Of a total of 54 previous pregnancies, only 9 infants survived. This gives an infant-salvage rate of 16.6 per cent. Table 2 shows the outcome of previous pregnancies in the 16 patients before their first cervical ligature.

Previous Trauma to the Cervix

When we looked into the question of mechanical injury to the cervix, we were surprised that not one case had a past history of cervical amputation, conisation, Manchester repair or traumatic delivery. The most notable findings were:

a) a history of normal vaginal delivery on 9 occasions and premature delivery on 5 other occasions.

b) A history of 21 curettages in 40 previous abortions.

Table 2
Outcome of Pregnancies in 16 Patients before the First Cervical Ligature

Abortions	40
Premature births (between 29th. and 33rd. weeks) with death of the babies	5
Livebirths (after the 36th. week)	9
	54

Diagnosis

The diagnosis of cervical incompetence was made from a clinical history of recurrent mid-trimester abortions. In 4 cases, the diagnosis was confirmed by the finding of a cervix dilated to 3 cm. or more. Since all patients were seen during pregnancy, no hysterosalpingograms could be done. Care was taken to exclude other causes of habitual abortion. A sub-septate uterus, for instance, might give a clinical picture very similar to that of cervical incompetence.

Methods

Of a total of 20 cerclage operations carried out during pregnancy, 16 were by the method of Shirodkar and 4 by the method of McDonald[7]. In each of the 4 occasions when the cervix was dilated to 3 to 5 cm. with bulging membranes, the McDonald purse-string suture was used, mainly because it was easier to apply. The suture material employed was limited to either the Ethicon tape or braided nylon, depending on the surgeon's preference. Table 3 shows the period of gestation when cerclage was done.

Table 3
Time of Insertion of Cervical Ligature

Gestation in Weeks	No. of Cerclage done
Before 12 weeks	3
13 to 16 weeks	9
After 16 weeks	8
Total	20

Results

Of the 20 pregnancies which had cerclage

operations, 11 resulted in 12 liveborn infants (a set of twins included), 6 aborted, 1 delivered a premature infant which died soon after birth, 1 was lost at follow-up and 1 was undelivered. Table 4 shows the overall results of the 20 cervical ligature operations.

Table 4
Outcome of the 20 Cervical Ligature Operations

Abortions	6
Premature Delivery	
Alive	4
Dead	1
Livebirths after 36 weeks	8
Lost to Follow-up	1
Un-Delivered	1
Total Live Infants	12

Among the 16 Shirodkar sutures applied as a prophylactic measure before there was any cervical dilatation, the success rate was 56.2 per cent. In the 4 McDonald sutures applied as an emergency procedure with the cervix dilated to 3 cm. or more, the success rate was 50 per cent. The results show that this procedure is worth attempting even though the cervix is dilated and the membranes are bulging. Table 5 shows the outcome of the pregnancies after the insertion of the McDonald suture.

Table 5
Outcome of Pregnancies after McDonald Suture

Gestation in Weeks at Time of McDonald Stitch	*Cervical Dilatation (in cm.)*	*Outcome*
19	3	Aborted at 20 weeks
23	3	Livebirth at 37 weeks
26	5	Livebirth Twins at 35 wks
21	3	Aborted at 22 weeks

Method of Delivery

Of the 12 liveborn infants, 10 were delivered by the vaginal route following removal of the stitches; the remaining two had Caesarean section. The indication for operative delivery was diabetes mellitus in one patient and prolapse of the cord in the other. Most authorities agree that for patients with cervical incompetence treated by cerclage, the vaginal route of delivery is suitable and safe[2,4]. Caesarean section should be reserved for those with some obstetrical indication, or in the event when the suture cannot be removed.

Discussion

The aetiology of cervical incompetence remains obscure. Although traumatic delivery is generally held to be an important factor, in practice, few cases have been shown to have had any operative procedure like forceps, version, or extraction[1]. In the present study, for instance, 9 of the 16 patients developed recurrent mid-trimester abortions following the spontaneous vaginal delivery of their first pregnancies. In this circumstance, the possibility of normal vaginal delivery playing a role in the pathogenesis of cervical incompetence cannot be dismissed. Likewise, the significance of curettage in abortion must be considered. According to Jeffcoate[5], a woman may abort her first pregnancy for some chance reason. Dilatation and curettage then carried out to complete the process may leave the cervix permanently damaged. This view is supported by the findings of Forster[6]. He has shown that D & C for criminal abortions definitely carries a high risk of cervical incompetence in subsequent pregnancies. In the light of these observations, it would appear that the pregnancy cervix is vulnerable to mechanical damage and that this may be related to changes in the reticular fibres and collagen concentration in the cervix during pregnancy[3]. In contrast, the traditional view that operative procedures on the cervix in the non-pregnant state are important factors in the causation of cervical incompetence has probably been exaggerated. There were no patients in our series who had a history of cervical amputation, conisation, cautery, biopsy, repair or laceration. This is in agreement with the observations by Forster[6].

Our results suggest that cerclage is a very effective form of treatment for recurrent mid-trimester abortions due to cervical incompetence. In the present series, the infant salvage-rate without treatment was 16.6 per cent, whereas with treatment it was 55.0 per cent. Even better results, however, have been reported by Weingold (74.6 per cent)[10] and Barter (70 per cent)[2]. In cases with cervical dilatation of 3 to 4 cm., an attempt at cerclage is justified, provided the membranes are intact. In this situation, the McDonald suture is the method of choice. Like Naver[8], we have 50 per cent success with this technique. Forster[6], however, has reported 80 per cent success in 78 pregnancies with cervical dilatation of 2 to 5 cm.

Summary

A 4-year review of the incidence of cervical incompetence at the University Hospital, Kuala

Lumpur, between 1968 and 1972 is presented.

A clinical analysis of 16 patients who had undergone 20 cervical ligature operations is made. Of the 20 procedures, 11 resulted in 12 liveborn infants. The infant salvage rate before treatment was 16.6%, and following treatment, 55%.

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An outbreak of rabies in West Malaysia in 1970 with unusual laboratory observations

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Historical Review

ALTHOUGH RABIES has been known in Malaysia since 1884, it was only since 1924 that records of human cases have been kept. Most of the cases have consistently been in states bordering Thailand which is highly endemic for rabies; sporadic outbreaks in other states have usually been quickly suppressed.

One major interior outbreak occurred in Province Wellesley and Perak state in 1945. Epidemiological evidence indicated that Allied troops arriving from India and Burma introduced the disease into these areas through their dogs. Although only sporadic cases continued to be reported from Province Wellesley, rabies became highly endemic in Perak and was not brought under control until 1953. In 1952, an extension southward resulted in

Four laboratory methods were promptly employed at IMR in the diagnosis of rabies.

Mouse inoculation tests (World Health Organisation, 1966 b)

Samples of hippocampal gyrus, cerebrum and cerebellar cortex were weighed and ground in sterile mortars with pestles. Physiological saline with 10% inactivated filtered rabbit serum was slowly added to prepare 10% tissue emulsions. Following centrifugation at 1000 rpm for 5 minutes, 0.5 ml. of supernatant fluids were mixed with 0.5 ml. of antibiotic solution containing 100 units of penicillin and 4 mg. of streptomycin per ml. The mixtures were incubated at least 30 minutes at 4°C. Six mice (10-15 grams) were lightly ether anaesthetised and injected intracerebrally with 0.03 ml. each. Mice showing signs of rabies after 5 days were harvested in a moribund state or following death and the diagnoses confirmed by microscopic tests. Mice remaining normal for 30 days were usually discarded. In some cases, serial passages were made of brain tissues from mice dying or remaining normal.

Seller's stained smear examinations (World Health Organisation, 1966 b)

Rubbed smears of the inner surfaces of the hypocampal gyrus (relatively free of glycerol-saline) were immersed while still wet in Seller's stain for 1-5 seconds, rinsed in running water and air dried. Stained smears were examined microscopically for Negri bodies.

Histopathological examinations

Zenker-acetate fixed tissues were paraffin blocked, sectioned and stained by Fast Green-Acid Safranin stain (Smith, 1953) by the Pathology Division of the IMR. Microscopically, Negri bodies were stained intensely bluish green with symmetrically arranged innerkorperchen corpuscles and vacuoles. Erythrocytes stained uniformly green, microglial and nerve cell nuclei and nucleoli stained bright red, and cytoplasm and general background stained pale pink or grey.

Fluorescent antibody (FA) microscopic examinations

The Communicable Disease Center (CDC), Atlanta, Georgia, USA (Cherry, et al., 1960) technique was followed except that commercial antirabies conjugate was diluted 1:40 to reduce non-specific staining while retaining specific sensitivity as measured by the positive controls.

Laboratory findings

During 1970, 50 brain specimens received from all over Malaysia were examined by the 4 diagnostic techniques. In all of the 6 positive findings (Tables 1 and 2), the mouse inoculation test was the only initial procedure yielding evidence of infection. In all of these, the inoculated mice were confirmed as positive by each of the 3 microscopic tests. Reisolation attempts on the field specimens following storage in 50% glycerol saline at −20°C for 7-9 months were positive only on the cat brain tissue. The negative microscopic examinations-positive mouse inoculation tests encountered during the 1970 outbreak were unusual; this pattern had not been observed during the 1954 and 1963 outbreaks.

Discussion

The control of rabies in Malaysia is based on coordinated functions of dog vaccination and stray dog control by the veterinary services, of rabies diagnosis by the IMR, and of post-exposure prophylactic vaccination of exposed persons by the medical services. An immune belt, in which compulsory dog vaccination and stray control are continuously carried out, is maintained along the Malaysia-Thailand border and similar zones are instituted wherever outbreaks occur in the rest of Malaysia. Although this programme cannot be expected to achieve eradication of rabies from Malaysia, it has enabled the country to control the disease with an expenditure that is economically feasible. During the 1970 outbreak in Perlis and Kedah states, the vaccination of more than 3000 dogs and destruction of over 8,000 dogs and cats must be credited with limiting the principal part of the epidemic to 3 months. However, it must be stressed that rabies spread rapidly throughout Perlis and Kedah following its introduction, and that 5 persons died of the disease before it was again brought under control.

The fact that 3 of the dogs and the single cat which were laboratory confirmed as rabid were pets, and that only 1 of these had been vaccinated, indicated that dog vaccination campaigns should be intensified, if possible on a house-to-house basis, in the border areas. The one confirmed case of canine vaccination failure emphasised the need for proper handling and use of these vaccines and the importance of confinement and observation of all dogs, whether vaccinated or not, which have bitten persons. The fact that all 5 human deaths, 1 of which was laboratory-confirmed, followed bites by stray dogs emphasised the need for continuous thorough control of stray and unvaccinated dogs in the immune belt.

Although adequate facilities for prompt diagnosis of rabies are maintained at the IMR, their

usefulness is dependent upon the receipt of specimens from field cases. Of the 10 dogs and cats proven to be involved in this outbreak, diagnostic specimens of only 5 were received and of 5 human deaths, tissues collected at necropsy were submitted from only one.

The 5 human cases were all clinically characteristic of rabies, with incubation periods of 1-3 months, clinical syndromes with hydrophobia and encephalitis, and death ensuing within 1-5 days. It is pertinent that 4 of the patients reported pruritis at the site of exposure; in one patient an intense pruritis extended along the arm and shoulder to the spine. The lack of Negri bodies and FA detectable antigens in the brain of the one patient examined at necropsy after a clinical period of 4 days could not be explained; the mouse inoculation test was strongly positive.

The dogs and cat diagnosed as rabid in Perlis and Kedah states all exhibited clinical illnesses compatible with rabies. The 4 dogs were all killed promptly after biting human victims; all were negative for Negri bodies, which may be explicable on the basis of their destruction early in the clinical course of the disease. The FA test should still have been positive; it is possible, however, that the FA procedure used at the time was not sensitive enough to detect only limited amounts of rabies antigen which might have been present. The brain tissues of each of these dogs yielded rabies virus by mouse inoculation tests. The cat died in confinement on the first day of observation. Negri bodies or FA detectable antigens were not found, although rabies virus was demonstrated by mouse inoculation tests on 2 occasions, 6 months apart.

The dog from Kuala Lumpur posed unique clinical and diagnostic problems. The source of exposure could not be determined although an extensive investigation was conducted. The clinical illness in the dog was compatible with rabies in the initial acute phase but the disease progressed to a chronic phase with divergent complications and the animal was ultimately euthanised. Although rabies virus was recovered from the brain of the dog, it is evident that it was present in very limited quantity. The brain was negative for Negri bodies, as was found in the cases of rabies in Perlis and Kedah. Following inoculation of 6 mice, 1 died on each of days 8 and 16 and 1 was killed in a moribund state on day 13. The first mouse was not further studied, the last two were positive for both Negri bodies and fluorescing antigens. One of the 3 surviving mice was sacrificed on day 20 for blind passage but proved negative for virus; the other 2 survived to day 30 and were disposed of. One of us (GWD), sent to Malaysia as a WHO consultant at the request of the IMR, found the laboratory capability in rabies diagnosis at the IMR to be reliable. While certain procedural modifications were recommended to increase the sensitivity, especially of the fluorescent antibody test, the lack of Negri bodies in the human and animal brains submitted to the laboratory in this epidemic remains an unusual observation. The findings in this incident again emphasise the importance of combining mouse inoculation tests with direct tissue examinations in the laboratory diagnosis of rabies.

Another of us (DSKT) has suggested that the rabies virus strain involved in this epidemic may have possessed some atypical characteristics, possibly having emerged as a variant strain through the continual co-existence during the past 2 decades of 2 live rabies viruses, the Flury LEP strain on the Malaysian side of the border and street rabies virus on the Thai side. It must be recognised that the coexistence of these 2 types of rabies virus in dogs is a unique situation prevalent only along the Malaysia-Thailand border.

Summary

Rabies is a public health problem in Malaysia only along the Malaysia-Thailand border where the disease has been periodically introduced through dogs crossing over from Thailand. There is no evidence of maintaining reservoirs in the wildlife of Malaysia. Rabies control is based on regulation of importation of dogs from other countries and upon the maintenance of a canine rabies immune belt 30-50 miles in depth along the Thai border to prevent the extension of the disease from the north. Dog movement between the immune belt and the rest of Malaysia is strictly regulated. Continual surveillance is maintained throughout Malaysia and prompt measures are taken to suppress any outbreaks of rabies.

During the first half of 1970, a rabies outbreak occurred in Perlis and Kedah states along the Thai border, presumably due to relaxation of rabies control measures in the immune belt because of increased communist terrorist activities in the area. A single case of canine rabies was found in Selangor state during the same period. Among 11 persons exposed to rabies during the outbreak, 7 were given anti-rabies vaccine (prepared at IMR) before the appearance of any clinical manifestations of rabies. No post-vaccinal reactions were recorded, and only 1 of these patients subsequently developed

Table 1

DETAILS OF REPORTED HUMAN RABIES CASES, KEDAH AND PERLIS, 1970.

Name	State (locality)	Age (years)	Sex	Race	Site of Bite	Date of Bite	Treatment (Date started)	Particulars of Patient			Particulars of Biting Animal			
								Date hospitalized	Date of death	Lab. Confirmation	Species	Stray or pet	Outcome	Lab Diagnosis
Cheong Kee Song	Perlis (Bkt. Ketri)	9	M	Chinese	Right popliteal fossa	Jan., 1970	Nil	24.4.70	26.4.70	+	Dog	Stray	Escaped	N.D
Ku Ah bte Ku Ahmad	Kedah (Kodiang)	30	F	Malay	Right thigh and leg	22.2.70	2ml.x14 (23.2.70)	19.5.70	20.5.70	N.D	Dog	Stray	Killed	N.D
Ibrahim bin M. Hassan	Kedah (Kodiang)	61	M	Malay	Right foot	21.4.70	2ml.x 6 (21.5.70)	21.5.70	26.5.70	N.D	Dog	Stray	Killed	N.D
Elias bin Che Mohd.	Perlis (Bkt. Ketri)	10	M	Malay	Right popliteal fossa	Apr., 1970	Nil	16.6.70	18.6.70	N.D	Dog	Stray	Escaped	N.D
Ng Doi Kuan	Perlis (Kaki Bukit)	8	M	Chinese	Unknown	Unknown	Nil	11.10.70	11.10.70	N.D	Dog	Stray	Escaped	N.D

Note: N.D = Not Done; i.e. not submitted for laboratory study.

in June after 2 days hospitalisation in Kangar.

An 8-year-old Chinese boy from Bukit Tasoh Kaki, 2 miles from the Thailand border, died in the Kangar Hospital in October with clinical diagnosis of rabies. His parents confirmed that he had been bitten some time earlier by a stray dog but the time or site of exposure could not be ascertained and he had been given no ARV. In none of these 5 human rabies cases were the exposing dogs submitted for laboratory diagnosis and only the first patient was examined at necropsy. (See Table 1)

Animal rabies cases

Aside from the 5 stray dogs in which rabies was confirmed by resultant human cases, 4 of 7 animal brains submitted to IMR from Perlis and Kedah during the first half of 1970 were confirmed as rabid. All of the 4 positive animals were submitted during June and all were from Kedah. One of the positive dogs, a stray, entered a village in Kodiang at about 10 one evening and viciously bit 4 goats, 5 cattle, 2 geese and a 7-year-old Chinese girl before it was killed at about 7 the next morning. Two other positive dogs, one from Changloon and the other from Tunjang, 5 and 16 miles respectively from the Thailand border, were pets which were killed after biting their masters. One of these had been vaccinated with Flury LEP strain vaccine 16 months previously. Three other dog brains submitted were negative for rabies. One cat in Jitra, about 20 miles from the Thailand border, was placed under veterinary observation after biting its master; it died during the following night and was confirmed as rabid upon examination at IMR.

A single case of canine rabies with many unusual features was diagnosed in Kuala Lumpur, Selangor state in May. A 3-year-old male Shetland sheep dog, one of a pair from a dam originally imported from Australia to Kuantan in 1968, had been kept in Kuala Lumpur since September, 1969. The owner reported that the 2 siblings had been kept in his neighbourhood since their arrival and had only limited contact with other local dogs. No other pets were kept on his premises. From 14 April, the male dog suffered a protracted febrile illness with anorexia, champing of the jaws and profuse salivation. Following initial treatment by a private veterinarian, the dog was apparently improving by 17 April, but relapsed on 26 April. It developed a goose-stepping gait, apparent blindness in the right eye and circling to the left. Further therapy was non-productive and the dog was euthanised on 8 May. Laboratory studies confirmed the presence of rabies infection. The source of exposure of this dog to rabies could not be ascertained. (See Table 2)

Treatment of persons exposed to rabies

Evaluation of all animal bite victims and administration of ARV are performed only at government hospitals. District and state veterinary offices are charged with epidemiological investigations of biting animals, confinement of such animals for a 10-day observation period where possible, and shipment of brain specimens to IMR for analyses. Post-exposure immunisation is administered promptly, or deferred pending clinical and laboratory findings, in accordance with the recommendations of the W.H.O. Expert Committee on Rabies (1966a)

Table 2

DETAILS OF HUMAN EXPOSURES TO PROVEN RABID ANIMALS, 1970

Name	State (locality)	Age (years)	Sex	Race	Site of Bite	Date of Bite	Treatment (Date started)	Particulars of Biting Animals				Remarks
								Species	Stray or pet	Outcome	Lab Diagnosis	
Ng Hoo Lum	Kedah (Kodiang)	60	M	Chinese	Right foot	21.4.70	2ml.x15 (21.5.70)	Dog	Stray	Killed	N.D	Diagnosis in dog based on fatal case in Ibrahim bin M Hassan bitten on same day by same dog
Shanta Kumari	Selangor (Kuala Lumpur)	22	F	Indian	Scratch on finger	10.5.70	2ml.x15 (10.6.70)	Dog	Pet	Killed	+	
LEE LAY TIN	Kedah (Kodiang)	7	F	Chinese	Right ear	2.6.70	1ml.x14 (12.6.70)	Dog	Stray	Killed	+	
Lim Pook Nyan	Kedah (Changloon)	14	M	Chinese	Scratch on right palm	10.6.70	2ml.x15 (24.6.70)	Dog	Pet	Killed	+	
Tan Kim Koay	Kedah (Tunjang)	74	M	Chinese	Right thumb	22.6.70	2ml.x15 (8.7.70)	Dog	Pet (vaccinated)	Killed	+	
M. Radzi bin A.Rani	Kedah (Jitra)	2	M	Malay	Left leg	30.6.70	1ml.x15 (13.7.70)	Cat	Pet	Died	+	

Note: N.D = Not Done, i.e. not submitted for laboratory study

and the IMR Bulletin Number 8 which has been distributed to relevant authorities and clinicians.

Semple-type phenolised sheep brain tissue origin vaccine is prepared and distributed by the IMR to medical officers throughout Malaysia. This vaccine is given in 14 daily subcutaneous injections of 2 ml. each, to persons 14 years and older, usually in the anterior abdominal wall. The dosage is reduced in children under 1 year to 0.25 ml., 1-3 years to 0.5 ml., 4-6 years to 0.75 ml.; 7-9 years to 1.0 ml., and 10-13 years to 1.5 ml. per injection. The administration of anti-rabies hyperimmune serum is recommended in accord with W.H.O. recommendations, but is available only by importation.

Of the 11 persons bitten by animals which were promptly or subsequently (through human death following exposure) proven rabid, administration of AVR was begun the day following exposure in one, within 2 weeks in an additional 3, within 1 month in an additional 3, on the day of onset of clinical rabies in one, and not at all in 3 animal bite victims. The one person given ARV beginning the day after being bitten on the thigh and leg died of rabies after an incubation period of 3 months. The one rabies patient administered ARV during the clinical phase of the disease was not protected. This latter patient, and the other 3 who received no vaccine, all died of rabies. The 5 victims who were given ARV following laboratory confirmation of rabies in the exposing animals have remained normal 5-7 months since their exposures. No post-vaccinal reactions have occurred in the patients given ARV. (See Table 3.)

Table 3

The Outcome Of Animal Bite Victims Given Or Not Given Anti-Rabies Vaccine Following Bites By Confirmed Or Unconfirmed Rabid Animals.

Anti Rabies Vaccination	Patient Outcome	Rabies Confirmed	Rabies Not Confirmed	Total Patients
Given*	Died	0	1	1
	Survived	6**	0	6
Not Given	Died	0	4	4
	Survived	0	0	0
Totals	-	6	5	11

* Vaccine given prior to onset of clinical rabies.

** One canine case confirmed on basis of rabies death in another person bitten by the same dog.

Laboratory Diagnostic Procedures

Initial processing

Brains were removed from cadavers (dogs, 1 cat, 1 human patient) at respective veterinary centres or hospitals. Excised brains were cut in two halves, anterior-posteriorly. One-half was placed in 50% glycerol saline for impression smear and virus isolation studies. The other half was placed in Zenker-acetate fixative for histological studies. The specimens were sent by courier, railway or air express or other rapid means to IMR.

a major epidemic in Selangor state. The severity of this outbreak prompted a national programme of compulsory vaccination of all dogs in rabies-infected states and a rigorous programme of destruction of unowned and unvaccinated dogs. The success of the control programme was such that in April, 1954, Malaya (as the country was known before 1963) was declared rabies-free. An immune belt was established in the states bordering Thailand and, except for this area, free movement of dogs was permitted throughout Malaysia.

In August 1963, small outbreaks of rabies occurred in Perlis, the most north-west state, and subsequently in Selangor. Epidemiological investigations indicated that rabies entered Perlis through dogs from Thailand and was carried to Selangor by army dogs air-transported from Perlis. Rapid laboratory diagnosis prompted swift and effective control measures against canine rabies, and with mass dog vaccination and elimination of unvaccinated dogs, the outbreaks were quickly suppressed before they could spread beyond the two states.

In 1965, sporadic cases of canine rabies were diagnosed in Kelantan, another state which borders Thailand. Intensification of control efforts quickly halted the spread of the disease. In 1970, an outbreak involving both dogs and man occurred in the Kedah and Perlis states along the Thai border (Fig. 1) and a single canine rabies case was recorded in Selangor. This outbreak is described in detail in this communication.

The Control of Rabies in West Malaysia

Reservoirs of rabies

In all outbreaks, dogs have been the principal animals involved. Elimination of dogs as susceptible reservoirs has led to the disappearance of the disease. No wild animal reservoirs have been incriminated in any part of the country. A survey of 478 bats of 12 species live netted in 17 localities in West Malaysia yielded no evidence of rabies upon laboratory analyses (Tan et al, 1969).

The national rabies control programme of Malaysia is based on continuous compulsory vaccination of all dogs in an immune belt along the Thai border and in any rabies-infected areas, continuous destruction of unvaccinated and stray dogs in the immune belt and in any rabies-infected areas, legislative regulation of dog movement, dog registration and public education on rabies control.

Compulsory vaccination

Triennial vaccination with Flury LEP strain rabies vaccine and annual registration of all dogs 3 months of age and over are compulsory in the

immune belt. Mass vaccination and registration of dogs south of the immune belt are mandatory only during outbreaks of rabies. When the presence of rabies is confirmed in previously rabies-free areas, the areas, states or adjoining states, if outbreaks occur near contiguous borders, will be declared rabies-infected and vaccination of all dogs within the declared zones will be mandatory. Dogs in such zones must also be maintained confined within enclosed areas, tied securely, or led on strong chains, or leather or cord leashes as long as rabies remains present.

Prior to 1952, Semple type brain tissue vaccines were used for immunisation of dogs. During 1952-1953, field trials proved Flury LEP strain attenuated live virus vaccine more effective if properly handled. During this extensive outbreak, the vaccination of 80% of the dog population with Flury LEP strain vaccine successfully removed rabies from the campaign areas.

Destruction of unvaccinated and stray dogs

Destruction of all unvaccinated dogs within the immune belt and infected zones is compulsory. In uninfected areas, efforts are made to destroy stray or unowned dogs. Even a slight relaxation in stray control, especially along the Malaysia-Thailand border, can lead to rapid development of a potentially dangerous stray dog population.

Rabies control legislation

The Animal Ordinance, 1953, of the Federation of Malaya prescribes the declaration of rabies-infected areas, including an immune belt along the Malaysia-Thailand border, and the compulsory vaccination and licensing of dogs within infected areas to suppress the disease. The legislative acts are designed to prevent the entrance of rabies into Malaysia from other countries by land, sea or air routes; to remove the population of stray and unowned dogs; to build up the population of immune dogs above the level to prevent rabies transmission; and to limit spread of any focal outbreaks of the disease.

Public education on rabies control

Press releases, radio, television and rediffusion features and announcements, cinema slides, brochures for public distribution and posters are used to give advance publicity and provide public information on rabies control programmes. It is not difficult to stimulate public interest in rabies control measures during outbreaks but continual efforts are necessary to maintain a sustained public response.

The immune belt

The entire state of Perlis and the districts of Kedah, Perak and Kelantan states which border Thailand are maintained as a canine rabies immune belt 30-50 miles in depth. Continual compulsory vaccination and registration of dogs and destruction of stray and unlicensed dogs are maintained to prevent the spread of rabies introduced through dogs infiltrating from Thailand. Movement of dogs out of the immune belt into the rest of Malaysia requires certification of rabies vaccination performed at least 30 days but not over 3 years previously. Dogs may be brought into the immune belt only upon permission of the state veterinary officer of the state being entered; immediate vaccination upon arrival, if not performed earlier, is mandatory.

The effective maintenance of the immune belt is integral to rabies control in Malaysia. Although this effort has been historically successful, recent communist activities and the necessity for greater security in the border area have hampered the effective maintenance of stray dog control. Dog shooting has had to be curtailed, especially during the night, to avoid alarming the public which might confuse any shooting as terrorist activity.

The Rabies Outbreak of 1970

Epidemiology

Epidemiological investigations of rabies in people and dogs in northern West Malaysia during 1970 provided evidence that stray dogs entering from Thailand, but not destroyed after crossing the border, introduced rabies in several areas of the immune belt. Dog vaccination and destruction records from Perlis and Kedah showed a reduction in numbers of dogs vaccinated and killed from 1967 until the outbreak, explained by the absence of the disease and by heightened unrest in the border area. Unfortunately, no records were available to determine whether there was an increased incidence of rabies in southern Thailand at the time of, or preceding, the outbreak in northern West Malaysia. During the first half of 1970, rabies spread rapidly throughout Perlis and Kedah, and 5 persons, all of whom were bitten by stray dogs, died of the disease before it was again brought under control.

Human rabies cases

The first victim, a 9-year-old boy living in Bukit Ketri, Perlis, 5 miles from the Thailand border, was exposed during January but received post-exposure immunisation. He was admitted at the State Hospital in Kangar in April with fever, backache, restlessness and inability to swallow for 3 days. At admission his temperature was 100°F, he was markedly dehydrated, and experienced spasmodic throat contractions upon sight of water. Only by retracting his neck could he reduce the spasms of the muscles of deglutition enough to permit him to swallow. The patient died the same day. Necropsy was performed and the brain sent to the Institute for Medical Research (IMR) for analysis. It was eventually confirmed positive for rabies.

A 30-year-old Malay woman in Kodiang, 10 miles from the Thailand border, Kedah, was bitten by a stray dog during February. The dog was promptly killed and buried and the woman was given 14 doses of anti-rabies vaccine (ARV). Approximately 3 months after exposure, she was admitted at the Kangar Hospital with clinical diagnosis of rabies; she died 2 days later.

A 61-year-old Malay man and his 60-year-old Chinese friend were bitten in the same district during April by a stray dog which was also promptly kiled and buried. Neither received any prompt anti-rabies prophylactic vaccination. The Malay man was admitted at the Kangar Hospital one month later with clinical diagnosis of rabies. He was started on ARV at admission but expired 6 days later. His companion was started on ARV at that same time and received a full course of 14 daily injections plus 1 booster dose 30 days later; he is still normal at the time of this writing.

A 10-year-old Malay boy in Bukit Ketri, Perlis, was bitten during the same months by a stray dog which escaped. He was not given ARV and died

rabies. Among the 4 animal bite victims known to these authors and not given anti-rabies vaccine (1 was given vaccine only after symptoms of rabies were already manifest), all died of the disease.

A total of 4 dogs, 1 cat and 1 human brains was confirmed in the laboratory as rabies positive. All of these were negative for Negri bodies and fluorescing antigens but were unequivocally positive by mouse inoculation tests. These perplexing laboratory observations are discussed in this communication and have led to a suggestion by one of the authors (DSKT) that the rabies strain involved in this epidemic may have been a variant strain with low Negri body forming characteristics in the field cases.

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Addendum

In January 1972, a dog was reported to have bitten a person and a buffalo in Jitra, Kedah. The dog was beaten to death and the brain sent to the IMR Virus Research Laboratory for investigation.

The preliminary findings were similar to those reported in this paper. The original specimen again did not show any typical Negri bodies or antigen by the FA test but the mouse inoculation results were positive. The brains of the infected mice all showed clear-cut Negri bodies in the stained smears and in the histological sections and were markedly positive in the FA test.

Samples of the original brain were sent to GWB (one of us) for more detailed study. Work is still in progress.

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Pregnancy and malaria

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Introduction

MALARIA EXERTS a profound influence on pregnancy. Indirectly, it undermines the health of the mother and reduces her to a poor state to withstand the stresses and demands of pregnancy. Of more importance is the fact that by its ill-effects, malaria often actually causes an interruption of the pregnancy itself. In malarious areas, it becomes an important cause of foetal loss and sometimes of maternal deaths as well. The control of malaria will, therefore, result in a marked improvement in perinatal and infant mortality as well as benefitting the health of the expectant mother. In this paper, cases of malaria occuring during pregnancy are studied as a means of defining the precise effects of malaria on pregnancy.

Materials and Methods

The study was carried out among patients admitted to the maternity unit of the General Hospital, Kuala Trengganu, during the three years 1969 to 1971 the author was attached there. Only those cases in whom the malaria parasite was positively identified on blood film examination were included in the study. A total of 37 cases were obtained.

Results and Discussion

Table 1 shows the time of presentation of malaria in relation to the duration of pregnancy.

Table I

Duration	*Cases*
Early Pregnancy	5
Late Pregnancy	17
Puerpuerium	13
Newborn Infants	2
TOTAL	37

All the patients came from an endemic area and it is likely that they possessed varying degrees of immunity to malaria. Acquired immunity to malaria is always precariously established and often does breakdown under conditions of stress, especially the stress of pregnancy. Hence clinical manifestation of latent malaria occurs. Breakdown in immunity occurs more commonly as the pregnancy advances and the above figures bear this out. As can be seen, most of the cases presented either in late pregnancy or in the immediate puerpuerium. Five cases also occured in early pregnancy and there were two cases of congenital malaria.

Of these five cases, three aborted. In early pregnancy, malaria can cause abortion. It is likely that hyperpyrexia itself is the precipitating cause of the abortion. Hyperpyrexia acts either by activating the uterus and causing it to expel its contents or by causing the death of the foetus

Malaria in Early Pregnancy

Table 2 gives details of the 5 cases.

Table II

Case	Pregnancy	Type	Fever	Initial Presentation	Outcome
1	8 weeks	BT	3 days	Threatened Abortion	Aborted
2	20 weeks	ST	3 days	Threatened Abortion	Aborted
3	10 weeks	ST	5 days	Incomplete Abortion	Aborted
4	12 weeks	ST	1 day	Threatened Abortion	Pregnancy continued
5	14 weeks	ST	2 days	Threatened Abortion	Pregnancy continued

which is followed by abortion. In all the three cases which aborted, the fever had been present for more than 48 hours. Where hyperpyrexia is of short duration, i.e. less than 48 hours, and prompt treatment is instituted, the pregnancy may be saved. This is shown by the remaining two cases, where the fever was of short duration and with treatment the pregnancy continued uninterrupted. Early diagnosis and treatment of malaria is therefore of great importance if the pregnancy is to be saved.

Malaria and Late Pregnancy

Table 3 shows an analysis of the cases of malaria presenting during late pregnancy. Of the 17 cases, 3 were primigravids and the rest multigravids. Lawson (1967) stated that breakdown in malaria immunity is most likely to occur during the first pregnancy. However, the above figures do not bear this out as most of the cases occured in multigravid patients.

The complications caused by malaria on advanced pregnancy are discussed below.

Premature Labour

Three out of the seventeen cases went into premature labour as a result of the malaria. Of these, one infant born at 32 weeks died in the neonatal period. In five cases (Case numbers 3, 13, 14, 15 & 16) the pregnancy continued on to term following the treatment for malaria. Thus again the value of early diagnosis and treatment of malaria in safeguarding the pregnancy is seen.

Intrauterine Death

Five patients presented with intrauterine deaths. In all these cases, the fever had been present for more than 3 days. Hyperpyrexia itself is the most likely cause of the intrauterine deaths. If a patient in late pregnancy develops acute malaria and a delay in seeking treatment occurs, there appears to be an almost 30% chance of the foetus dying in utero.

Foetal Loss

In the series, 6 infants (35%) were lost — five due to intrauterine deaths and one neonatal death due to prematurity. Thus it is clear that malaria exerts a high toll in terms of foetal wastage.

A further point of interest is that the mean birth weights of infants born of malarious mothers is reduced compared to normal mothers (Lawson 1967). The reason for smaller infants is that placental parasitisation occurs in pregnant women and the cellular reaction caused in the placenta interferes with and impairs the growth of the foetus.

Cerebral Malaria

There were three cases of cerebral malaria (Case Nos. 7, 8, & 17). All of them presented late, the minimum being after three days. In two cases, the infant was already dead in utero and the third patient delivered a live infant.

All the three cases were in a poor state on admission — comatose, hyperpyrexic, severely anaemic, etc. — and in spite of vigorous therapy, all three died. Lawson was of the opinion that cerebral malaria is very uncommon in the immune pregnant woman, but I do not believe this to be so as these women who had cerebral malaria were all from an endemic area. With the stress of pregnancy and the lowering of immunity, cerebral

Table III

Case	Gravida	Hb	Type of Malaria	Fever	Pregnancy	Complication
1	4	51%	ST	2 days	32 weeks	Premature del. Neonatal death
2	3	67%	ST	5 days	Term	I.U.D. stillbirth
3	7	40%	ST	7 days	32 weeks	Pregnancy continued
4	3	54%	BT	3 days	30 weeks	I.U.D. stillbirth
5	2	52%	ST	1 day	Term	Normal delivery
6	1	59%	ST	3 days	Term	I.U.D. stillbirth
7	5	40%	Cerebral Malaria	5 days	Term	I.U.D. s/birth. *Maternal death*
8	4	31%	Cerebral Malaria	3 days	Term	I.U.D. s/birth. *Maternal death*
9	1	71%	ST	1 day	34 weeks	Premature del. Live infant.
10	4	60%	ST	2 days	35 weeks	Premature del. Live infant.
11	7	55%	ST	1 day	Term	Normal delivery
12	6	65%	BT	2 days	Term	Normal delivery
13	1	60%	ST	2 days	36 weeks	Pregnancy continued to term.
14	4	70%	ST	3 days	32 weeks	Pregnancy continued to term.
15	3	55%	ST	2 days	34 weeks	Pregnancy continued to term.
16	6	60%	BT	2 days	28 weeks	Pregnancy continued to term.
17	2	81%	Cerebral Malaria	3 days	Term	Normal delivery *Maternal death*

malaria would be commoner in the pregnant woman. There is also no doubt that cerebral malaria occuring in pregnancy has a high mortality indeed. This high mortality rate was also seen in Ceylon during the great epidemic 1934-1935, where the mortality in pregnancy was twice that of the non-pregnant women.

Although most textbooks make much about confusing cerebral malaria in pregnancy with eclampsia, in practice this is not so and diagnosis is often straightforward.

In the majority of these cases (10 out of 13), the fever manifested within 24 hours of the delivery. In the differential diagnosis, uterine, urinary, and breast infections have to be kept in mind, but malaria should be high on the list in endemic areas. In late pregnancy or in the immediate puerpuerium, latent malaria often unmasks itself and presents as clinical malaria. During the puerpuerium, no special complications are likely to occur as a result of the malaria and the treatment and response to drugs present no problems. Malaria is no contraindication to breastfeeding.

The above two cases were definitely congenital malaria as the malaria appeared soon after delivery. Both the mothers of the infants were symptomless but had enlarged spleens and were most likely latent cases of malaria. These two cases show that congenital malaria is not extremely rare as stated by Lawson (1967). As stated before, placental parasitisation commonly occurs during pregnancy, but the exact route by which the parasites cross the placenta into the infant is unknown. The infant normally gets passive immunity from the mother.

Malaria in the Puerpuerium

Table 4 shows the 13 cases which manifested malaria in the puerpuerium.

Table IV

Case	Gravida	Type of Malaria	Hb	Time of onset of fever
1	7	QT	37%	1 day after delivery
2	1	BT	60%	1 day after delivery
3	1	ST	78%	1 day after delivery
4	6	ST	50%	1 day after delivery
5	2	BT	60%	10 days after delivery
6	5	ST	37%	13 days after delivery
7	3	ST	49%	immediately after delivery
8	2	ST	65%	2 days after delivery
9	9	ST	60%	1 day after delivery
10	1	ST	55%	1 day after delivery
11	4	ST	42%	1 day after delivery
12	11	ST	40%	1 day after delivery
13	3	ST	70%	1 day after delivery

Congenital Malaria

Table 5 shows cases of malaria occuring in newborn infants.

Table V

Case	Mother's Particulars	Infant	Type of Malaria	Onset of Fever
1	Gravida 4. No symptoms Enlarged spleen Blood film negative	Term	BT	14 hours after delivery
2	Gravida 6. No symptoms Enlarged spleen Blood film negative	Premature	ST	20 hours after delivery

If this passive immunity is low, then congenital malaria occurs. In both the infants, the response to treatment was excellent.

General Effects of Malaria

The general debilitating effects of malaria — anaemia, chronic ill health, lassitude, etc., although not specifically referred to, underline all these patients. A glance at Tables 3 and 4 show that nearly all the patients were extremely anaemic, and many needed blood transfusion and nutritional buildup. These debilitating ill-effects of

chronic malaria have been well pointed out by Sandosham (1970).

Conclusion

The striking breakdown in malaria immunity as a result of a pregnancy and the unmasking of clinical malaria can be seen in this series. Bearing in mind the high toll exerted in terms of foetal loss and maternal illhealth, the question of prophylaxis comes in naturally. The control and eradication of malaria will markedly improve the health of the expectant mother and her unborn child. Prophylaxis, as an integral part of antenatal care, can markedly reduce the illeffects of malaria on pregnancy. In countries where this has been tried out, e.g. Nigeria (Lawson - 1967), beneficial effects have been noted. Therefore, in endemic areas there is a strong case for routine malaria prophylaxis as a part of antenatal care.

Summary

1. Malaria causes serious complications in pregnancy. In early pregnancy, it can cause abortion. Premature labour and intrauterine death of the foetus are the other complications which can occur later on in pregnancy.
2. Malaria may present as a puerperal pyrexia following delivery.
3. Celebral malaria occuring during pregnancy is associated with a high mortality.
4. The malaria parasite can cross the placental barrier and cause congenital malaria.
5. Routine malaria prophylaxia as a part of antenatal care is advocated, to eradicate the illeffects of malaria in endemic areas.

Acknowledgements

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Small haemoglobin components accompanying Hb Bart's in newborns

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NORMAL Hb A consists of 2 alpha chains and 2 beta chains (Hb alpha 2 beta 2), Hb F of 2 alpha chains and 2 gamma chains (Hb alpha 2 gamma 2) and Hb A2 of 2 alpha chains and 2 delta chains (Hb alpha2 delta2). Hb Bart's is made up solely of gamma chains and Hb H solely of beta chains. They are thought to result from the suppression of alpha chain production, leading to surplus of gamma chains or beta chains which form Hb Bart's (Hb gamma 4) or Hb H (Hb beta 4). The presence of Hb Bart's in the newborn period is therefore thought to represent alpha thalassaemia since under alpha thalassaemia is understood impaired production of alpha chains without the synthesis of abnormal haemoglobin chains.

An excessive amount of Hb Bart's in the newborn was found to be the cause of non-immune erythroblastosis foetalis leading to death (Lie-Injo and Jo, 1960; Lie-Injo, 1962; Lie-Injo et al., 1962). Lie-Injo and colleagues thought that these cases represent homozygous alpha thalassaemia. This idea was supported by the findings of Pootrakul et al., (1967) in Thailand — Todd et al., (1970) in Hongkong, and Weatherall et al., (1970) in Singapore.

According to current concepts alpha thal$_1$ represents the severe type of alpha thalassaemia and is represented in the newborn period by the presence of Hb Bart's in appreciable amount, alpha thal$_2$ represents the milder type of alpha thalassaemia and is represented in the newborn period by the presence of Hb Bart's in trace amount. Accord-

ing to this concept, combination of alpha thal$_1$ with alpha thal$_2$ will result in Hb H disease (Wasi et al., 1964), and combination of 2 alpha thal$_1$ in hydrops foetalis.

In the present paper, the author wants to discuss the evidence that Hb Bart's in the newborn period is not specific and is often an accompaniment of abnormal haemoglobin synthesis of different types and that the above concept has to be revised.

Material and Methods

Cord blood obtained from the delivery room of the Maternity Hospital at Kuala Lumpur were examined for unusual haemoglobin components.

Haematological examinations followed standard methods. Methods of haemoglobin studies are the same as previously reported by the author (Lie-Injo et al., 1966; Lie-Injo et al., 1971). However, haemolysates prepared for analysis were much more concentrated than usual. Starch gel electrophoresis, using tris-EDTA boric acid buffer pH 8.0 and 8.6 and discontinuous tris-boric acid buffer pH 9.5, were routinely carried out for separation of haemoglobin components and benzidine was used for staining of haemoglobin patterns.

Results

Among 1,431 newborns studied (492 Malays, 501 Chinese and 438 Indians) 98 had Hb Bart's in the blood. Of these, 39 were found to have Hb Bart's level above 5% and 58 with Hb Bart's below 3.8% with only one with a level in between. The rest did not show Hb Bart's. Relatively more cases with trace amounts of Hb Bart's were detected than in our previous study (Lopez and Lie-Injo, 1971). This is probably due to the use of more concentrated haemolysates. In the group with trace amounts of Hb Bart's, a variety of abnormalities of haemoglobin production was found. Those findings will be published in detail elsewhere. In short, among the cord blood samples with Hb Bart's below 3.8%, many showed an additional abnormality.

This additional abnormality of haemoglobin synthesis is of different types. One type of abnormal haemoglobin synthesis is associated with the presence of a slow-moving abnormal haemoglobin slower than Hb A2 consisting of two components we tentatively called slow-moving Hb X components which are similar to those described earlier in association with Hb H disease and which have opened new aspects regarding the inheritance of Hb H disease (Lie-Injo et al., 1971). Newborns with such abnormal slow-moving components invariably had one parent with the same abnormal haemoglobin. These slow-moving components in newborns have apparently been overlooked in studies in Thailand and other areas, including our own earlier study (Lopez and Lie-Injo, 1971) using less sensitive methods. Structural studies of these X components showed them to have an abnormality in the alpha chains.

A second type of abnormal haemoglobin synthesis accompanying Hb Bart's in the newborn period, probably also overlooked in earlier studies, is an abnormal gamma chain variant which the author called Hb F Kuala Lumpur. A detailed report on the structural studies of this new haemoglobin will be discussed elsewhere. The abnormality was not found in either parents since adults do not produce gamma chains. This abnormal haemoglobin occurs in slightly less than one per cent of Indian newborns and is often found together with Hb Bart's. When the child grows older this Hb F Kuala Lumpur, as well as the small amount of Hb Bart's, disappeared and there are no signs of alpha thalassaemia in the blood of the child.

A third type of abnormal haemoglobin sometimes accompanying Hb Bart's in the newborn is Hb E, a beta chain variant. Four of 12 babies with Hb E in the cord blood had Hb Bart's as well. Hb E in the cord blood occurs in low concentrations and may be overlooked if studied only in the standard buffer pH 8.6 where it has the same mobility as Hb A_2 and not at pH 9.5 where it has a slightly faster mobility than Hb A_2. Follow-up study of one of the four babies with Hb E and Hb Bart's shows the child, when he was older, to be just a Hb E trait carrier without alpha thalassaemia.

Among the newborns with appreciable amounts of Hb Bart's, usually two haemoglobin components were detected in addition to Hb Bart's, Hb F, Hb A and sometimes Hb A_2. One moves slightly slower than Hb F and faster than Hb A_2 clearly seen at pH. 8.6, which the author tentatively designates the Y_1 component (Fig. 1). The other moves between Hb A and Hb Bart's which is clearly seen at pH 8.0 and is tentatively designated Y_2 component (Fig. 2). At pH 8.6, the Y_2 component cannot be seen properly because it overlaps with Hb A_2. Only after a prolonged run can an indication of the Y_2 component be demonstrated at this pH. At pH 8.0 however, the Y_2 component stands out clearly. Follow-up study of 8-day-old babies, who had the abnormality in their cord blood showed that fresh haemolysates, prepared immediately after bleeding from the washed red blood cells still showed the Y_1 and Y_2 components in

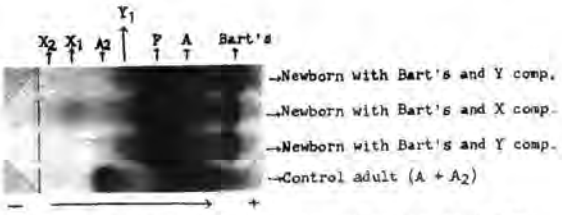

Fig.1. Starch gel electrophoresis in tris-EDTA-Boric acid buffer pH 8.6 showing the haemoglobin patterns of newborns with Hb Bart's and small moving haemoglobin components. Y_1 component is clearly seen at this pH , Y_2 not.

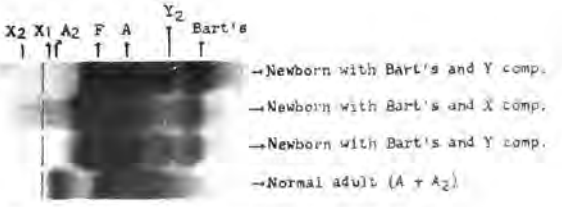

Fig. 2 Starch gel electrophoresis in Tris-EDTA-Boric acid buffer pH 8.0 showing the haemoglobin patterns of newborns with Hb Bart's and small haemoglobin components. Y_2 is clearly seen at this pH, Y_1 not.

addition to Hb Bart's, Hb F and Hb A. Our attempts to purify the Y_1 component was not very successful. Everytime the Y_1 component was eluted from the starch gel, concentrated and rerun, the electrophoretic pattern obtained from it curiously had the mobility of Hb A_2 with Hb F as contaminant.

The author was also able to show the Y_1 and Y_2 components stained with benzidin, in cases of hydrops foetalis thought to be due to homozygous alpha thalassaemia, or Bart's hydrops foetalis syndrome. In most of these cases, these small components could clearly be detected in addition to a large amount of Hb Bart's and small amount of Hb H (Fig. 3).

The component Y_1 and Y_2 could not be demonstrated in the parents.

Discussion

This present survey on newborns in Malaysia shows that Hb Bart's in the newborn period can accompany different types of abnormalities in haemoglobin synthesis involving an alpha chain variant (slow-moving Hb X components), a beta chain variant (Hb E), a gamma chain variant (Hb F

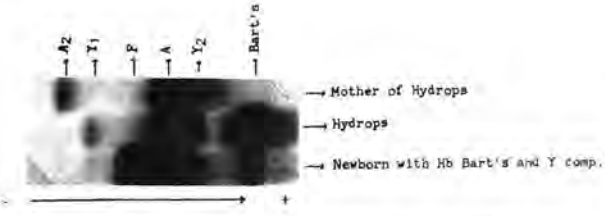

Fig. 3 Starch gel electrophoresis, Tris-EDTA-Boric acid buffer pH 8.6 showing the Hb pattern of a newborn with Hb Bart's and Y comp. compared with small Hb comp. in hydrops foetalis. The Y_1 comp. in the newborn has the same mobility as the slow comp in the hydrops foetalis.

Kuala Lumpur) as well as the synthesis of the Y_1 and Y_2 components, the significance of which is not yet clear. It can, therefore, be concluded that contrary to current belief, the presence of Hb Bart's is not specific for alpha thalassaemia since under alpha thalassaemia is understood the suppression of alpha chain production without abnormality of structure of any chain. The concept of Hb Bart's in the newborn being always the expression of alpha $thal_1$ or alpha $thal_2$ is therefore not anymore valid. Hb Bart's in the newborn seems to be the result of an aspecific imbalance of chain production, which may occur in various types of abnormality. A more detailed description and discussion of the different abnormalities which the author often found accompanying trace amounts of Hb Bart's will be published elsewhere.

Studies on Hb Bart's in the newborn period have so far failed to report the Y1 component although the Y_2 component may have been described before. Todd et al., (1970) and Weatherall et al., (1970) in studies of respectively 15 and 14 cases of Bart's hydrops foetalis, did not report any small haemoglobin component moving slower than Hb A. However, they did describe a component which migrates between Hb A and Hb Bart's and structural studies showed that this component is identical with Hb Portland described earlier by Capp et al., (1967). This component may be the same as the component we designate Y_2 in our healthy newborn babies with appreciable amounts of Hb Bart's and which we also found in our cases of Bart's hydrops foetalis syndrome.

However, the other component moving much slower, which the author designates Y_1 and which she found in healthy newborns with appreciable amount of Hb Bart's as well as in cases of Bart's hydrops foetalis syndrome has never been reported by others in newborns. This small component may be of theoretical importance. Todd et al., (1970) and Weatherall et al., (1970) were unable to find

any alpha chains in Bart's hydrop foetalis syndrome. Trace amounts of alpha chains detected by Weatherall et al., in 2 of their 14 cases were thought to be due to contamination with maternity blood. Todd et al., (1970) as well as Weatherall et al., (1970) showed that the component which moves in between Hb A and Hb Bart's (probably the same as our Y_2 component) had gamma chains combined with another type of chain which is not identical with normal alpha, beta, gamma or delta chains and which was also described earlier by Capp as Hb Portland (1967). Hybridisation studies in vitro showed that, when this Hb Portland was hybridisised with normal Hb A (Hb alpha 2 beta 2) it gives as one of the hybrids a haemoglobin which moves slightly faster than Hb A_2 and which had alpha chains combined with the unusual chains of Hb Portland. If the component we call Y_1, which also has a mobility slightly faster than Hb A_2, is identical with this last mentioned hybrid, it would mean that in the Bart's hydrops foetalis syndrome, contrary to general belief, alpha chains are present and that in this condition, the alpha chain synthesis is not completely suppressed.

If, on the other hand, the Y_1 contains abnormal chains not physiologically produced, than the term alpha thalassaemia for the condition would not be valid since under thalassaemia is currently understood the suppression of the synthesis of a particular chain without the production of abnormal non-physiological haemoglobin chains. In either case, it would not fit into current concepts. One has also to keep in mind the possibility that a trace amount of the mother's blood has entered the babies' blood through the placenta before delivery and that the alpha chains of the mother's Hb A (Hb alpha 2 beta 2) would have bound with the unusual chains of Hb Portland (Y_2 component) of the baby to form the hybrid haemoglobin. This is not very likely because, when a haemolysate was immediately prepared from blood, obtained in ACD as well as in EDTA solution, from an 8-day-old baby, who had the abnormality in his cord blood, the fresh haemolysate still showed the Y_1 and Y_2 components in addition to Hb Bart's, Hb F and Hb A, while no time for hybridisation was allowed in the preparation and study of the haemolysate prepared from the freshly-drawn washed red blood cells. If some mother's blood was still present in the baby at this age, her haemoglobin would have been found in the fresh haemolysate of the baby in the form of Hb A and not in the form of a hybrid.

Isolated Y_1 component resolved into a haemoglobin with the mobility of Hb A_2 with Hb F as contaminante when rerun on starch gel electrophoresis. This curious quantity switching over to Hb A_2 (or a haemoglobin with the mobility of Hb A_2) is also demonstrated by the Hb X component described earlier in Hb H disease (Lie-Injo et al., 1971) and is especially seen in the homozygous case for the X component discovered recently by Lie-Injo.

Summary

In an attempt to discover small haemoglobin components which might throw new light in the problem of alpha thalassaemia associated with Hb Bart's, a new survey of newborns was carried out. As in a previous study, two groups of newborns with Hb Bart's in the blood could be found, one with appreciable amounts of Hb Bart's and the other with trace amounts. It was found that Hb Bart's in the newborn may accompany different types of abnormal haemoglobin production involving alpha, beta, as well as gamma chains.

Further, new borns with appreciable amounts of Hb Bart's usually have two small haemoglobin components tentatively designated Y_1 and Y_2 components. Hb Y_1 component is clearly seen at pH 8.6 moving between Hb F and Hb A_2 and Hb Y_2 component is clearly seen at pH 8.0 moving between Hb Bart's and Hb A. Similar components with the same mobility as Y_1 and Y_2 components could also be demonstrated in cases of hydrops foetalis thought to be due to homozygous alpha thalassaemia.

It is concluded that contrary to current concepts, the presence of Hb Bart's in the newborn is not specific for alpha thalassaemia and that its presence in the newborn is the result of an aspecific imbalance of chain production which may occur in various types of abnormality involving haemoglobin synthesis.

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Medical ecology and epidemiology

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ECOLOGY HAS BEEN DEFINED as the study of relationships between organisms and their environment. The environment includes physical, chemical and biotic factors. Biotic factors include all other organisms in the environment including plant cover, food species, predators, parasites and pathogens. Thus, *medical ecology* can be defined as the study of those relationships between organisms and their environment that are of medical significance.

Audy (1965) considered the terms *medical ecology* and epidemiology as being essentially synonymous. In practice, however, epidemiological studies have been primarily concerned with disease epidemics in human populations. Vectors and host species have been an integral part of such studies, yet the focus has been on man's involvement. There are many zoonotic disease pathogens, however, that involve man as part of their life cycles only accidentally and very occasionally. To focus solely on man's contraction of such diseases in epidemiological studies may not be the most direct route to an overall understanding of such diseases. The transmission link to man may even be based on unusual environmental or temporal factors and secondary or abnormal vectors. Thus, in some cases at least, the traditional approach of epidemiological studies may not establish awareness of the principal events of the enzootic transmission cycles and thereby limit the predictability of man's overall risk of contraction of the disease.

Medical ecology appears to be a useful term

to distinguish between studies that focus on zoonoses in general compared with epidemiological studies which often seem to concern themselves primarily with man's involvement in zoonoses. Medical ecology differs from epidemiology in dealing more with endemic disease transmission cycles in species other than man. In a way, medical ecology deals with pre-epidemics. Major epidemiological studies usually are not begun until after an epidemic begins in man or livestock. By that time, the factors that were important in leading up to the epidemic may no longer exist. For example, the enzootic vectors may no longer be abundant and epizootic vectors may not be known. Thus, it can be seen that studies of medical ecology are complementary to and necessary for epidemiological studies.

With the recent interest of the public and the press directed toward problems of environmental pollution, the term ecology has become popular, but restricted in its popular definition. Another side of the human ecological problem is his involvement with pathogens usually associated with life cycles of other species, the various types of zoonoses. Man sometimes contracts zoonotic pathogens, the transmission cycle of which he is neither a normal nor a necessary part. Thus, to understand the circumstances of man's involvement in zoonoses, the overall ecology of the disease transmission cycles must be known, including the ecology of natural hosts, vectors or intermediate hosts.

In Malaysia, over 70 per cent of the land is still covered by forests or scrub vegetation (Wyatt-Smith 1954). Diseases contracted by people active in these areas often fall into the category of fevers of unknown origin (FUO), resulting not only in deaths, but in economic losses in numerous man-hours lost and human suffering. Often when the origins of FUO's are investigated, the pathogens are found to be zoonotic agents that have accidentally found their way into man. There are many examples, notably leptospirosis, scrub typhus, tick-borne encephalitis and Japanese "B" encephalitis.

The lives of zoonotic pathogens, like those of other organisms, are governed by various ecological factors. Survival and dispersal depend on adaptations on the part of the organisms. In equatorial ecosystems, where the species diversity exceeds that of other regions in the world and where the ecological relationships are most complex, we understand these ecological factors the least.

The zoonotic diseases most frequently contracted by man appear to be common pathogens of man's closest relatives, the mammals. In an accidental host, infections sometimes take a bizarre form and morbidity and mortality may be much greater than in the normal host. This seems to be the case in leptospirosis, scrub typhus, tick-borne encephalitis and other zoonotic diseases in man. Because of the cryptic nature of these diseases in their normal hosts, it is important to determine the characteristics of the endemic life cycle of the pathogens with regard to vector and host biology in order to evaluate the potential for a given zoonosis becoming epidemic.

The various aspects of host biology that may be important in disease transmission include their specific distribution (including altitudinal, habitat, vertical and temporal), feeding habits, periodicity of reproduction, population dynamics and behavioral factors (Muul, 1970). Studies of these factors would enable the epidemiologist to ascertain the potential roles of the various species in zoonotic disease cycles.

As far as habitats are concerned, in Malaysia the Lowland Dipterocarp forests usually give way to Hill Dipterocarp forests at elevations above 1,000 feet (Wyatt-Smith, 1952). Above 2,500 feet, the forest is called Upper Dipterocarp, with species compositions of trees differing from those found at lower elevations. Montane Oak forests occur from 3,500 to 5,000 feet. Here many of the trees are related to those occuring in temperate regions. Many of the mammals occuring as isolated populations at elevations above 3,000 feet (Lim, 1970) also have continuous distributions of their nearest relatives (conspecifics) in more temperate regions in the north. Good examples of such are *Callosciurus flavimanus, Dremomys rufigenis, Rattus fulvescens,* and *Rattus edwardsi.*

These ecological communities above 3,000 feet can be thought of as "ecological islands" in a "sea of lowland forest". They are often isolated from other similar communities, such as in the case of Gunong Benom in Pahang. These communities appear to be remnants of a continuous distribution in this region during earlier times when climates were cooler, perhaps at times of maximal glaciation in the northern hemisphere during the Pleistocene. Apparently as the regional climates became warmer, these communities were replaced elsewhere by communities better adapted for the warmer climates. The hill top communities survived owing to the lower temperatures at high elevations.

There appear to be differences also between mammalian species in various habitats, such as primary and secondary forests. For example, associations of arboreal mammals appear to be represented by different species in the various size categories in the two habitats. Among ground

mammals, such as rats, similar species associations tend to encompass both primary and secondary forests. Differences in prevalence in parasites in the various habitats are also becoming apparent. Most recently, for example, it has become evident that scrub typhus rickettsiae occur at a higher rate in forest rats than in those that occur in scrub habitats, the classical habitat of scrub typhus.

In West Malaysia, about 200 species of mammals are known. Each species occupies its peculiar ecological niche within the various ecosystems. The ecological niche of a species is its total way of life within the ecosystem. The infection of man by zoonotic disease organisms may be accidental, but the involvement of endemic hosts is not. The predisposition of various species to involvement in zoonotic disease cycles depends to a large extent on their ecological niches. Thus, on the basis of knowledge of the niches of the various species, an epidemiologist could assess their potential involvement in a given zoonosis, singling out certain species so that not all of the 200 species of mammals need to be of concern. But this type of detailed information takes a long time to accumulate.

There are preliminary data to illustrate differences in the distribution of pathogens in host species with differing ecological niches. For example, arboreal mammals seem to be much less involved in the transmission cycle of scrub typhus rickettsiae than are ground species. Arboreal species, on the other hand, seem to have much higher rates of infections with red blood cell protozoa, including *Plasmodium* (Dunn et al, 1968).

Thus far, surveys of prevalence to ascertain foci of activity of zoonotic diseases have been conducted mostly on the ground. According to Harrison (1957), about two-thirds of the species of mammalian hosts and potential hosts, except bats which are all arboreal or cave dwelling, occupy the canopy zone of the forests. Primary forests in the lowlands grow to over 200 feet high. Because some of the canopy species seldom descend to the ground or are not readily trapped, it is difficult to determine their densities and involvement in zoonoses. Some have been considered rare, but with varied collecting techniques they have been found to be as common as others (Muul and Lim, 1971). This means that if epidemiological studies depended solely on results of trapping on the ground, species that may be important in a zoonosis could be overlooked.

Very few studies of arboreal mammals have been attempted. Few investigators in the past have resorted to constructing ladders and platforms on trees or towers to study the ecology of canopy species, (McClure, 1966). Currently the staff of the IMR is using a transect walkway constructed in the canopy of a rain-forest at heights from 30 to over 120 feet from the ground. Over 1,200 feet long, this transect affords a large sampling area in the canopy, unlike the point sampling possible with the use of platforms (Muul and Lim, 1970). The trapping results, thus far, indicate that the biomass represented by small mammals is about the same in the canopy as on the ground. However, there are several arboreal species known to be present that do not enter traps. Most of the ground species can be trapped readily.

To further clarify the roles of various vertebrates in the tropical ecosystems and to relate their niches to their involvement in transmission cycles of various diseases, a great deal more information is required. Studies in medical ecology such as those discussed in this paper and elsewhere (Muul, 1970) should help to elucidate the various disease problems involving wild animals and perhaps provide clues for eventual limitation of man's contraction of those diseases. Such studies should go hand in hand with epidemiological studies of factors that predispose man's involvement in the various zoonotic disease transmission cycles. This sort of team effort by epidemiologists (including veterinarians), ecologists, mammalogists, entomologists, as well as scientists in other disciplines, should prove fruitful in dealing with various disease problems in equatorial areas.

Summary

The terms of epidemiology and medical ecology are clarified. Epidemiology has been defined as the study of disease epidemics in man. Medical ecology is concerned with the endemic disease transmission cycle and factors that may predispose epizootics. The two approaches have different emphases, but are complementary. Knowledge of ecological niches of various mammals enables an epidemiologist to single out certain species so that not all 200 species of mammals occuring in West Malaysia, for example, need to be of concern. Mammals are not distributed randomly but occur in associations with certain altitudes, types of habitats and vertical zones within forests. Their predisposition for involvement in zoonoses depends on their ecological niches.

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The uses of gamma globulin in the prevention of virus diseases

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ON MANY AN OCCASION, the clinician finds himself faced with a situation in which his client has been exposed to a highly infectious virus disease, where the use of vaccine would be too late to prevent the infection and where, if he does become infected, serious consequences are likely to result.

Chemotherapy of viral diseases is still very much in the experimental stage and even then, is applicable to only a very limited range of virus diseases. The only resort left to the clinician under these circumstances would be to give immune or hyper immune gamma globulin with its high concentration of specific antibodies. Unfortunately, the limited availability and the high cost of human immune globulin precludes its use by the general public.

The virus diseases which have been subjected to treatment with gamma globulin may be dealt with under three categoris:

1. Those which can be modified or prevented by gamma globulin:
   (a) Infectious hepatitis
   (b) Serum hepatitis
   (c) Rubeola (measles)
   (d) Varicella (chickenpox)
   (e) Variola (smallpox) and vaccinia
   (f) Mumps
2. Those which give equivocal results with gamma globulin and require further investigation:
   (a) Rubella (German measles)
   (b) Rabies

3. Those which are generally not affected by gamma globulin:
   (a) Poliomyelitis
   (b) Influenza.

Infectious Hepatitis

Infectious hepatitis, like poliomyelitis, occurs most often in children and may have a latent, mild and anicteric course. In fact, it may be so mild in children and young infants as to escape notice altogether. The disease is detected usually by the presence of icterus while inapparent infections have been detected on the basis of elevated serum transaminase activity. In Asian countries, the prevalence of hepatitis has been estimated to be 1% to 2% in recent studies using liver biopsy as well as the other criteria mentioned above (cited from Editorial, J.A.M.A., 1969).

Over the past 25 years or so, a number of studies have demonstrated the efficacy of gamma globulin in modifying the clinical features of infectious hepatitis without reducing the attack rate when administered during the incubation period (20-40 days). Wart et al. (1960) found that gamma globulin can be effective even when given as late as 6 days before onset of the disease.

Yarrow (1964) reported the efficacy of gamma globulin in bringing to a quick end an outbreak of infectious hepatitis in a rural school. It has also been found that a single dose of gamma globulin given to intending travellers protects them for about 6 months (Pollock & Reid, 1969). Peace Corps volunteers, given semi-annual injections of 0.05 ml. of immune serum globulin per pound of body weight, showed a marked reduction of cases over those unprotected (Woodson & Clinton, 1969).

Groups of children inoculated with gamma globulin and subsequently heavily exposed to hepatitis virus under endemic conditions over a period of several months sustained a more permanent protection (Krugman & Ward, 1961-62) as the partial passive protection is supplemented by active immunity.

Doses of 0.06 to 0.12 ml./lb given intramuscularly are protective. As passive immunity conferred by gamma globulin lasts from 3 to 6 months, the administration of gamma globulin every 4 months to western travellers to the east for prolonged periods would give adequate protection from infectious hepatitis.

Serum Hepatitis

The effect of gamma globulin on serum hepatitis is similar to that on infectious hepatitis in that the course of the illness is modified and the incidence of jaundice reduced without a reduction in the attack rate itself (Mirick et al., 1962). The use of gamma globulin in conjunction with transfusion significantly reduces the severity of post-transfusion hepatitis.

Statistical data concerning morbidity and mortality associated with post-transfusion hepatitis (Allen & Sayman, 1962) suggest that serum hepatitis is a very dangerous disease for patients over forty years of age. However, it is not practicable to give gamma globulin with every tranfusion with the present inadequate supply of gamma globulin. In specific cases, the dosage recommended is 2 doses of immune globulin, 10 ml. each one month apart, with the first dose given within a week after the blood transfusion (Grossman et al., 1945).

Rubeola (Measles)

Measles has been recognised as a clinical entity for at least 1,900 years and has generally been accepted as an inevitable feature of childhood. Although it is usually mild and therefore often treated with contempt, its dangers, especially for malnourished and debilitated children and for young infants, are real.

The past ten years have seen great strides in the development of measles vaccines and countless trials of these vaccines have been conducted. However, they still remain relatively expensive and produce many reactions not experienced with vaccine for other diseases. Moreover, it is still not known how long the effect of the several vaccines lasts and vaccination may merely postpone the attack of measles to another year and not prevent it altogether.

Although immune human globulin has no therapeutic value, it is usally effective in preventing or modifying measles when given soon after a known exposure. Its administration is indicated for the following groups of people exposed to the risk of catching measles;

(a) young children, especially those below 1 year of age,
(b) malnourished and debilitated children, and
(c) children with chronic medical conditions undergoing steroid therapy.

The choice of dose and time of injection of globulin is usually based on whether prevention or attenuation is desired. It is frequently believed that the resulting immunity is only transient if no sign of the disease appears and that a modified form of measles, rather than total prevention, should be aimed at. However, as the available data

supporting this view have not been convincing because most of the investigations of immunity were short-term studies, this presumption remains controversial.

To prevent overt disease, it is recommended that a dose of 0.1 ml/lb be given within 5 to 6 days after exposure to the infection. If a modified form of measles is desired, 0.02 ml/lb may be given, also within 5 to 6 days after exposure.

Varicella (Chickenpox)

Although chickenpox is usually a relatively mild disease, it sometimes tends to be more serious with generalised systemic involvement in the young adult and infant 6 months old or younger. Prevention or modification of the disease is therefore highly desirable in such cases.

Several reports of the use of gamma globulin in individual cases have been made since 1948 but none of these were controlled observations. Ross (1962) conducted a significant study and established that human immune serum globulin given to exposed contacts will modify but not prevent varicella. He suggested that gamma globulin should not be administered to exposed normal susceptible children or routine household contacts but should be reserved for contacts in which varicella has a high risk. These are neonates and infants less than 6 months old and individuals with a blood dyscrasia or those on alkylating, antimetabolite or high-level steroid therapy. He pointed out that although administration of gamma globulin to aduts with no prior history of chickenpox might be valuable if he should contract chickenpox, an enormous amount of gamma globulin would also be wasted in this way, owing to extreme unreliability of histories of adults.

Recommended dosages range from 0.1 to 0.6 ml/lb depending on the degree of risk involved. The material is available only from very limited resources even at the present time.

Variola (Smallpox) and Vaccinia

The chief indications for the administration of hyperimmune gamma globulin in the prevention of smallpox are in post-exposure cases where vaccination would be too late to prevent the disease and in children with chronic dermatitis where vaccination may cause serious complications. It is also of great value in the treatment and prevention of generalised vaccinia, vaccinia gangrenosa and eczema vaccinatum; and in the prophylaxis of post-vaccinal encephalitis.

Serious complications of vaccination tend to occur at or just after the height of primary vaccination. In uncomplicated vaccination, this period coincides with the presence of antibodies which help to prevent the development of viraemia likely to cause complications. However, in some children, this antibody response is absent or inadequate, and vaccination tends to result in viraemia with the subsequent appearance of peripheral lesions. It is presumed that the administration of passive antibody in the form of hyperimmune vaccinal gamma globulin provides sufficient antibodies to terminate viraemia promptly and prevent development of further lesions until the patient develop his own antibodies, if he can. There is, however, no clinical evidence that hyperimmune vaccinal gamma globulin influences the course of vaccinal encephalitis for the better.

Hyperimmune vaccinal gamma globulin may also be given prophylactically to children suffering from eczema and requiring vaccination for overseas travel, after exposure to vaccinated siblings or in the event of a smallpox epidemic in the community. It has been shown that 2 ml. of hyperimmune gamma globulin one or two days before vaccination does not interfere with active immunisation (Grispen et al., 1956).

As the severity of smallpox relates directly to the quantity of the virus liberated in the blood, the object of administrating the gamma globulin in the prevention of smallpox in closed contacts is to reduce or prevent viraemia at the end of the 12-day incubation period of smallpox. Trials using immune gamma globulin prepared from serum of recently vaccinated adults and conducted on close contacts of smallpox cases in Madras showed that the incidence of smallpox in those given the gamma globulin was about a quarter of that in the control contacts — a statistically significant difference (Kempe et al., 1961). However, Downie et al., (1961) found that the antibody levels in gamma globulin, prepared from convalescent serum, were 20 to 100 times higher than those prepared from serum of recently vaccinated subjects and therefore recommend the use of the former in preference to the latter. Ordinary gamma globulin contains less neutralising antibodies than hyperimmune vaccinal gamma globulin.

The usual recommended dosages for hyperimmune vaccinal gamma globulin is 0.2 ml/lb in adults, 0.05 ml/lb in children and from 0.1 to 0.2 ml/lb in infants under 1 year of age.

An effective chemoprophylactic agent in variola and vaccinia is methisazone (Marboran) the dosage of which is 2-4 gm daily orally for 2 days beginning 1-2 days after exposure.

Mumps

Prevention of mumps in children is not considered of great importance because, as a rule, the disease is mild in childhood and leaves a lasting immunity. The main indications for passive or active immunisation are in adults in whom orchitis and other "complications", e.g. encephalitis and meningitis, are more frequent and troublesome.

About 40% of all mumps infection are inapparent and many adults with no history of past experience may, nevertheless, be immune. In susceptible adults, even transitory protection is desirable after exposure to mumps. This may be achieved by passive immunity in the form of concentrated gamma globulin prepared from convalescent serum which has been shown to be of some value in preventing the development of orchitis if given after the onset of parotitis. (Gellis et al., 1945). Concentrated normal gamma globulin has proved to be of no value under these circumstances.

Treatment of established orchitis and meningitis has been attempted but with equivocal results. It is thought that once the virus has caused cellular injury, a procedure of this sort would not prove to be efficacious.

Durable immunity for 3 years, following vaccination of children with Jeryl Lynn strain live mumps virus vaccine, has been shown by Weibel et al., (1969) who observed that the pattern for mumps antibody persistence after vaccination paralleled that following natural mumps infection. Moreover, the vaccinated children developed CF antibodies against both the soluble (S) and the viral (V) antigens indicating that the resulting immunity equates with that of natural mumps infection.

Rubella

The problem of rubella prophylaxis, from the practical viewpoint, concerns primarily the management of the woman who is exposed to rubella during the first trimester of pregnancy. Although "normal" and "rubella convalescent" pools of gamma globulin have been found to contain significant levels of rubella antibody (Krugman, 1963; Schiff et al., 1963) the use of gamma globulin has been attended with equivocal results.

While earlier studies (Krugman & Ward, 1958; Lundstom et al., 1961), performed before the development of more reliable laboratory methods for assaying the rubella antibody, indicated some efficacy in the prevention of rubella in administrating large doses of gamma globulin to pregnant women exposed to the disease, more recent studies have shown otherwise. Krugman (1963) found that the administration of immune globulin known to contain rubella antibody to children within 24 hours of exposure showed no protective effect. Moreover, as the rubella virus may be recovered from pharyngeal secretions as early as 7 days before the appearance of the rash, gamma globulin, even if effective when given prior to the development of the rash, may have limited value for a pregnant woman who is in continuous daily contact with a child incubating rubella. A recent study by the Public Health Laboratory Service Working Party on Rubella (1970) revealed that immune globulin of known antibody content given to 5,449 pregnant women after exposure to rubella, did not appear to affect the incidence of rubella when compared with an uninoculated group of 652 adult women exposed to the same risk.

There is, therefore, no definite recommended course of action to take in the management of the pregnant woman who contracts rubella during the first trimester. The alternate long-term prophylactic measure is vaccination with the attenuated live vaccine virus. Even then, caution in the use of this vaccine must be exercised. Because it contains a live virus likely to affect foetal formation, care must be taken not to give it when the woman is in the first 4 months of pregnancy and the vaccinated woman must practise birth control for at least 3 months after inoculation. As it is difficult for a married woman to know whether or not she is pregnant during the first month of her pregnancy, the vaccine should be given only to women after medical consultation to ensure that they are not pregnant and to girls on reaching puberty. The male population and children may be left unvaccinated to allow the virus to circulate among them, as natural infection is a much better barrier to reinfection than vaccination.

Rabies

Possibilities for obtaining convalescent-phase serum from persons who have had active immunisation after bites from suspected rabid animals exist. Hosty et al. (1959) prepared human gamma globulin from serum of volunteers inoculated with duck-egg inactivated vaccine followed by attenuated chick-embryo vaccine and found that on administrating the human immune globulin, the decline in circulating antibody was more gradual than with horse anti-rabies serum although the passive antibody levels were much higher with the more potent horse serum than the weaker human anti-rabies gamma globulin. Further work is required to achieve the preparation of a more potent human immune globulin.

Poliomyelitis

The course of poliomyelitis is not altered by convalescent serum or gamma globulin. The present availability and effectiveness of the vaccines, killed or live, precludes the use of any other material for the prophylaxis of this disease.

Influenza

Extensive studies by the Commission on Influenza (1943) with large inhalation of sprayed human convalescent serum followed by induced infection showed no evidence of protection from or therapeutic effect on influenza.

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Hypersensitivity reactions due to tetracyclines

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SEVERE HYPERSENSITIVITY reactions due to tetracyclines are almost unknown. I doubt if there was ever a case reported. Mild reactions like generalised maculo-papular rash and urticaria are well documented; in fact, I came across two cases belonging to this category in the 2½ years of private practice. However, recently I encountered a severe case of hypersensitivity reaction due to oxytetracycline which I feel is worth reporting.

Case Report

The patient, Mrs. D. T. S., aged 49, a housewife, is a known diabetic and has been on diabenese 1 tablet daily and dietary control. She has a mild lower motor neuron left facial nerve palsy resulting from an attack of Bell's Palsy about 5 years ago. Because of this, she has frequent exposure conjunctivitis of her left eye.

She came to see me for the first time in the afternoon of May 15, 1972 for her painful left conjunctivitis. On examination during this visit, apart from her left conjunctivitis, left facial paresis and the presence of sugar^{+++} in her urine, she was an obese woman apparently enjoying good health. Her BP was 120/80 and she was afebrile.

For her exposure conjunctivitis and secondary infection, she was given 150 mg oxytetracycline intramuscularly, to be followed by oral oxytetracycline and chloramphenicol eyedrops.

Within about one hour, the patient returned complaining that half an hour after the injection, she felt a tightening sensation of her face and body. This was soon followed by swelling of the face and the appearance of generalised urticaria. In addition, she also complained of a pounding headache, palpitations and an oppressive discomfort in the chest. On examination then, her face was swollen with angioneurotic oedema, her body was covered with fine urticarial rash, her skin was flushed and hot, her temperature was 103.6°F, her

pulse rate was 70/min. regular but pounding, so was her apex beat, and her BP at this time was 240/140. The patient looked sick.

As an medical emergency, 10mg chlorpheniramine meleate was given intramuscularly, followed about 5 minutes later by 100mg hydrocortisone sodium succinate also intramuscularly, when the patient did not show improvement (BP now was 260/140). The response was almost miraculous.

Within about 15 minutes, her BP came down to 180/100 and her skin less flushed, T=100°F. In another 15 minutes the urticarial rash had started to subside, the headache lessened, and she felt and looked better. The next day when I saw the patient again after about 12 hours, she had completely recovered. Her BP was 120/80.

Discussion

The combination of generalised urticaria, flushing, pyrexia and acute hypertensive crisis is most unusual for a hypersensitivity reaction. The only plausible explanation is that nor-adrenaline or adrenaline or both are released in addition to the usual chemicals released during a normal hypersensitivity reaction. Normally adrenaline is usually given in addition to the antihistamine to counteract the vasodilating effect of histamine. But in this case, because of the acute hypertensive crisis adrenaline was contraindicated. As might have been noted, a hypotensive agent was not used. In a moment of urgent decision, hydrocortisone was the drug of choice because of its overall counteracting effect. However, if the hypertension had persisted, a parenteral hypotensive agent would have been used.

Conclusion

This a case report of a severe and most unsual hypersensitivity reaction due to oxytetracycline, and its sequelae, and its response to emergency medical treatment.

Primary glioblastoma multiforme of the spinal cord in infancy and childhood

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TUMOUR WITHIN THE spinal cord is rare in infancy and childhood [5, 12, 13, 19, 24, 25]. In 1944, Hamby [13] reviewed a total of 214 cases of intraspinal tumors in children under 16 years of age. There were 44 gliomas (20.6%) in that group. However, he did not delve into the nature, biology or pathologic features in any of the 44 cases. It is not possible, therefore, to state the number amongst them that may have been glioblastomas. Stookey's [25] 165 cases yielded 8 intraspinal tumors in children. One was an intramedullary tumor. Again, no specific diagnosis or details were given regarding it. Of the 5 astrocytomas in children reported by Elsberg [7], there was also no instance of a glioblastoma multiforme. Similarly in the following series of spinal cord tumors in children, 16 cases of Richardson [23], 12 cases of Arseni et al [1] and the 40 proven cases of Svien et al [26], there was no documented case of a glioblastoma multiforme.

It is obvious from a review of the literature that in pediatric practice, the occurrence of primary intraspinal glioblastoma multiforme is uncommon. There are only 9 documented cases in children. It is often taken for granted that like their intracranial counterpart, their clinical course, pathologic features and biological behaviour distinguish them from the benign astrocytomas, ependymomas and oligodendrogliomas. They are grouped here separately to examine if this indeed be true for such tumors of the spinal cord. Again, the

radical extirpation of intramedullary tumors advocated for better long-term results, [15] while being true for the benign tumors, does not hold for the glioblastomas. This impression is reinforced by the present review and a case report.

Geisner[11], Lowenberg[17] and Tauber et al[27] reported cases in which glioblastoma multiforme was found in the spinal cord. However, these were not primary intraspinal tumors and are hence excluded from the present study. They were clearly intracranial tumors that secondarily involved the spinal cord. Further, a number of cases were excluded for want of sufficient data. Case 15 of Ford[9] that of a spongioblastoma reported by Grant et al[12], case 1 of Geisler et al[10], case 14 of Iraci[15] and the two cases of Dereymaker et al[6] (2 and 15-year-old girls) are not being included for this reason. The diagnosis in each instance was spongioblastoma. Excepting the 2 cases of Dereymaker et al[6], there was no indication in the rest as to the exact tumor type. Therefore, it was not possible to confirm if they belonged to the benign spongioblastoma polare group or if they were meant to designate the malignant multiforme variety. The first two of the above cases besides lacking adequate pathologic verification had no comments as to the location, specific follow-up or clinical course. Quite similarly, Parkinson et al[20] described a "malignant glioma? neuroepithelioma" in a newborn. Besides mitotic figures, there were no features one would ordinarily ascribe to a glioblastoma multiforme. Moreover, there was no consensus amongst the various pathologists who examined the sections as to the diagnosis. It is, therefore, being excluded from the present series.

Astrocytomas with localised areas of malignant change with none of the features of a glioblastoma multiforme have also been excluded from this study. The relatively long survivals in these cases would attest to their being a different type of a tumor from the glioblastoma multiforme. Ingraham et al[14] had 9 astrocytomas in their series of 63 intraspinal tumors in children. None of them was stated to be a glioblastoma multiforme. In a subsequent report, Matson et al[18] illustrate a 6-year-old girl operated upon at the age of 2 years for a malignant astrocytoma. An identical case was reported by Ver Brugghen[28] in a 13-year-old girl.

Case Report

The patient, a six-year-old girl, was admitted following complaints of intermittent neck pain of one-and-one-half years' duration. Her pain had been insidious in onset and was described as being sharp and knife-like. It was aggravated by looking upward or on extending her neck. It was relieved by holding her head somewhat forward.

Four months prior to her admission, she was noticed to hold her head tilted to the left. At this time, she was seen by a doctor who placed her on cervical traction. This relieved her pain but her head tilt persisted. However, the week following, she complained of difficulty in raising her left arm above her shoulder. It was also noticed that she was not as deft with her left hand as she had been previously. Her grip became progressively weaker in that hand. Soon she experienced considerable difficulty in handling a spoon or holding a glass to her mouth.

A week prior to her admission, she had difficulty in walking. She required support to bear weight on the left leg.

There was no history of trauma to the head or neck. There had been no febrile episodes of significance. She volunteered no bladder or bowel problems. There was no history of recent weight loss. Her past history was unremarkable.

On examination, the child was normal mentally for her age. She was afebrile. In obvious pain, she resented any movement or manipulation of her head or neck. Her blood pressure was 120/70 mm. of mercury. There was no lymphadenopathy.

Her pupils were equal and reactive to light and accomodation. There was no papilloedema. A Horner's syndrome was not present.

Examination of the left hand showed considerable wasting. The thenar, hypothenar and interossei muscles were atrophic. No fasciculations were seen. Her left grip was extremely weak. In addition, there was marked weakness of her left biceps, triceps and brachioradialis muscles. By measurement, there was no disparity between the sizes of the left and right arms. Her left arm was somewhat hypotonic.

Her left leg was weaker than her right. This weakness was not confined to any one muscle group. There was some increase in tone but the leg could not be described as being spastic. There was no wasting apparent in the leg. She had difficulty standing on her left leg and needed some support and assistance in walking.

She had a sensory level to light touch, pain and temperature at T6. The superficial abdominal reflexes were intact. There was marked hypereflexia and a Babinski response could be elicited on the left side.

Radiologic studies

X-rays of her chest and skull were normal and unremarkable. X-rays of the cervical spines

revealed a 5 mm. forward subluxation of C3 on C4. There was no widening of the interpedicular distance. The intervertebral foramina were also normal.

A pantopaque (diiodophenylundecylate) myelogram was done. The cerebrospinal fluid opening pressure was 70 mm. of water. No Queckenstedt test was attempted. Fluoroscopy revealed a complete subarachnoid block at T4. In view of this, the pantopaque was not removed from the spinal subarachnoid space. The cerebrospinal fluid within the manometer was estimated for protein content. It was 98 mg.%. The myelographic defect and the clinical findings referable to the arm indicated a rather extensive intramedullary tumor

Operation

Under general anaesthesia, a wide laminectomy was performed in the sitting position. The laminectomy extended from C5 to T5. This exposed a tight dura mater. The latter did not pulsate. On opening the dura mater, the spinal cord was seen to fill the canal. As the exposure progressed, it was obvious that the cord was hypertrophied and edematous. It was the seat of a fusiform swelling. It was maximally dilated at about the C6 C7 interspace. An intramedullary mass was now obvious. A posterolateral myelotomy was now done on the left side. As this neared completion, a purplish-blue mass began to extrude. It was obvious that the spinal cord was reduced to a mere shell, having been compressed and stretched by the expanding neoplasm. There were no cysts to be identified. Spatulas and various blunt dissectors were used in an attempt to preserve what appeared to be the semblance of a cleavage plane between the tumor and the spinal cord.

As this was done, it was quite apparent that the tumor was frankly infiltrative. This was especially so at the upper and lower poles of the tumor and also on its anterior surface. All gross evidence of tumor was removed. Care was taken not to interrupt large vessels in the spinal cord or those accompanying the nerve roots.

Hemostasis assured, the dura mater was closed. The wound was then apposed in layers.

Histopathology

Hematoxy and eosin preparations of both small and large fragments of the tumor showed considerable numbers of neoplastic glial cells. These cells had ovoid to elongated nuclei and were pleomorphic. They were quite hyperchromatic.

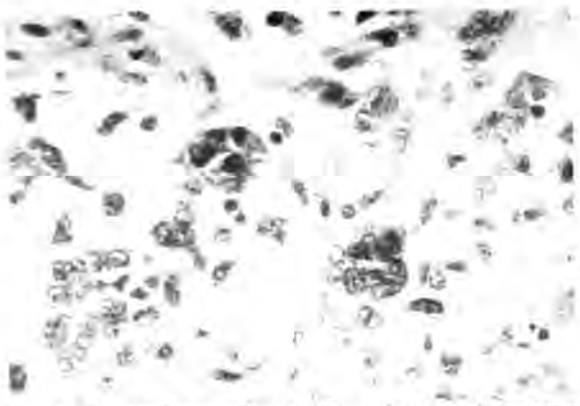

Fig. 1: Photomicrograph of the spinal cord tumour. Hematoxylin and eosin stain. Multinucleated giant cells and pleomorphism of the glial cells support the diagnosis of glioblastoma multiforme x 350.

In addition, there were large areas of necrosis. In the more cellular areas, multinucleated giant cells and abnormal mitotic figures were abundant (see photomicrograph). In yet other areas, there were large atypical astroblasts which showed tendencies to form a cartwheel-like arrangement about vessels. Endothelial proliferation with vascular hyperplasia was evident in many of the sections examined. There was no sarcomatous component to the tumor. In some areas, "gitter cells" were seen impregnated with hemosiderin pigment attesting to small past bleeds within the tumor.

Examination of all the speciments failed to reveal evidence of recognizable spinal cord tissue or nerve roots.

Diagnosis: Glioblastoma multiforme.

Postoperative course

On the day following surgery, a tracheostomy was performed to help with her airway. On the 14th postoperative day, she developed hyperthermia (T° 105F). This was, in part, due to her inability to sweat below her neck. In addition, she had abdominal distension, no doubt secondary to the loss of intestinal tone.

Her progress was slow but steady. In two weeks, she was able to sit out of bed. At this time, cobalt treatments were begun to her entire spine. She received a total of 3,000 rads over a 6-week period. Her neurological status, however, was unchanged from that previous to surgery. Seven months later, she complained of neck pain again. Examination at this time revealed a quadriplegia. Her progressive downhill course continued. Intercurrent urinary tract infection complicated exten-

No.	Year	Author	Sex	Age	Location	Survival Postop	Diagnasis
1	1901	Fischer[8]	F	8 yrs.	C.T.	—	**Glioblastoma multiforme**
2	1930	Bergonzi[3]	M	12 yrs.	C.T.L.	—	"
3	1934	Berkwitz[2]	F	14 yrs.	C.T.L.	3½ mos.	"
4	1934	Browder[4]	F	10 yrs.	C.	3 mos.	"
5	1935	Weil et al[29]	?	5 yrs.	C.T.	—	"
6	1944	Klackenberg[16]	M	11 mos.	C.	10 mos.	"
7	1960	Rand et al[22]	F	11 yrs.	T.	3 mos.	"
8	1960	Rand et al[22]	F	7 yrs.	C.	25 days	"
9	1966	Iraci[15]	F	13 yrs.	T.	12 mos.	"
10	1969	Arumugasamy	F	6 yrs.	C.T.	9 mos.	"

C = Cervical
T = Thoracic
L = Lumbar

Table of documented cases of primary spinal cord glioblastoma multiforme in the literature.

sion of her tumor into the medulla oblongata. She died 9 months after her surgery.

Autopsy

A post-mortem was performed on 1.19.68. Besides bilateral chronic pyelonephritis and cystitis, there was tumor recurrence at the site of the surgery. In addition, there was considerable contiguous extension of the tumor into the medulla oblongata and cisterna magna. The microscopic appearance of this tumor was identical to that of the operative specimens.

Discussion

Poser[21], in his review of syringomyelia with associated neoplasms, drew attention to 4 glioblastomas in children[2, 3, 8, 29]. They were all variously related to intramedullary cystic cavities. Although Fischer[8] does not state the sex of his patient there are definite indications that he was speaking of a girl. Bergonzi's[3] patient had extensive involvement of the cervical, thoracic and lumbar segments of the spinal cord. Berkwitz[2] described a glioblastoma multiforme of proportions identical to that of Bergonzi[3]. His case was included in Hamby's report[13] but not that of Bergonzi.

There are 2 cases in the literature where a spina bifida with a meningocele was associated with a spinal cord glioblastoma multiforme. One is that of a 5-year-old child (the sex of the child is not stated in the report)[29] and the other, an infant reported by Klackenberg[16]. Browder's[4] case I of a cervical glioblastoma multiforme in a 10-year-old girl was surgically verified. The patient died 3 months later but was not autopsied. Iraci's[15] case 19 and the 2 cases of Rand et al[22] are unequivocal examples of spinal cord glioblastoma multiforme. A further case is being added here.

Spinal cord glioblastoma multiforme is rarer in infancy than in childhood. Klackenberg's[16] case (alluded to earlier) of an 11-month-old boy is the youngest patient being reviewed here. Subsequent

reports, of spinal tumors in infancy by Mosberg[19] and Schwartz[24] did not add further new cases, of the type presently under review, to the literature.

It would appear from the cases tabulated, that girls far outnumber the boys (3.5:1). However, the number of cases is too small to warrant any definite conclusion regarding this. All the patients were dead in under a year following surgical verification.

Gliomas of the spinal cord should be removed as completely as possible[15]. Following radical removal, the immediate postoperative course may be trying and stormy, but the long-term results are better than with subtotal resections[15]. While this is true for the benign tumors of the spinal cord, it cannot be extended to include the glioblastomas. Iraci[15] makes no distinction between the glioblastomas and other gliomas in this regard. It is agreed that in each instance as complete a removal as is possible should be done irrespective of the tumor type. However, the prognosis with the glioblastomas has been uniformly poor. In spite of a radical extirpation and X-ray therapy, the patient reported here died nine months after surgery. It is entirely possible that should the tumor have been located in the lumbar or low thoracic area, she may have lived longer.

In general, the duration of survival has been less in those with glioblastomas than those with benign gliomas. Our table would indicate that in all where details were available (7 patients) death occurred in under one year. In the 9 cases of Grade I and II astrocytomas reported by Rand et al[22], seven were alive at the end of one year. The remaining two had been recently operated upon and were alive at the time of their report. Further, one of their patients (case 3) lived 14 years after surgery. But both their patients with a glioblastoma multiforme were dead in under 3 months following surgery. Iraci's[15] surgically verified cases also showed a similar trend for the benign tumors. His girl with the glioblastoma multiforme died 12 months following surgery.

Many earlier reports of intraspinal tumors failed to classify the gliomas into their various type. It is not enough to talk of intramedullary tumors in the broad category of gliomas. Correct histopathologic verification should be obtained in each instance. This is because prognosis and therapy will vary with the tumor type. The glioblastoma multiforme should be considered separately from other gliomas by virtue of its nature, biological behaviour and pathology. This study indicates that as in its intracranial counterpart, the prognosis is uniformly poor. Spinal cord gliomas are rare in children. It is evident from this report that glioblastoma multiforme is more so. That the patient in this report had symptoms only referable to the spinal cord would support the diagnosis of a primary intraspinal neoplasm. On autopsy, other than local contiguous recurrence, there was no evidence of tumor intracranially or elsewhere.

Summary.

1. Reported cases of children with spinal cord glioblastoma multiforme are reviewed and tabulated. A further case has been added making a total of 10 such cases.
2. Girls seem to be more commonly affected. Although the few cases in the literature do not allow firm conclusions regarding these tumors, it is hoped that more meaningful deductions will be forthcoming as more cases are reported.
3. It is evident that with present methods of treatment, the prognosis is uniformly poor. All patients reviewed were dead in under a year.

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An improved technique of anaesthesia for Caesarean section

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Introduction:

EVER SINCE JENNERIAN vaccination was widely adopted in the control of smallpox in many endemic countries, attention had been focussed on its complications. With the virtual eradication of smallpox in many Western countries, these complications have raised major controversies about the very usefulness of vaccination in controlling outbreaks of smallpox. We have now sufficient knowledge of smallpox from many epidemiological studies to justify a proper assessment of the exact place of vaccination.

Malaysia has been free from smallpox since the last outbreak in Kedah in 1946-47 when 599 cases were reported with 293 deaths. In the middle of September 1971, a suspected case of smallpox seen in the University Hospital, Petaling Jaya, aroused the fear of imported smallpox in Klang, followed by a mass vaccination campaign. This paper presents the results of a study of the complications seen following the mass vaccination, and reviews the present role of vaccination.

Materials and Methods

Between 15th and 19th September 1971, 186,329 people of all ages were vaccinated in Klang. All doctors in the hospital and in private practice were asked to look for complications and to refer patients to the hospital for this study. Forty cases were studied in detail. Where necessary, patients were treated as in-patients.

Results

The following complications were seen during the study.

1. Generalised vaccinia 12

2.	Toxic erythema	12
3.	Auto-inoculation	4
4.	Erythema exudativum	2
5.	Local necrosis	1
6.	Miliary eruption	1
7.	Herpes zoster	1
8.	Angio-neurotic edema	1
9.	Steven-Johnson syndrome	1
10.	Eczema vaccinatum	1
11.	Encephalomyelitis	3
12.	Vaccinia in newborn	1

Discussion

Complications of smallpox vaccination may be broadly classified into three types:

1. Cutaneous complications
2. Neurological complications
3. Miscellaneous complications.

Cutaneous Complications:

1. *Secondary Bacterial Infections*: These are quite common, especially in children. Being a minor complication, few were referred to the hospital. Local application of an antibiotic cream, such as achromycine, usually heals most lesions.

2. *Local Necrosis*: This can occur as a result of severe secondary bacterial infection or severe pustulation itself. In the case seen in this study, severe necrosis in a Malay male, aged 27, was accompanied by brawny edema of the whole upper limb.

3. *Auto-inoculation*: This follows scratching and transfer of the vaccine material to other parts of the body or to another person in close contact with the vaccinated person. This usually occurs during the first 9 days after vaccination.

Case 1. A 38-year-old Chinese female developed typical vesicles over the upper and lower eyelid with edema of the surrounding area, on the fifth day after vaccination. Recovery was uneventful.

Case 2. A recently vaccinated mother brought her 8-month-old child with typical vesicles over the back of the child's neck, due to auto-inoculation while carrying the child on her left arm.

4. *Toxic Eruptions*: These were the commonest cutaneous complication seen, accounting for 15 cases.

(a) *Miliarial eruptions*: One patient presented with miliarial eruptions along the lymph channels leading from the site of vesiculation.

(b) *Erythema Multiforme*: This is a very common complication, occurring usually 7 to 10 days after vaccination, sometimes up to the 14th day. The eruptions may be localised or generalised, cause little constitutional disturbance and clear in 3-5 days. Sarkany and Caron (1962) described toxic erythema, erythema nodosum, pityriasis rosea, eczema and granuloma annulare after vaccination. Of these, toxic erythema was the commonest type seen in the present study.

(c) *Erythema exudativum*: This is a more severe form of toxic erythema with generalised bullous formation, fever and protracted course, often described in dermatological literature. Three of our patients had this complication.

Case 1: A Malay female, aged 60, had localised bullous eruptions over the deltoid with echymotic areas.

Case 2: A 9-year-old Malay girl was admitted to the hospital, 8 days after vaccination, with high fever and vomiting. She had developed generalised erythematous eruptions, affecting the whole body, including the soles and palms, with multiple

only thing surgically different is it means that "all the water comes his (surgeon's) way".

5. **Position for Intubation.**

The patient lies in a horizontal plane. Her head rests on a headring with the neck flexed and head extended in a position most suitable for intubation.

6. **Rapid and Safe Intravenous Induction** ("short gun" or "crash" technique).

a. Methohexitone 1 — 1.5 mg per kg as administered into the drip tubing injector to produce a "bolus" effect. Half the dose in a 10 ml syringe is first given and flushed through.

b. Then suxamethonium about 75 — 100 mg in a 2.5 ml syringe is given through the rubber injector with the 2nd half of the methohexitone. This gives the effect of "premixed methohexitone-suxamethonium" mixture and yet does not give any chance of consciousness of fasciculations or awareness. (Liew 1972). Or the second half dose of methohexitone is premixed with the suxamethonium in a 5 ml syringe and given after the first half dose. This is likened to the premixed thiopentone-suxamethonium mixture for rapid intubation (Khawaja 1971). Others (Bradford 1969) used Propanidid for elective Caesearean section, while Baraka (1971) preferred propanidid to thiopentone.

No prior inflation of the lungs using the mask is required. For obstetrics anaesthe-

sia, intermittent positive ventilation is an important cause of regurgitation!

c. Adequate suction is ensured first.

d. Intubation is performed using the self-applied cricoid pressure technique (Liew 1972). The anaesthetist has previously felt the exact position of the cricoid cartilage before induction and marks it with a ball-pen. The patients were intubated with the balloon of the endotracheal tube "ready inflated" technique. The lungs are immediately checked for air entry and adventitious sounds.

e. Hypertensive response to intubation. This methohexitone-suxamethonium intubation technique always cause a rise in blood pressure and tachycardia, which tends to offset any fall in blood pressure after induction of anaesthesia.

Initial Hyperventilation

For the first 5 minutes, hyperventilation with 70% nitrous oxide at a minute volume of 8 — 9 litres will ensure the establishment of amnesia-analgesia before the amnesia effect of the barbiturate wears off.

Maintenance of Anaesthesia

a. In four patients, the speed of surgery resulted in delivery of the babies before the return of muscular activity following suxamethonium. One patient had two doses of suxamethonium for a trial of forceps, which proceeded to Caesarean section. The anaesthetist watches for any return of muscular activity and also places his fingers on the cricoid cartilage to feel for first sign of swallowing, spontaneous respiration, while his eyes are on the operation site surveying the colour of the blood at the wound and the amount of blood loss. Thereafter for maintenance, di-allyl-nor-toxiferine (Alloferine) 0.25 mg per kg was administered.

b. Concentration of Nitrous Oxide/Oxygen mixture for maintenance: A flow of 2 litres/min of oxygen, 5 to 5.25 litres/minute nitrous oxide giving 27 — 28.5% oxygen will provide, through the Manley Ventilator (minute volume divider), adequate oxygenation and depth of anaesthesia with little chance of awareness (triad of anaesthesia, Gray, 1960).

c. Once the placenta is delivered, the operation table is set level again.

d. Oxygen flushing: This was not done. Also the effect of nitrous oxide wash-out to raise the foetal muscle po_2 comes only after 1 minute and longer in the presence of foetal distress (Althabe, 1967).

e. Mild Hyperventilation: Since marked hyperventilation produces foetal acidosis in some animals (Morishima 1965) (Motoyama, 1967) and in patients (Scott 1969) but not well proven, the author only uses mild hyperventilation till this problem is better understood. Studies done on gas flows with the Manley ventilator (Liew, 1972) showed the arterial pco_2 to be in the region of 28 — 32 mmHg. Subsequent to delivery of the infant, Morphine 5 mg I/V or omopon 10 mg I/V or pethidine 25 mg I/V is given. Morphine 5 mg I/M or pethidine, 25 mg I/M or at extubation) is given to the mother.

Others administer 0.5% halothane in 50% oxygen throughout the operation (Moir 1970), or 0.1% methoxyflurane (Crawford 1971) after the baby is delivered.

f. Intra-operative aspiration (Vandam, L R. 1965): None of the patients required aspiration during operation to empty the stomach. Gastric aspiration was done for testing in 2 patients (emergency Caesarean section) which showed a gastric pH of 5 and 5.4 respectively (Astrup pH meter 27). This is a safe pH even if pulmonary aspiration occurs. The danger pH range is 2.5 and less.

Position for Extubation and Technique of Extubation.

All the patients, but one for emergency operation, were turned to the left lateral side. Reversal was then given, nitrous oxide turned off and the patient extubated with continuous suction applied to the left buccal cavity. The patients usually become conscious with 20 — 25 breaths of pure oxygen (since the blood gas solubility coefficient of nitrous oxide is 0.47) from the non-rebreathing circuit of the Manley ventilator for an operation lasting less than one hour.

The one heavy patient for emergency Caesarean was extubated supine and horizontal, but oropharynx suction was given before reversal. The heavy weight of the patient is a factor against left lateral extubation, during which the patient may also fall from the operation table.

The author used an endotracheal tube one size smaller than required usually 7.5 — 8 mm with the cuff optimally inflated. Extubation is done in a curved direct (the direction of the curved tube) during inspiratory stroke of the Manley ventilator. Too early washingout of nitrous oxide with oxygen

before administering reversal will result in a conscious but paralysed patient in pain and fear.

Post-operative Recovery in the Recovery Room

The patient is nursed in the left lateral position till fit to return to the ward or labour room.

Post-operative interview

All the patients were interviewed within 36 hours. They were questioned on the period of amnesia, and recall or pain during operation; pleasantness immediately after operation. All of them remembered only up to time the oxygen mask was placed on the face, only to come round in the ward. Since the intravenous cannula drip was inserted under local analgesia on the dorsum of the hand, it also gives comfort to the hand and allows free movement of patient in bed. None had a sore throat and all except one patient were analgesic till she was up in bed.

All patients described the anaesthetic and operation as very pleasant and amnesic. This was a period in their lives they "never wish to know or remember". Two patients, who had previous Caesarean sections, described the experience as more pleasant.

The lack of pain along the arm on injection of methohexitone through the rubber tube was probably due to dilution by the free flowing drip. One patient anasthetised previously for a D & C experienced severe pain in the arm on I/V injection but not this time.

The Baby

The resuscitation officer in the University Hospital is the paediatrician.

Discussion

The confidence of these 5 patients (all doctors) was great when they knew (some requested) that their wellbeing was in the care of a competent obstetrician and anaesthetist.

Maternal mortality from anaesthesia remains a serious problem. For every death, several non-fatal accidents occur contributing to serious maternal morbidity. The anaesthetists are also increasingly concerned with intra-operative problems of the foetus.

Magnesium Trisilicate BPC 1968 mixture used in the University Hospital contains the following:-

Light mangesium carbonate	5 g
Magnesium trisilicate	5 g
Sodium bicarbonate	5 g
Peppermint water	100 ml

The magnesium trisilicate BPC (1968), which differs from the 1963 formula, needs to be given 15 ml 2-hourly and not 10 ml 2-hourly, to ensure that the pH of gastric Hcl will be kept above 2.5 or 3 (Williams and Crawford J.S. 1971). If such contents are aspiration, the acid-aspiration syndrome will be mild if it at all develops. The author is presently using also Gaviscon and Digene. These lighter-than-water, anti-foaming demulcents and antacids combination will neutralise Hcl and forms a stop-cock foaming mixture at the cardiac sphincter rendering it more competent.

Scopolamine (Hyoscine) 0.4 — 0.6 or even 0.8 mg causes drowsiness, euphoria, amnesia, together with an increase in the respiratory rate, minute volume and heart rate. Used with morphine (10 — 15 mg), omnopon (20 mg), or pethidine (100 mg), it does not cause excitement, restlessness and hallucinations or delirium seen with hyoscine alone.

Morphine is given 5 mg or omnopon 10 mg intravenous after the baby is born; and 5 mg or 10 mg respectively intramuscular at extubation. It relieves pain, discomfort and is anxiolytic and euphoric. This "omp follows scop" combination tends to decrease the incidence of awareness and recall.

Pethidine similarly produces analgesia, sedation and euphoria. It is given 25 mg I/V after the baby is out and 25 — 50 mg at extubation. The tachycardia and hypotension due to increased peripheral blood flow is minimal with the small intravenous dose.

The problem of awareness and factual recall has been accentuated under light anaesthesia with the use of relaxants (Lancet, 1968). Proper choice of drugs, especially premedication (Wilson, 1969) has an important function in light relaxant anaesthesia to prevent any form of operative awareness, though other factors may be important such as parity, preoperative tension, previous unpleasant operation, level of nitrous oxide narcosis, nitrous oxide wash-out with oxygen, degree of hyperventilation, use of intravenous analgesics or inhalation anaesthesia.

The periods during operation which offer scope for study of awareness (Wilson 1969) may include: Predelivery under light relaxant anaesthesia, often intermittent suxamethonium; during incision of uterus and delivery of baby under oxygen augmentation or nitrous oxide wash-out with oxygen; thereafter, when anaesthesia is deepened by use of adjuncts; twilight phase during recovery from anaesthesia.

The act or effect of hyperventilation was found

to have analgesic properties (Robinson & Gray, 1961). The author is presently looking into the degree of hyperventilation possible in obstetric anaesthesia, as it has been suggested that it is difficult to lower the arterial pco_2 by more than 10 mm Hg by mechanical ventilation! (Scott, 1969).

Normally pain is not a feature in recall. Opiate premedication within 6 hours of operation is effective (Wilson, 1969), but since it is not advisable in obstetrics, we have to rely on other venues like use of hyoscine benzodiazepine drugs.

Aortacaval compression by the uterus in late pregnancy and in labour occurs in 3% of pregnant women. The uterus virtually divides the maternal circulation into two zones.

(1) a caudal zone, distal to the obstruction which is both venous (inferior vena cava) and partly arterial (aorta). This area therefore has low arterial blood pressure with reduced blood flow and high venous congestion and relatively anoxic area.

(2) The cephalad zone proximal to the obstruction has a hyperkinetic circulation. Uterine contractions and maternal hypotension from other causes (e.g. ante-partum haemorrhage) greatly enhance these obstructive effects, with the inferior vena cava totally obstructed and aorta partly compressed and displaced laterally, (Bieniarz, 1968) as studied by angiograms. Other vessels may be occluded or kinked (e.g. common iliac artery, renal vessels).

The University Hospital so far has treated two cases of pulmonary aspiration. Both had magnesium trisilicate 15 ml, and the mild pneumonitis responded rapidly to the usual lines of management in the intensive care unit. Our Caesarean section rate is 8 — 10 operations per month.

It is suggested that anaesthetic care for the obstetric patient consists of total care from the time the patient is listed for operation to throughout the intraoperative and postoperative period. The anaesthetist chooses the technique he is most familiar with, incorporating the various recent advances in obstetric anaesthesia. The worst situation is when both anaesthetist and obstetrician are in distress. Only trainee-anaesthetists, with more than one year's experience, should be allowed to give obstetric anaesthetics alone . The ideal anaesthetic for operative obstetrics does not exist (Utting and Gray, 1968)

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***Gaviscon** tablet contains alginic acid, sodium alginate, mag. trisilicate, sodium bicarbonate, aluminium hydroxide and mannitol. It is a gastric reflux suppressant. Digene contains antacids and dimethylpolysiloxane.

A case of Sindbis virus infection in Kuala Lumpur

by T. W. Lim
Virus Division

Megat Burhainuddin
Rural Health Research Division

and

Amir Abbas
Rural Health Research Division

Institute for Medical Research, Kuala Lumpur.

ANTIBODY SURVEYS ON SERA from persons resident in different parts of West Malaysia indicate that there was evidence of low activity for Group A arbovirus (Rudnick 1967). However, no case of human disease by Group A has yet been recorded in West Malaysia, although it was evident that there was infection occurring. The presence of these viruses had been observed as several Group A arboviruses, including Sindbis, have been isolated from mosquitoes before. This is probably due to mild disease produced as a result of infection with Group A and consequently the patients were not hospitalised and no laboratory investigations were carried out. It was thus fortuitous that this case was picked up routinely as it was being investigated for dengue infection.

This report describes briefly the clinical and serological findings in a patient seen at the Institute for Medical Research, Kuala Lumpur.

Case Report

A 20-year-old Malay male was seen at the outpatient clinic of the Institute for Medical Research suffering from fever, cough, headache, rash and generalised body aches for 1 day. There were no joint pains.

On examination, he had a temperature of

102°F, generalised erythematous rash all over the body and infected pharynx. There was no lymphadenopathy or hepatosplenomegaly or other positive findings. He was treated symptomatically with

Tetracycline 250 mgs —
6 hourly daily for 5 days.
Paracetamol lg —.
3 times daily for 4 days.
Chlorpheniramine maleate (Piriton) 4 mgs —
3 times daily for 4 days.

He came back after 4 days with the fever and generalised rash still persisting and was again treated symptomatically. A sample of blood was taken for viral studies as dengue was suspected clinically and he was asked to come back again after 2 weeks for a second specimen of blood to be taken. He made an uneventful recovery and was quite well when the 2nd specimen of blood was taken.

Methods and Materials

(1) **Sera** — The 2 samples of serum were taken from clotted blood after overnight storage at 4°C; they were then centrifuged and stored at -20°C before testing at a later date.

(2) **Viruses** —
- (a) Dengue 1. Hawaii strain; 131st mouse passage
- (b) Dengue 2. Trin. 1751 strain; 66th mouse passage
- (c) Dengue 3. H-87 strain; 23rd mouse passage
- (d) Dengue 4. H-241 strain; 31st mouse passage
- (e) Japanese Encephalitis (JE), Nakayama strain; 52nd mouse passage
- (f) Tembusu, AMM 1775 strain; 16th mouse passage
- (g) Zika, B 24982 strain; 155th mouse passage obtained from Dr. A. Rudnick, University of California.
- (h) Sindbis, P 886 strain; 29th mouse passage
- (i) Chikungunya, African strain; 180th mouse passage.

(3) **Haemagglutinin — inhibition test.** The test as described by Hammon and Sather (1969) was used. The antigens were prepared according to the sucrose-acetone method of Clarke and Casals. The sera were treated by the acetone-extraction method and the titration was carried out by the microtechnic using perspex plates with U-shaped cups. The results were expressed as a reciprocal of the highest serum dilution causing inhibition. The lowest serum dilution tested was 1/10.

(4) **Neutralisation test** — Sindbis seed virus was prepared from brains of suckling mice which had been inoculated intracerebrally. The constant serum-varying virus dilution method was used and the neutralisation index and log rise in titre calculated.

Laboratory Results

(a) **Virus Isolation**

An attempt at isolation of virus was made in this case but proved negative. The first blood specimen was taken on the 4th day of illness and it was passed in suckling mice. Failure to isolate the virus in this case was probably due to high antibody content in the blood or low concentration of free virus and not loss of viability during transportation as the patient was bled at the Institute where the virus investigation was carried out.

(b) **Serological Findings**

Haemagglutination-inhibition test

Virus antigen	Serum specimen	
	1st specimen 4th day of illness	2nd specimen 21st day of illness
Group A		
Sindbis	320	2560
Chikungunya	<10	<10
Group B		
Dengue 1	<10	<10
Dengue 2	<10	<10
Dengue 3	<10	<10
Dengue 4	<10	<10
Japanese Encephalitis	<10	<10
Tembusu	<10	<10
Zika	<10	<10

The haemagglutination-inhibition test against Group B antigens were all negative but when carried out against Group A, i.e. Sindbis, there was a significant rise in titre. Sindbis virus antigen is routinely used in the laboratory as a representative for Group A in the haemagglutination-inhibition test. To rule out the possibility that this reaction could be the result of a Chikungunya infection, the haemagglutination-inhibition test was carried out

Neutralisation test			
Serum Specimen	Virus antigen Sindbis; log LD_{50}	Neutralisation index	Log rise in titre
1st specimen	-4.1	3.6	—
2nd specimen	-4.2	3.5	-0.1
Control normal rabbit serum	-7.7	—	—
Positive control serum	-3.4	4.3	—

against Chikungunya virus antigen. This turned out to be completely negative on 2 separate occasions tested. Chikungunya and Sindbis virus antigens are the only 2 Group A antigens used in this laboratory.

The neutralisation test showed that neutralising antibodies were present to almost the same extent in both specimens of blood (Neutralisation index of 3.6 and 3.5) although there was no rise in titre. It would appear from these results that there was an accelerated response to haemagglutination-inhibition antibody but a poor response to neutralising antibody in the 2nd specimen of blood. Although there was no rise in titre of the neutralising antibody, there was, however, a large amount of antibody present. This is probably due to a secondary response as a result of a secondary infection with Sindbis virus or one that is antigenically closely related to it.

Discussion

There is little doubt that this is a case of Sindbis virus infection. The clinical findings, however, are minimal and the only signs and symptoms of any significance are fever, headache, rash and generalised body aches. These features are indicative of a mild form of the disease. In severe cases (Malherbe et al 1963), the rash proceeded to painful vesiculisation, and hands and feet were swollen. In addition, there were joint pains and soreness of tendons leading to prostration. A virus was isolated from these vesicles which was later characterised and identified as Sindbis virus. In our case, no vesicles were noted and attempts at virus isolation from blood was unsuccessful. Further, there was no swelling of the hands and feet and joint pains.

In the cases studied by McIntosh (McIntosh et al 1964), he described upper respiratory symptoms in 4 cases. There was mild sore throat with small ulcers irregularly distributed in the mouth and pharynx. In our case, no ulcers were seen in the mouth or pharynx although the latter was injected.

Finally, our patient made a complete and uneventful recovery in 2 weeks and there were no residual signs or symptoms.

On carrying out epidemiological investigations, it was found that this patient had come to Kuala Lumpur from Kedah (a state about 250 miles by road to the north of Kuala Lumpur) 21 days prior to the onset of fever. The purpose of coming to Kuala Lumpur was to join the Institute for Medical Research as a trainee laboratory assistant. On first arrival, he stayed with relatives at a military camp on the outskirts of Kuala Lumpur and was still staying there at the onset of illness. It would appear that he developed the disease whilst staying at the military camp. This camp is a sprawling complex of stores, offices and residential buildings. It is bounded on one side by large areas of currently used as well as disused tin mining pools. On first glance, it would appear that this would be an ideal breeding area for Culex mosquitoes from which species Sindbis virus have been isolated before in West Malaysia. Detailed entomological investigations are being planned and antibody surveys among the population there are being carried out. Preliminary results indicate that there is some evidence of low activity with Group A arbovirus.

No virus was isolated from this case and the diagnosis was based on clinical and serological evidence.

Summary

A case of Sindbis virus disease in man occurring in Kuala Lumpur is presented. This is the first time that it has been observed in Malaysia.

Acknowledgement

We wish to thank Mr. Victor Chew and Mr. Othman bin Mohd Said for providing the technical assistance. We are grateful to the Director, Institute for Medical Research, Kuala Lumpur, for permission to publish.

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A case of chronic melioidosis responding to tetracycline therapy

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MELIOIDOSIS, A GLANDERS-LIKE DISEASE, was first described in 1912 by Whitmore and Krishnaswamy who discovered it in the bodies of vagrants and morphine addicts brought to the public mortuary in Rangoon (Whitmore 1912). The following year it was recognised in the then Federated States of Malaya where it appeared as a severe epizootic among the guinea pigs and rabbits in the Institute for Medical Research laboratory in Kuala Lumpur (Fletcher 1919). In 1917, Stanton discovered human cases in Kuala Lumpur. Altogether, 39 cases were reported in Malaya between 1917 and 1929 (Stanton and Fletcher 1932).

The causative bacteria has been given a multitude of names, including *Pseudomonas pseudomallei* (according to the classification of Bergy 1957), *Pfeiferella Whitmori, Pf. pseudomallei, Bacillus Whitmori, Loefflerella Whitmori* and *L. pseudomallei.*

The disease is essentially one of rodents and is transmissible to man and is seen particularly in the region to the east and southeast of India. It is a widespread saprophyte found in soil, ditches and fields. Strauss et al (1969) found the organism in the surface water in Carey Island, off the coast

of Selangor and postulated that the probable source is the underlying soil.

Man is probably infected by ingestion of food contaminated with the excreta of rats (Stanton and Fletcher 1932), by inhalation (Green 1968) or through skin abrasions. Experimentally, the disease has been found to be transmissible by the rat flea, Xenopsylla cheopis, and by the mosquito, Aedes aegypti (Blanc 1941). Direct man-to-man infection has not been reported.

In man, both acute and chronic forms of the disease are recognised, the majority of cases being of the acute variety which is fatal in about 95% of cases (Couture 1935). Occasionally, cases survive the acute stage and go on to a chronic stage which may last from a few months to several years. Rarely benign forms are seen which have very little constitutional symptoms and the patient presents with superficial abscesses (Green 1949). If treated with suitable antibiotics, these cases may respond well (Khaira 1959 and Maegraith 1964).

The case in this report is an example of chronic melioidosis presenting as multiple abscesses in a diabetic. His lesions appear to be responding to appropriate chemotherapy. The case is presented to emphasise the need to consider *Pseudomonas pseudomallei* infection in the differential diagnosis of abscesses.

Case report

A 42-year-old Indian gardener with a two-year history of diabetes mellitus was admitted on the 17th January 1972 to the Klang District Hospital for stabilisation of his condition. He had been hospitalised a month earlier for drainage of a perianal abscess.

Physical examination

There was slight pallor of the conjunctiva. He was afebrile. His blood pressure was 130/80 and pulse rate 72/min. All the peripheral pulses were palpable and there was no atrophy or ulcerations of the skin. The heart and lungs were normal while the liver was palpable one finger breadth below the costal margin.

Investigations: Hb — 11.5 gm.%

Total white cell count — 9,600/mm³

Differential white cell count — neutrophils 76%
lymphocytes 22%
monocytes 2%
eosinophils 0%
basophils 0%

Random blood sugar — 684 mg.%

Blood urea — 52 mg.%

E.C.G. and chest X-ray — normal

Clinical course

The patient was put on a sliding scale of soluble insulin.

Three days after admission, he complained of pain in the right palm. Subsequently, it was found that the distal part of the palm over the third metacarpal bone was inflamed. The patient became febrile. A diagnosis of suppurative tenosynovitis was made and a drainage procedure was done. The patient was put on crystalline penicillin and streptomycin.

In spite of the treatment, the patient continued to have a swinging temperature. A week later, he complained of pain over the left ankle. The posterior part of the foot, inferior to the medial malleolus, was inflamed and a few days later an abscess formed. It was drained and pus sent for bacteriological examination showed growth of *Pseudomonas pseudomallei*. According to the sensitivity reports, the penicillin and streptomycin were discontinued and the patient was put on bactrim.

The fever persisted. A sinus developed over the abscess site. Within the next week, he developed three more abscesses on the dorsum of the same foot. These abscesses were drained and *Pseudomonas pseudomallei* was isolated from all of them. Sinuses formed at these abscess sites. X-ray of the hand and foot showed no bone lesion.

Bactrim was discontinued after one week and tetracycline, 250 mg. six-hourly, was instituted. His fever subsided after two weeks of tetracycline. Repeated bacteriological examination of the sinuses have since then been negative. The sinuses are granulating well. We intend to continue tetracycline therapy until the lesions are fully healed.

Bacteriology

The specimen sent was pus from the abscess in the left ankle. Direct smear showed many gram negative rods. Primary culture was done on blood agar and further sub-cultures were done on glycerine agar and MacConkey plate. Gram staining of isolated colonies showed gram negative rods with clear bi-polar staining giving a "closed safety pin" appearance.

On glycerine agar, the colonies were grey, opaque, with a raised centre and radial striations towards the periphery. The edge was crenated and the surface rough giving it a wrinkled, corrugated appearance. There was a thick surface pellicle on

broth cultures. The strain was actively motile. On blood agar and MacConkey, the colonies had a metallic sheen.

The sensitivity pattern of the strain was as follows:—

Sensitive to bactrim, chloramphenicol, tetracycline and sulphadiazine.

Resistant to methicillin, ampicillin, penicillin G, erythromycin, gentamycin and polymyxin B.

The strain did not ferment glucose, mannitol, dulcitol, inositol, adonitol, salicin, sucrose and lactose. It was also negative for the indole, methyl red and voges-proskauer reactions. However, citrate was utilised. The oxidase reaction was positive. The findings were highly suggestive of *Pseudomonas pseudomallei* and Strauss's reaction was carried out as a confirmatory test. 0.2 ml. of bacterial suspension was injected intraperitoneally into a guinea pig. When examined 48 hours later, there was swelling and inflammation of the testes. *Pseudomonas pseudomallei* was cultured from this swelling.

Discussion

Three interesting features are seen in the case reported. These are that the patient is a diabetic, that he is a gardener and that his lesions are responding well to tetracycline therapy.

The fact that he is a diabetic lends support to the view that melioidosis appears to be more common in persons with debilitating disease. Whitmore's (1912) original cases were mainly in morphine addicts and debilitated beggars. Remington (1962) reported five cases of melioidosis where three of the patients were diabetics, one a chronic nephrotic and the other had cystic disease of the lung associated with pregnancy.

Tarlow (1971) reported a case of melioidosis in a three-year-old boy who had chronic granulomatous disease.

The patient is a gardener and since *Pseudomonas pseudomallei* is known to be a widespread saprophyte of moist soil, it is possible that the mode of infection was through contamination of skin abrasions.

Similar to the cases reported by Khaira (1959), Maegraith (1964) and Tarlow (1971), the patient is responding to chemotherapy. Sensitivity tests showed that the strain isolated from the patient was sensitive to bactrim, chloramphenicol, tetracycline and sulphadiazine. It will be noted that the patient was put on bactrim for a week and since the condition appeared to be getting progressively worse tetracycline was given instead. The response was then favourable.

Summary

An Indian gardener, a diabetic, presented with multiple abscesses in the palm and foot. Bacteriological examination of pus from these abscesses revealed *Pseudomonas pseudomallei* infection. The majority of cases of melioidosis reported in the literature have been of the acute, fatal variety while this patient falls into the smaller group of cases of chronic melioidosis which is amenable to suitable chemotherapy. At the time of writing, the patient appears to be responding very well to tetracycline.

Acknowledgements

We wish to record our thanks to the staff of the bacteriology division of the Institute for Medical Research for technical assistance; Dr. Sia Tuan Hong, physician, District Hospital, Klang, for his advice and Mrs. Nancy See for typing the manuscript.

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OBITUARY

Raymond Lewthwaite,

C.M.G., O.B.E., D.M., F.R.C.P.

DR RAYMOND LEWTHWAITE, a former director of the Institute for Medical Research, Kuala Lumpur, died in London on 20 March 1972 at the age of 77.

Educated at Magdalen College, Oxford, and the Middlesex Hospital Medical School, Dr Lewthwaite came to Malaya in 1926 as a research student in tropical medicine. He was posted to the Institute for Medical Research for work on tropical typhus, an infection which Dr William Fletcher and Dr J. E. Lesslar had identified in their distinctive urban and rural forms shortly before. Fletcher retired from the Malayan service a year later and Lewthwaite took over from him the typhus investigations which were to be his main research interest throughout his career in Southeast Asia.

He was appointed pathologist to the Institute in 1928 and Director in 1941. During this period, assisted by Dr. S. R. Savoor, he made important contributions to knowledge of the epidemiology, pathology, clinical features and zoological background of the typhus fevers of Malaya. He clarified the confusion in nomenclature and identity, showing that the mite-borne forms of typhus known as "rural" or "scrub" typhus and as tsutsugamushi disease are essentially the same, and his painstaking efforts to establish the virus in laboratory animals were a model of patient and rewarding endeavour.

Extending the studies to the urban form of typhus, he isolated the virus from man and from rats and, infecting fleas with the virus, he showed the faeces to be infective — investigations which formed a link in the chain of evidence that flea-borne typhus has a world-wide distribution and that the domestic rat is the reservoir of infection. Twice, in 1934 and 1936, he was commended for research by the Secretary of State for the Colonies and in 1937, his work was recognised by the award of the North Persian Forces Memorial Medal. Admitted in 1939 to membership of the Royal College of Physicians, he became a Fellow of the College in 1948.

He left Malaya under orders from the Administration just before the Japanese forces entered Singapore, taking with him the typhus strains with which, in the Commonwealth serum laboratories of Australia, he was to attempt the preparation of a protective vaccine.

Meanwhile, British workers had produced a vaccine which seemed to hold greater promise. Heavy casualties from typhus had been reported among the Allied troops in Burma and field trials of the new vaccine were imperative. Lewthwaite was recalled from Australia to promote the trials and was attached to the Southeast Asia Command as Field Director of the Medical Research Council Typhus Committee. But the campaign was nearing an end when the first batch of vaccine reached Burma late in 1944 and the trials, hampered by the changes in troop dispositions with the rapid advances of 1945, were inconclusive.

Soon after the cessation of hostilities, he returned to Kuala Lumpur. He re-established the Institute as an effective research organisation and continued in Malaya the British and Allied typhus work of the war period.

His wartime liaison with American workers was soon to bring an unexpected dividend. In 1948, a U.S. Army Medical Research Team was accorded the hospitality of the Institute for clinical trials of Chloromycetin in scrub typhus. Collaborating with Lewthwaite and Savoor, the team treated typhus patients with the new antibiotic and showed that the fever was quickly brought under control — a dramatic demonstration of the first effective remedy. No less successful were the later field trials which established the protective value of the drug among persons exposed to typhus in heavily-infected territory.

He left the Malayan service in 1949 to take up in London the appointment of Director of Colonial Medical Research. In 1961, he became Medical Research Adviser to the Department of Technical Co-Operation, and from 1964 until 1968, he served the Ministry of Overseas Development in a similar capacity. For 12 years, until his retirement in 1971, he was a Council member of the Royal Society of Tropical Medicine and Hygiene.

He continued in this wider field of responsibility to promote the interests of medical research in Malaya and his personal contacts with Malayan workers were not lost; but his former colleagues and their successors will best recall the achievements and attitudes of his earlier years — his fundamental studies on tropical typhus, his confidence in the international approach to the problems of tropical disease, and his inspired guidance and support in the American effort which gave to the peoples of Southeast Asia the first effective remedy for one of their most serious fevers.

J.W.F.

CORRESPONDENCE

The Editor,
Medical Journal of Malaysia.

Dear Sir,

Strokes, Scalds and Monoarticular Arthritis

During the last three years, I have had astonishingly successful results in treating these cases.

STROKES

If mixed vitamins are injected and also given by mouth, rapid improvement takes place. An Indian man, aged 63, was treated within one hour of his stroke occurring. In three days, he was able to walk. After 9 months, he is still walking, though rather feebly. Another even faster case, aged 70, was treated within four hours of his stroke occurring. After a few days he could walk, and he still can walk although the stroke took place nearly two years ago. These are the most dramatic of many cases of stroke treated here.

SCALDS

If scalds are treated immediately after their occurrence with liquid brown honey, they will recover in eight days. The treatment is soothing, effective and inexpensive. No heloids ever ensue.

MONOARTICULAR ARTHRITIS

If his affliction, either traumatic or idiopathic, is treated by giving 600 units of Vitamin E or 2400 mgm of Vitamin C daily, complete recovery can be expected in a matter of weeks or months.

I should be most grateful if a research team would investigate these treatments. I would submit my detailed paper to them. I consider that the matter is urgent because an estimated 100,000 cases of stroke occur in England and Wales annually and 200,000 cases in the U.S.A.

Reid Tweedie,
Sungei Siput, N., Perak.

Book Reviews

HEALTH IN A DEVELOPING COUNTRY.

By R.L. Pulsford and J. Cawte. Jacaranda Press, Milton, Queensland, Australia, 1972.

IRRESPECTIVE OF GEOGRAPHICAL location, the signs and symptoms associated with any disease state are the same. What differs from one region to the next is the epidemiological or ecological context in which the disease manifests, and the socio-cultural response of the community and of its individual members. It has become increasingly recognised that the conventional system of medical education, in which a great deal of, if not total, emphasis is placed on basic and clinical medical sciences with a consequent neglect of the factors that make up the socio-cultural environment in which the doctor will practise, leaves a hiatus in the training of the doctor. The newer medical schools around the world have responded by including in the medical curriculum varying quantities of the social sciences together with some practical field work.

This book by Mr. Pulsford and Professor Cawte is the result of seven years of teaching anthropology and sociology to medical students in the University of Papua New Guinea, and fulfills the local need for a general textbook with a distinctly Melanesian background. Unfortunately the very nature of anthropology and sociology implies that the content is primarily local and undoubtedly each region, be it Melanesian, East African, Spanish-American or Indo-Malaysian, will require a book that provides the local socio-cultural background.

The chapters on "Beliefs" and "Traditional Medicine" are very interesting but somewhat brief. Notwithstanding that each chapter is designed to be a brief statement, it would have been more valuable had the authors chosen to highlight some aspects, possibly even at the expense of excluding other aspects.

As pointed out by the authors, many principles outlined by them apply with equal force to other people faced with transition from agricultural communities to industralisation and urbanisation, and from this point of view "Health in a Developing Country" will prove useful to those who will be practising in developing countries.

PAUL C. Y. CHEN

THE WORK OF WHO, 1971
Official Records of WHO No. 197. pp.402.

THIS IS THE ANNUAL REPORT of the Director-General of WHO, Dr. M. G. Candau for 1971.

Part I gives a general review of the work by subject, opening with communicable and non-communicable diseases. These follows chapters on immunology, environmental health, the organisation of health services, health statistics, family health, education and training, pharmacology and toxicology, and research. Part II deals with the particular problems and developments in each of the six WHO regions, and Part III contains a list of the 1900 WHO-assisted projects throughout the world. Maps and graphs and photographs illustrate various aspects of WHO's activities.

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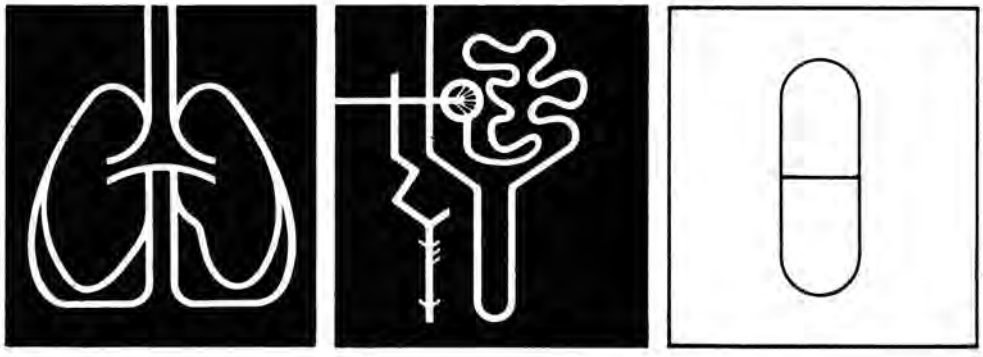
cephalosporin

Ceporex (cephalexin)

the more completely
absorbed oral antibiotic

prompt high concentrations
give better success rates



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Kodak

For more information call

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