Vol XXX No. 3 MARCH 1976

The Medical Journal of Malaysia

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Published by Malaysian Medical Association. M.M.A. House, 124, Jalan Pahang, K.L. 02-14. Editor: Prof. A.A. Sandosham, M.M.A. House, 124, Jalan Pahang, K.L. and printed by Rajiv Printers, 73, Jalan Ampang, Kuala Lumpur.

Editorial

The Institute for Medical Research – Its Diamond Jubilee

A. A. Sandosham

THE OPPORTUNITY was taken on the occasion of the 75th anniversary of the founding of the Institute for Medical Research, Kuala Lumpur in February 1976 to underline its success story.

Dr. G.F. de Witt, the Acting Director of the Institute, at the Opening Ceremony of the Diamond Jubilee Celebrations outlined its history starting with the establishment of the Pathological Institute in 1900, on the recommendation of Sir Frank Swettenham, the then Resident-General of the Federated Malay States. It was to "carry out scientific and sustained research into the causes, treatment and prevention of such scourges as beri-beri and all forms of malaria fevers". The following year, with the construction of the first buildings, the name was changed to the present one.

At the close of the last century, beri-beri was claiming its victims by the thousands and malaria caused great suffering and loss among the labourers engaged in opening up the country for cultivation. The Institute staff got down to work immediately and produced wonderful results. Since then the I.M.R. has tackled a wide variety of medical and health problems including malnutrition, small pox, rabies, drug prophylaxis, scrub typhus, leptospirosis and filariasis to mention only a few.

From the very beginning the Institute has adopted an open door policy providing every opportunity for scientific workers from abroad to undertake collaborative research. Over the years the Institute's research activities have been broadened through its association with the British Medical Research Council, the U.S. Army Medical Research Command, U.S. Public Health Research Unit, the University of California International Centre for Medical Research, SEAMEO-Tropical Medicine Project, etc.

The Institute suffered a temporary set back with the departure on Malayanisation of a large number of expatriate research staff with Independence. However, the I.M.R. managed to survive and soon began to improve on its former record. The Institute's main functions have been to carry out research into local medical problems, provide diagnostic laboratory facilities and produce vaccines. With the appointment of Dr. Ungku Omar-Ahmad as director there was a change in policy to meet national needs resulting in the running of a three-year course for medical laboratory technologists and a one-year course for junior laboratory assistants. Greater emphasis was laid on rural health research and the training of staff for post-graduate qualifications abroad. The Institute became recognized as the National Centre for Tropical Medicine under the South East Asian Ministers of Education Organisation (SEAMEO) and undertook a six month course leading to the Diploma in Applied Parasitology and Entomology (D.A.P. & E.). Many senior members of the I.M.R. staff have became obligated to undertake other teaching duties at the University of Malaya, Universiti Kebangsaan, the Public Health Institute, the School of Nursing and at other SEAMEO-TROPMED Centres in Jakarta, Bangkok and Manila.

The late Tun Abdul Razak envisaged the future of the I.M.R. in his address to the Malaysian Society of Parasitology and Tropical Medicine in 1973. He said, "Indulging in a little crystal gazing it appears to me that the area bounded by Jalan Pahang, Jalan Raja Muda and Jalan Pekeliling will become one of the finest medical centres in South East Asia for medical research and teaching and training of medical and para-medical scientists".

The medical profession, represented by the Malaysian Medical Association, has the keenest interest in the future of the Institute for Medical Research. If research is given its rightful place in its development plan and the staff is not allowed to be swamped by the urgent needs of the country to provide training for technicians and others, diagnostic routine, vaccine production, etc. then all augurs well for the future of I.M.R. and the M.M.A. wishes it every success.

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Human Placental Lactogen – Physiological Role in Pregnancy

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HUMAN PLACENTAL LACTOGEN (HPL) is a polypeptide hormone of molecular weight 19,000. It is produced by the syncytiotrophoblast of the placenta (Josimovich and Atwood, 1964; Josimovich et al, 1969; Sciarra et al, 1963). It is secreted mainly into the maternal circulation, into the intervillous space and maternal blood pool and to a lesser extent into the fetal compartment (Josimovich, 1968; Josimovich and Atwood, 1964; Kaplan and Grumbach, 1965). Very little therefore reaches the fetal compartment. It is believed therefore that the effect of HPL is mainly on the maternal organism and not on the fetus.

HPL Trends in Pregnancy

HPL has been detected as early as six weeks pregnancy using radioimmunoassay methods (Hart, 1971). From six weeks to 36 weeks of gestation, there is a steady rise in HPL values, this rise being parallel to the placental growth curve (Josimovich, 1969). From 36 weeks to 40 weeks, placental growth continues to increase while a plateau in mean HPL values occurs. Following delivery, the hormone is cleared rapidly from the maternal circulation; its half-life being about 20 minutes (Hart, 1971).

Control of HPL Secretion

Investigators have shown that HPL levels have no relationship to maternal age and parity, maternal activity, fetal sex, fetal abnormality, diurnal status, or to use of oestrogens and progestogens in pregnancy.

(i) **Placental Mass**

There appears to be a significant correlation between active placental mass and HPL levels before 36 weeks of gestation (Josimovich et al, 1969). Investigations indicate that HPL secretion does not determine placental size but rather that placental size seems to determine the amount of HPL produced during pregnancy.

(ii) **Fetal Weight**

A lower but statistically significant correlation exists between HPL mean values and fetal weight. High HPL values are expected to be seen with multiple pregnancies (Spellacy, 1973; Spellacy et al, 1971).

(iii) **Maternal Blood Glucose Levels**

Since HPL resembles the human growth hormone in some of its biological effects, it was thought that variations in maternal blood glucose levels might affect HPL secretion. Samaan et al (1966) showed that no relationship between HPL secretion and maternal blood glucose levels exists and Spellacy et al (1971) pointed out that any change in HPL secretion in this respect was small.

(iv) **Fetal Glucose Levels**

Dawes (1968) raised the possibility of fetal glucose alterations affecting HPL secretion. No data is available, presently, on this aspect of HPL control.

Biological Effects of HPL in Pregnancy

The physiological role of HPL is not yet clearly understood. That its biological effects have not been finally determined can be judged by its varied terminology. The hormone has been referred to

as Chorionic Growth-hormone – Prolaction (CGP) (Sciarra et al, 1963), Human Chorionic somatomammotropin (HCS) (Li et al, 1968), and purified placental protein.

(i) **Lactogenic Role**
This has been suggested because HPL has pronounced lactogenic effects on experimental lower animals (Josimovich and MacLaren, 1962). In pigeon crop assays, the hormone is 30 per cent as active as pituitary prolactin.

In mice, HPL accelerates casein synthesis in mammary tissue. It is logical therefore to suggest a possible role of HPL in the preparation of the breasts for early lactation.

(ii) **Growth-hormone-like Effects**
One cannot ignore this fact that HPL levels in maternal blood at term are 100 times over what human growth hormone levels ever reach (Kaplan and Grumbach, 1964). HPL has been shown to potentiate the actions of growth hormone (Josimovich and Atwood, 1964); and like growth hormone, HPL promotes nitrogen retention, increased mobilisation of free fatty acids, potassium retention and decreased glucose tolerance. It is likely that HPL has an important influence on fetal growth.

(iii) **Glucose-sparing for Fetal needs**
HPL brings about decreased maternal glucose tolerance by increasing maternal resistance to endogeneous insulin; and this metabolic change spares glucose for fetal needs at the time of its greatest growth (Spellacy and Goetz, 1963). This glucose-sparing action is supplemented by increased insulinase activity in the placenta and maternal liver during pregnancy, and also by the increased levels of blood oestrogen and progesterone in pregnancy (Spellacy et al, 1968). How important this effect is still remains to be seen.

(iv) **Promotion of Steroidogenesis**
A fundamental role of HPL is in the promotion of steroidogenesis in the pregnant mother (Josimovich, 1968; Josimovich et al, 1963). This is because HPL helps human chorionic gonadotrophin in maintaining a balanced production of progesterone and oestrogen. In addition, HPL has a limited luteotrophic effect of its own. It is also said to aid the maintenance of the decidual changes in pregnancy.

(v) **Erythropoietic Role**
HPL has been shown to augment the action of erythropoietin on erythropoiesis in mice (Jepson and Friesen, 1968). For this action of HPL, endogeneous production of erythropoeitin is essential. This is because HPL does not stimulate production of erythropoietin.

The importance of this observation would be in the erythropoietic capacity of this hormone to enhance the acceleration of erythropoiesis during pregnancy.

(vi) **Aldosterone Production**
An increase in aldosterone production by the adrenal cortex has been associated with the experimental use of highly purified HPL in human beings (Melby et al, 1966). HPL induced an average increment of 30 per cent in aldosterone secretion on normal sodium intake and it is possible that the hypersecretion of aldosterone in pregnancy results from this stimulation.

(vii) **Diabetogenic Activity**
Just as the other diabetogenic agents, HPL might be responsible for exacerbation of diabetes in pregnancy (Lancet-leading article, 1969). This is because this hormone, when administered to stable diabetics, increases glycosuria and fasting blood sugar levels and further impairs glucose tolerance (Samaan et al, 1968).

Conclusion

The important functions of HPL probably centres around the preparation for lactation, the sparing of glucose for fetal needs and the promotion of steroidogenesis. Which of these functions is the primary role of HPL remains to be determined. Nevertheless though the physiological role is still uncertain, because of its diverse biological effects, HPL must play some important role in the feto-maternal physiology of pregnancy.

Acknowledgements

The author thanks Professor T.A. Sinnathuray for encouragement and Miss Magasvari for secretarial assistance.

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Thrombo-Embolism in Pregnancy

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IT IS GENERALLY believed and taught that venous thrombosis and thrombo-embolism is uncommon among Asians (Hwang 1968, Tinckler 1964, Srivastava 1964). Few cases of puerperal thrombo-embolism have been described among Asians.

We present the clinical histories of 4 cases of puerperal thrombo-embolism as seen in the Obstetric Unit of the University Hospital, Kuala Lumpur.

Case Histories:

I. Patient, S.T. was a 36 year old Indian Gravida 3 Para 3 who had a normal delivery at term after oxytocic induction of labour in September 1973. She had a mild toxaemia of pregnancy and was not anaemic. On the 3rd post-partum day, she had a tubal ligation done under lumbar epidural block (using 0.05% lignocaine with adrenaline). She had stilboesterol for suppression of breast milk. There was no past history of significance.

At about 0300 hours on the 4th post-partum day, she had a fainting spell while walking towards the nurses' station to request for a vulval pad. She recovered but became apnoeic and pulseless soon afterwards. Cardiac massage and artificial ventilation were performed but in spite of further resuscitation measures, she was pronounced dead at 0750 hours. Her clinical presentation and electrocardiographic changes suggested the probable cause of death as acute massive pulmonary embolism.

No post-mortem was performed.

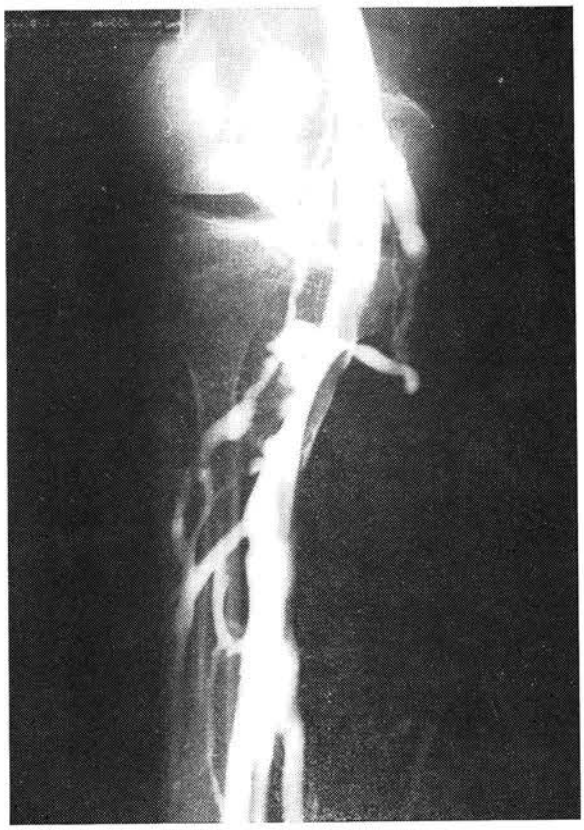
II. Patient, K.C.H., was a 29 year old Chinese primigravida who booked with us at 37 weeks of gestation. She was found to be well except for marked varicose veins on both legs. There was no past history of significance. Her father and elder sister had had marked varicose veins. Her younger brother had been admitted and treated for deep vein thrombosis in the University Hospital. She had a normal delivery of a baby of 3220 gm. on 4.12.1974 after a labour of 16 hours.

Her post-partum period was uneventful until the 4th day when she was observed to have pitting oedema of the left leg. The circumference of the leg at mid-calf was greater than that of the right by 2 cm. There was no tenderness of the calf muscles and Homan's sign was negative. She had slight discomfort in the left groin.

A thrombosed superficial vein was palpable on the medial aspect of the right leg. (See photograph) There was some redness, increased warmth and tenderness on palpation. A diagnosis of deep vein thrombosis of the left leg and superficial thrombophleblitis of the right leg was made. A venogram showed filling defects in the left ilio-femoral veins extending almost up to the common iliac vein.

An emergency thrombectomy was performed. Post-operatively, the patient was put on intravenous heparin and sodium warfarin. She made an uneventful recovery and was discharged 25 days later with maintenance dose of warfarin daily. Extensive haematological studies were performed but did not show evidence of hypercoagulation defect.

III. S. bte D., a 26 year old Malay rubber tapper, was booked early at 11 weeks of gestation. She



Venogram showing filling defect in Politeal Vein (R) Leg of Patient K.C.H.

had a bad obstetric history with only one full term delivery followed by 4 abortions at 3 to 6 months gestation. No cause could be found for her habitual abortion. There was no other past history of significance. She was started on 17 α-hydroxy progesterone caproate 250 mgm. by intramuscular injections twice a week. She progressed well in her pregnancy until the 30.12.1975, when at 14 weeks of gestation, she was admitted with fever and right calf pain and swelling of 5 days duration. She was found to have a swollen right calf with oedema. Homan's sign was negative. The right calf felt warmer than the left. A provisional diagnosis of deep vein thrombosis was made. An emergency venogram showed deep vein thrombosis of the right calf, irregularity of the deep veins of the left calf suggestive of previous deep vein thrombosis followed by re-canalization. The deep veins of both thighs were not affected. She was immediately started on intravenous heparin and sodium warfarin. Prothrombin time was maintained at 30 percent of normal. She was kept in the ward for a month. Three days after discharge she started to abort. This was completed with evacuation of the uterus with minimal bleeding. Pathological report did not indicate an accidental haemorrhage.

IV. A d/o F., a 23 year old Indian Gravida 2 Para 1 was admitted on 5.5.1975 at 37 weeks of gestation for severe pre-eclamptic toxaemia. She was heavily sedated and induced. Labour lasted 16 hours and she delivered a baby of 2270 gm.

On her first post-partum day she was found to have a low haemoglobin of 7 grams/100 ml. She had total dose infusion of Imferon (R). On the fourth post-partum day, she was found to be febrile with tenderness of the right calf. The right calf was swollen, slightly warm with positive Homan's sign. There was no abnormality of the thigh. She was clinically suspected to have deep vein thrombosis and a venogram confirmed the diagnosis. The femoral and iliac veins were not involved.

She was heparinised. Her prothombin time was kept well controlled. However, on the tenth day, she developed deep vein thrombosis of the left calf. Symptoms and signs referral to both legs subsided after a week of continual anti-coagulant therapy. She was discharged after a month stay in hospital.

Discussion:

It is well recognised that pregnancy and puerperium predispose to venous thrombosis and embolism. Several factors are involved. Infection especially at the time of delivery can spread to the lateral pelvic walls leading to thrombosis of pelvic vessels. Stasis of blood occurs because of poor venous return from the foot and calf muscles. This effect becomes more apparent if patients need prolonged bedrest in the antenatal period and in puerperium because of some complications, for example, toxaemia of pregnancy.

An important factor is the changes seen in the constituents of the blood. The plasma concentration of fibrinogen has been shown to be increased during pregnancy from about 250 mgm/100 ml. in the non-pregnant state to 400 – 500 mgm/100 ml. at term. The concentrations of Factors VII, VIII, IX and X are all raised considerably above non-pregnant levels. Changes in the platelets are uncertain but the balance of evidence suggests that platelet count is somewhat lower in pregnancy but seem to be increased after delivery. Shaper et al (1968) found no change in platelet adhesiveness.

It is generally believed that there is some decrease in fibrinolytic activity in pregnancy and puerperium. There seems to be a decrease in

Table I

Clinical Features of Patients

Patients	Race	Age	Parity	Family History	Delivery	Hormones
1. S.T.	Indian	36	3		Normal	Stilboesterol in puerperium
2. K.C.H.	Chinese	29	1	Brother has D.V.T.	Normal	—
3. S. bte D.	Malay	26	6		Antenatal	"Prolution" for threatened abortion
4 A d/o P.	Indian	23	2		Normal	Stilboesterol in puerperium

level of available circulating plasminogen activator in the latter part of a normal pregnancy. Also, the levels of two protease inhibitors, namely α_1 anti-trypsin and α_2 macro-globulin are considerably raised in pregnancy plasma. There seems to be only minimal increase in plasma plasminogen in late pregnancy. All these changes in blood constituents suggest a "hypercoagulation" state in pregnancy. But the likely effects are difficult to predict though it must contribute in some degree to the higher incidences of venous thrombosis and thrombo-embolism in pregnancy.

A factor of some importance is the administration of oestrogens for suppression of lactation in puerperium. Daniel et al (1967) noted that the incidence of puerperal venous thrombosis was increased 10 fold in mothers of more than 25 years whose lactation were suppressed with oestrogens. Daniel (1968) later showed that the level of factor IX in the blood is raised following administration of high doses of oestrogen.

Deep vein thrombosis is not common during pregnancy, though it is commoner in puerperium. The incidences of antepartum deep vein thrombosis and puerperal venous thrombosis have been quoted as 0.086 percent and 0.27 percent respectively of all deliveries in the United States (Husni 1967). Deep vein thrombosis can lead to pulmonary embolism which has recently become the second most common cause of maternal mortality in England and Wales (Report of Confidential Inquiry Maternal Mortality). There were 352 maternal deaths due to pulmonary embolism in England and Wales over a period from 1958 to 1966. 263 of such deaths occurred in the post-partum period (1 death per 28,000 deliveries) and 89 deaths occurred in the ante-partum period.

Venous thrombosis and pulmonary embolism are uncommon in Malaysia. Hwang (1968) found only 29 cases of pulmonary embolism in over 36,000 consecutive necropsies in Singapore from 1952 – 1966. The incidence seems greater among females and Indians. Of these 29 cases, only one could be attributable to puerperal thrombo-embolism. He also noted that over a five years period (1962-1966), there were 52,861 major operations in the Singapore General Hospital. Among these patients there were only 5 cases of pulmonary embolism giving a very low incidence of 0.094 per 1000 operations. The comparable incidence is 0.14 per 100 operations in the United States (De Bakey 1964).

Using more sensitive methods, Cunningham and Yong (1974) showed that post-operative deep vein thrombosis in Malaysia is not oncommon as was once thought. They used the 125 I-labelled fibrinogen uptake test in 68 post-operative patients. They found unequivocal evidence of deep vein thrombosis of the leg in 8 patients in the first post-operative week producing an incidence of 12 percent. This incidence is still much less than similar series in the Western World when incidences varied from 15 percent (Bonnar and Welsh 1972) to 33 percent (Kakkar et al 1970).

The four patients whose clinical histories have been presented were all seen over a period of 2 years. During the same period of time there were 8,000 deliveries, in the University Hospital giving an incidence of 1 in 2,000 deliveries. It is highly possible that this may be only a fraction of the true incidence of deep vein thrombosis in puerperal patients. This can probably best be assessed if a study using 125 I-labelled fibrinogen can be made on normal puerperal patients.

Clinical diagnosis at best can only detect the late and obvious case. But clinical signs should not be disregarded. Pain over the legs is a very useful symptom. Tenderness, swelling and increased warmth over the affected lower limb are the best clinical signs (Hall and Clark 1971); these signs were apparent in all the 3 patients with deep vein thrombosis (See Table II). In the absence of better diagnostic techniques, clinical signs continue to be important. If the condition is continually kept in mind and clinical signs sought for diligently, earlier diagnosis is possible.

Summary:

Clinical histories of four cases of thromboembolism are presented. A brief discussion of pathogenesis and incidence in Malaysia is made. It is hoped that clinical signs suggestive of deep vein thrombosis should not be dismissed too lightly.

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Table II

Clinical Features of Patients

Patients	Onset of Symptoms	Pain	Fever	Swelling of Limb	Warmth of Limb	Homan's Sign	Local Tenderness	Site of Thrombosis	Investigations	
									Hb. gm. %	Blood Group
1. S.T.	4th day Puerperium	–	–	–	–	–	–	Not Known	12	A
2. K.C.H.	4th day Puerperium	+	–	+	+	–	+	Left Ilio-femoral	11	A
3. S. bte D.	Antenatal	+	+	+	+	–	±	Deep Veins Right Calf	11.2	AB
4. A. d/o P.	4th day Puerperium	+	+	+	+	+	+	Deep Veins Both Calves	7	O

Current Status of Oral Contraceptive

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WHEN ORAL CONTRACEPTIVE was first introduced in 1956, there was considerable sceptism about the potential for widespread usefulness of this new family planning innovation. Since then there has been a slow but steady increase in number of users so that by 1975, approximately 50 million women were on it. This increase was influenced to a great extent by numerous reports of the side effects of the oral contraceptive in medical journals and in mass media. The latter contributed in no small way to the adverse publicity on the taking of the Pill. Oral contraceptives have raised numerous problems in family planning but over the years, there have been great attempts to minimize them.

The original Pill was a "combined" type, consisting of oestrogens and progestogens given together over a period of 3 weeks out of every four. These initial tablets contained 10 mgm. of norethynodrel and up to 230 ugm. of mestranol. These were associated with a very high incidences of side effects including nausea, vomiting, headaches, weight gain, breakthrough bleeding, amenorrhoea, anxiety, changes in libido and other less common manifestations. In general, it was found that these side effects tended to last for a few cycles but because they determine the acceptability of the drug, much attention was paid to them. Some of these side effects were diminished by lowering the dose of oestrogens and progestogens in the combined pill. Sometimes, these side effects could be diminished by altering the type of oral contraceptive for a particular patient. Some workers developed theories covering the mixture of oestrogen and progestogens that is suitable for particular patients (Dickey and Dorr 1969). A variation of prescription of oral contraceptives was introduced using oestrogen alone for the first few weeks of a cycle to inhibit ovulation, followed by a week of oestrogen-progestogen combination (the serial or squential pills). This was considered more physiological with a closer simulation of the changes in endogenous hormones during a menstrual cycle. It was soon demonstrated that sequential contraception was similarly effective but though not quite to the same degree as the combined Pill. They however contain higher amounts of oestrogens over each cycle.

Major Side Effects:

By the late 1960's, it became evident that there were certain serious side effects associated with the oral contraceptives. By 1968, Vessey and Doll implicated the oral contraceptive as a causative factor of the increased incidence of venous thrombosis and thrombo-embolism among patients on the Pill. It seemed that the oestrogenic rather than the progestogenic component was responsible and the incidence of venous thrombosis was greater with oral contraceptives containing more than 50 ugm. of oestrogens (Inman et al 1970).

Steriod hormones have a marked influence on liver function (Kappas 1968). Large dose of steriod seem to induce cholestasis and hepatocellular damage but low dose seemed to have minimal effects. These changes in liver function seemed to be of no consequence to a healthy woman but they contribute to a case of not prescribing oral contraceptive to patients with recent hepatic dysfunction.

*Lecture given to Post-graduate Seminars in Seremban, Alor Star, Penang, and Ipoh.

Impared glucose tolerance were found by investigators as early as 1964 (Gershberg et al). Both combined and sequential pills could produce disturbances in carbohydrate metabolism and these side effects seemed to be related to the oestrogen dose (Spellacy 1969). These abnormal changes seemed to disappear with discontinuation of the oral contraceptive. Whether these changes are related to development of chemical diabetes is still unknown.

Lipid metabolism was shown to be disturbed by oral contraceptive (Wynn et al 1966 and Gershberg 1968). There seemed to be an increased mean serum levels of triglycerides, low density and very low density lipoproteins and a smaller increase in cholesterol in oral contraceptive users. These rise in triglycerides seem to be greater with increased oestrogen content in the Pill. The cholesterol rise seemed to be correlated with the progestogen content. These values seem to return to normal with discontinuation of the oral contraceptive though Wynn and Doar (1969) warned that the potential reversibility may not be maintained after prolonged usage of the Pill.

Minipills:

One development of oral contraception was the introduction of the "micro-dose" progestogen alone method. The thought was that minute doses of progestogens alone might provide contraception with no necessity for oestrogens. Studies were made on numerous progestogenic compounds and it became obvious that the progestogens achieved their effect by alteration of the cervical mucus so that sperms do not penetrate and of the endometrium so that implantation becomes impossible. The "micro-dose" pills were shown to provide effective contraception, although not in the same range as the combined oral contraceptive. One of these was chlormadinone acetate which was once withdrawn because they produce mammary lesions in beagle dogs, though relevance of this to human toxicity is debatable. There has been recent reports (Bonnar 1974, Hawkins 1974) that the minipill may not protect against ectopic pregnancy.

Once a Month Pill:

To solve the problem of regular taking of the Pill, the "once a month" pill was investigated. This pill is a combination of an long acting oestrogen, quinestrol, and a relatively shorter acting progestogen, quingestanol acetate. This has been proved effective and useful in substantial studies in Latin America (Rubio et al 1972). Unfortunately, there was a high incidence of breakthrough bleeding and cycle irregularity thereby limiting its acceptability. Efficiency was also not as good as combined pills.

Post-coital Contraception:

In the search for an effective antifertility agent, Morris and Van Wagener (1966) studied effects of oestrogens on inhibition of ovum implantation in rabbits and rhesus monkeys. They concluded that certain oestrogens given post-coitally prevented implantation of the ovum in primates. The present "morning after" pill consists of prescription of large doses of stilboesterol after coitus. The impression is that the method is effective (Haspels 1970, Kuchera 1971). There is, however, need for additional and more detail data, particularly about users' fertility and age. The majority of women in these studies were young college students, a number of them possibly still in the low fertility range. At present there is no positive evidence that the restricted post-coital use of diethyl stilboesterol carries a significant carcinogenic risk to either mother or foetus. However, a statistical association has been demonstrated between di-ethyl stilboesterol taken by women later in pregnancy to prevent spontaneous abortion and the appearance of adenocarcinoma of the vagina or cervix in their daughters at an early age. (Herbst et al 1971, Greenwald et al 1972). The possibility of teratogenic and other adverse effects on the foetus with very early administration of di-ethyl stilboesterol warrants further investigation. Until these investigations are complete, voluntary termination of pregnancy should be carefully considered when pregnancy occurs in spite of the use of di-ethyl stilboesterol.

Royal College of General Practitioners' Report:

Recently, there have been a number of large scale epidemiological studies on the effects of oral contraceptives. Among these was a long term prospective study launched in 1968 by the Royal College of General Practitioners' of Great Britain. It was a controlled investigation of the natural history of a large group of women (initially 46,000) half of whom had chosen the Pill as a contraceptive. The interim report (1974) sheds further light on the side effects of oral contraceptives. Deep vein-thrombosis of the leg was found to occur 5.6 times more often in Pill users than in controls, while no difference was reported between former users and controls (See Fig. 1). A related condition, superficial thrombosis of the leg occurred 48 percent more frequently among Pill users than among controls. The investigators found an apparent dose relationship of deep vein thrombosis to oestrogen with higher incidence rates for higher oestrogen doses (Fig. 2).

No apparent relationship to progestogen dosage or duration of Pill use was apparent. There was an increase incidence with increasing age and a possibly similar relationship to parity. The investi-

Fig. 1

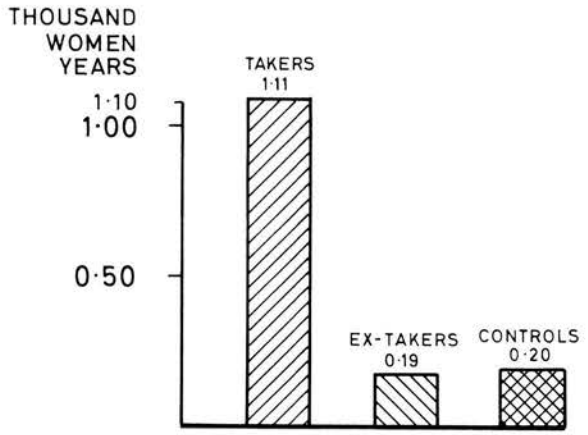

Fig. 1

Comparison of incidences of deep vein thrombosis in oral contraceptive users and non users (rate per 1,000 women per year)

Fig. 2

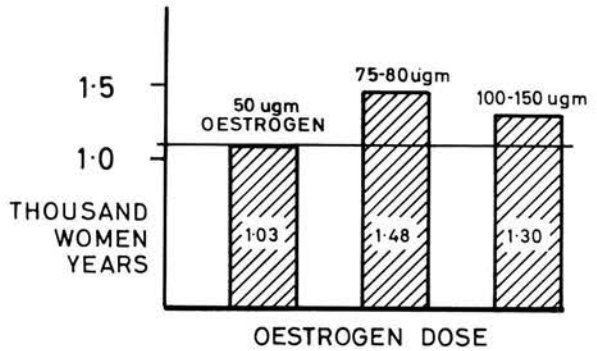

Fig. 2

Comparison of incidences of venous thrombosis in relation to oestrogen dose (ratio to low dose 50 ugm. oestrogen)

gations estimated that Pills with high oestrogen dosages were responsible for 112 cases of deep vein thrombosis per 100,000 women per year. This was much higher than 81 cases of deep vein thrombosis per 100,000 women per year seen with the oral contraceptive containing 50 ugm. of oestrogen per pill. This seems to confirm the findings of the Committee of Safety of Drugs in the United Kingdom (Inman et al 1970).

The study also showed that there is no correlation with cancers of the cervix and breast. In fact, it showed that Pill users of more than 2 years seems to be apparently protected from benign growths of the breasts. This slight reduction in breast disease in women using oral contraceptives raise the hope that use of this method by young women may eventually have some protective effect later against breast disease. (See Fig. 3)

Fig. 3

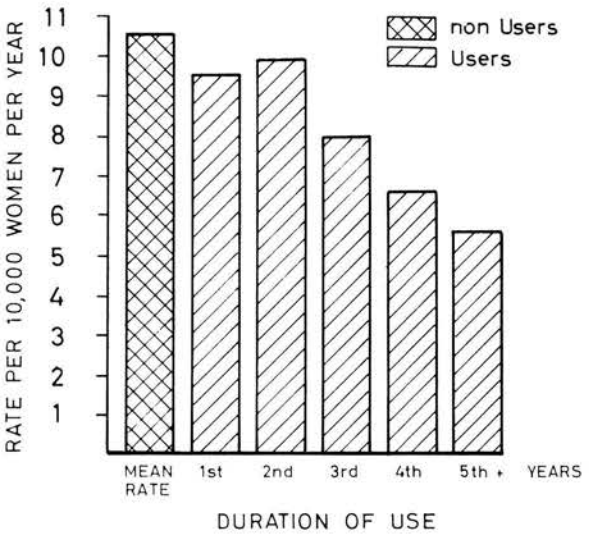

Fig. 3

Comparison of incidence of benign breast neoplasia in oral contraceptive users and non users by duration of use. (Rate per 1,000 women per year)

Hypertension seemed to be more commoner with increased duration of Pill usage so that by the fifth years, the incidence was 5 times that of the first year. These seemed to be a relationship between incidence of hypertension and progestogen dosage with the highest rates observed for women using pills with more than 3 mgm. of progestogens. Age definitely correlated with the development of hypertension in Pill users.

Pill users showed much higher incidence rates for coronary artery disease than controls but the numbers involved were too small for the difference to be statistically significant. This is because heart disease is extremely rare in young women. Pill users seemed to have more than 4 times the risk of developing cerebro-vascular disease of all forms than did non users.

A relationship was found between Pill use and these disease involving circulation in small blood vessels, namely, Raynaud's syndrome, chilbains and spontaneous bruising.

There seemed to be no increased incidence of psychosis among Pill users. There were more patients on Pills complaining of change in libido but it was thought that there were many reasons and opportunities to do so which were not related to the pharmacological action of the drug.

An increased incidence of gall bladder disease and gallstones among Pill users was also observed in this study. Although, the number of cases was not large enough for statistical differences, investigators felt that this was a definitive side effect of Pill. Also, a relationship to progestogen dosage was found, with increasing incidence of gall bladder disease accompanying increased progestogen dosage.

Urinary tract infectious were reported 20-50 percent more often in Pill users. The infection rate increased with increased oestrogen dosage. Increased sexual activity of pill users may be an important factor in this relationship.

Pill users had higher incidence rates for various vaginal infections, which are associated with sexual activity. Cervicitis seemed to be more common with increased progestogen dosage and with prolonged usage.

Post Pill Amenorrhoea and Infertility:

There are no satisfactory data on the prevalence of anovulatory menstrual cycles in healthy woman. Resumption of ovulation after discontinuation of oral contraceptives usually occur within 4 to 8 weeks. In a few women there is persistence of amenorrhoea and/or anovulation for 6 months or more. The estimated incidence is about 1 percent (Larson-Cohn 1969, Shearman 1971). It occurs with both the combined and sequential regime. It is commonly accompanied by galactorrhoea suggesting a hypothalamic effect. It seems to occur more commonly with women who have irregular menstrual cycles originally. There is no evidence that this is related to longer use of oral contraceptive. There is no scientific evidence that stopping the pill after 2 years will materially effect the incidence of anovulation.

Present studies undoubtedly indicate a delay of about 3 months in conception in women who have used the pills. In spite of the delay, it must be emphasised that almost 90 percent of previously pregnant cases conceived by the end of two years.

Biochemical Developments:

In the search for an effective, acceptable contraceptive with minimal metabolic effect, investigations of the biochemical effect of the Pill were instituted. It became apparent that ethinyl oestradiol seems to be more potent than a comparative dose of mestranol (3 methylether of ethinyl oestradiol). There is now sufficient evidence that mestranol is de-methylated to ethinyl oestradiol in the liver. This conversion seems to be interfered with by many progestogens as shown in vitro data (Kappus et al 1972), raising the question of invivo hepatic conversions of mestranol of various oral contraceptives. From this, it would seem prudent to avoid mestranol in favour of ethinyl oestradiol as the oestrogenic component of the pill.

Recent studies of the progesterone receptors seemed to show that a similar problem occurs with the progestogens. Nor-ethisterone acetate, ethynodiol di-acetate, norethynodiol and lynesterol all have to be metabolised in the liver to norethisterone before they can exert their biological effects.

These conversions could be affected by a number of exogenous and endogenous factors. Several drugs have already known to reduce contraceptive efficacy (Mumford 1974). Rifampicin, an anti-tuberculosis drug, is known to cause a high incidence of menstrual disorders in women on oral contraceptives and appears to affect the effectiveness of the pills (Reimers et al 1973). It is suggested that oestrogen breakdown is speeded up by Rifampicin. Other drugs that may interfer with the efficacy of oral contraceptive are ampicillin and barbiturates. These findings suggest interactions with other drugs may affect the efficacy of oral contraceptive adversely.

Low-dose Method:

It was natural that as some side effects of the Pill were dose related to the hormones in the Pill that attempts were made to reduce the dosages further. Other than a high incidence of breakthrough bleeding, good results were obtained from field trials of the low dose Pills (Woutersz 1974, Allen 1974, Brosens et al 1974, Moggia et al 1974, Wong & Puvan 1975). It also became obvious that the low-dose ethinyl oestradiol-norgesterol. combination seemed to have added advantages. Brigg (1974) showed that abnormal hepatic functions induced by oral contraception seemed to be less severe when the oral contraceptive used was the low dosage ethinyl-oestradiol norgesterol combination. Carbohydrate metabolism, as reflected by glucose tolerance, insulin secretion and blood pyruvate levels were little disturbed when low dose

ethinyl oestradiol-norgesterol was used as compared with other oral contraceptives (Wynn et al 1974). Serum lipid levels also seemed to be less disturbed (Wynn et al 1974). There is a great possibility that the minimal hepatic dysfunction and minimal disturbances of carbohydrate and fat metabolism could mean, in the long run, less side effects and that disturbances in weight and hypertension may not occur. If this was true, and field trials already suggest this may be so, then, we may be on the threshold of developing the ideal oral contraceptive.

Summary:

There have been considerable advance in oral contraception in recent years. Much of these have great relevance to a better prescription and management of patients on the Pills. The general impression is that with careful patient selection and careful medical supervision, oral contraceptive is and will continue to provide an excellent form of contraceptive with minimal side effects and metabolic disturbance.

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Medical Certification of Cause of Death in Peninsular Malaysia

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THE VALUE OF mortality statistics is not always as apparent to doctors dealing with individual clinical problems as to workers in medical research and public health. Evidence concerning the distribution and trend of many diseases provide an indication of the character and relative importance of various medical problems encountered in medical practice. Much of the usefulness of mortality statistics depends on medical certification of cause of death.

Death registration in Peninsular Malaysia is provided for by the Births and Deaths Registration Ordinance, 1957 (Malaya, 1957). This Ordinance mandates that "Every registered medical practitioner, upon the death of any person who has during his last illness been attended by such medical practitioner, shall sign and deliver within twelve hours of the death to one of the persons required by this Ordinance to furnish particulars of the death or to the Registrar a certificate in the prescribed form". (Section 22(1)). In the event that no doctor has been in attendance, the cause of death is ascertained and recorded by the registrar, who is usually a police officer or the village headman. In some local authority areas, special personnel with some medical training are appointed as inspectors to certify deaths for which no medical certification is available. The number and percentages of these three types of registration in Peninsular Malaysia in 1972 is shown in Table 1.

The proportion of medically certified deaths is low compared to that in Singapore and England and Wales (Table 2). This percentage should improve with time if concomitant with improvement in

Table 1
Number and Percentage of Deaths by Type of Certification, Peninsular Malaysia, 1972

Type of certification	Deaths	
	Number	Percentage
Medically certified	20,140	31.7
Inspected*	2,135	3.4
Uncertified	41,247	64.9
Total	63,522	100.0

*Inspected by personnel with some medical training
Source: Vital Statistics, West Malaysia, 1972, Table 51.00

Table 2
Number and Percentage of Medically Certified Deaths, England and Wales, Peninsular Malaysia and Singapore, 1972

Country	Total deaths	Medically certified deaths	
		Number	Percentage
England and Wales	591,889	591,354*	99.9
Peninsular Malaysia	63,522	20,140	31.7
Singapore	11,522	9,670*	83.9

*Includes coroners' cases
Sources: The Registrar General's Statistical Review of England and Wales for the Year 1972, Part I, Tables, Medical, Appendix H5.
Vital Statistics, West Malaysia, 1972, Table 51.00
Report on the Registration of Births and Deaths and Marriages, 1973, Republic of Singapore, p. 12.

public education, availability and utilization of health services, a more favourable distribution of doctors, and perhaps a restructuring of the registration system. These considerations are too extensive for discussion within the scope of this paper.

In anticipation of such improvements it is appropriate at this point in time to examine the present practice in medical certification of cause of death in so far as it affects the accuracy of the information that is collected and published. Such knowledge will be useful in the planning of any future improvements of the system. The objective of this paper is to examine the portion of deaths that are medically certified with respect to accuracy, in particular by identifying the points where errors can arise.

In the process of contributing to statistics on cause of death, the doctor becomes involved in two critical steps: 1) making the diagnosis and 2) certifying the cause of death.

1) **Making the diagnosis**

The fact that a cause of death is certified by a doctor does not necessarily mean that it will be accurate, particularly if the diagnosis is based solely on clinical evidence of uncertain quality that could be enhanced by post-mortem examination. Heasman and Lipworth (1966) demonstrated the frequent lack of agreement between clinical and post-mortem diagnosis. Some idea as to the quality of certification diagnosis can be obtained by looking at the proportion of deaths allocated to the category reserved for ill-defined conditions, namely, B45 – "symptoms and ill-defined conditions" (WHO, 1967). Table 3 gives the number and percentage of deaths classified to this cause group among medically certified deaths for the same countries as shown in Table 2. It must be remembered that this proportion could have been inflated by varying degrees due to failure to report the underlying cause of death as the cause of death even when it is known, or by mistake in the selection from multiple entries during coding.

2) **Certifying the Cause of Death**

For international comparability, rules for selection of cause of death have been promulgated for primary mortality tabulation. They are based on the concept of an underlying cause of death which is defined as "(a) the disease or injury which initiated the train of events leading directly to death, or (b) the circumstances of the accident or violence which produced the fatal injury" (WHO, 1967).

Table 3
Number and Percentage of Deaths Classified to Cause Group B45* Among Medically Certified Deaths, England and Wales, Peninsular Malaysia and Singapore, 1972

Country	Medically certified deaths	Deaths classified to cause group B45	
		Number	Percentage
England and Wales	591,354***	3,802	0.6
Peninsular Malaysia	20,140	1,430	7.1
Singapore**	10,018***	616	6.1

*B45 – Symptoms and ill-defined conditions
**Data are for 1973 and includes 57 cases pending coroner's inquest
***Includes coroner's cases

Sources: The Registrar General's Statistical Review of England and Wales for the Year 1972, Part I, Tables, Medical, Appendix H5.
Vital Statistics, West Malaysia, 1972, Table 51.00
Report on the Registration of Births and Deaths and Marriages, 1973, Republic of Singapore, Table 39.

In practice many doctors in Malaysia are still unaware of the importance of the requirement of specifying the underlying cause of death. Inaccuracies due to failure to distinguish between the underlying disease and the complications or incidental conditions occur frequently. The problem is compounded by the fact that a large variety of forms are employed in certifying cause of death even though the Births and Deaths Registration Ordinance requires this to be done on a "prescribed form" (Fig. 1). Some of the methods used locally include:

a) *The prescribed form* (Fig. 1)

Although this form is prescribed under the Births and Deaths Registration Ordinance, its existence is not widely known among doctors. The form itself tends to cause confusion as it would appear that three entries are required, one each against "cause of death", "primary" and "secondary". Moreover, these terms are not defined and have been variously interpreted.

For clarity, the part of the form for entering the cause of death would be less ambiguous if laid out in the following manner:

Cause of death :

Primary.....

Secondary.....

In the old terminology, the "primary cause of death" is equivalent to "the cause of death", "principal cause of death" and "fundamental cause of death", but these various descriptions can be better understood if the present-day recommended terminology, "the underlying cause of death" is used. The "secondary cause of death" is the disease or condition directly leading to death, that is, the disease, injury or complication which caused death.

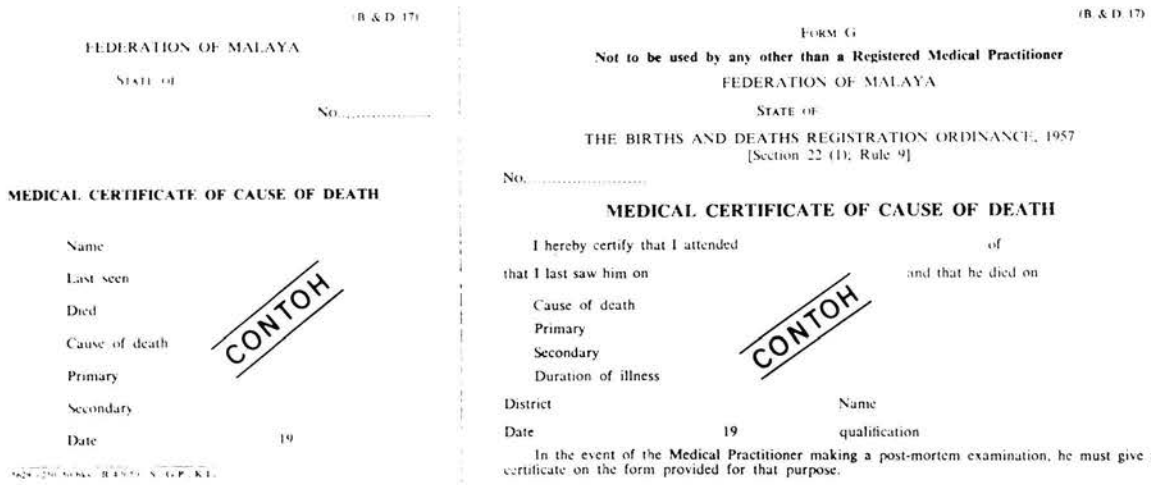
Illustrative example :
A patient with typhoid fever died of peritonitis resulting from intestinal perforation.

Cause of death :

Primary Typhoid fever

Secondary Peritonitis from intestinal perforation

A different form is provided for in the Births and Deaths Registration Ordinance for certification of those deaths that are subjected to a post-mortem examination (Fig. 2).



(B. & D. 17)

FEDERATION OF MALAYA

STATE OF

No.....

MEDICAL CERTIFICATE OF CAUSE OF DEATH

Name
Last seen
Died
Cause of death
Primary
Secondary
Date 19

CONTOH

(B. & D. 17)

FORM G

Not to be used by any other than a Registered Medical Practitioner

FEDERATION OF MALAYA

STATE OF

THE BIRTHS AND DEATHS REGISTRATION ORDINANCE, 1957
[Section 22 (1); Rule 9]

No.....

MEDICAL CERTIFICATE OF CAUSE OF DEATH

I hereby certify that I attended of
that I last saw him on and that he died on

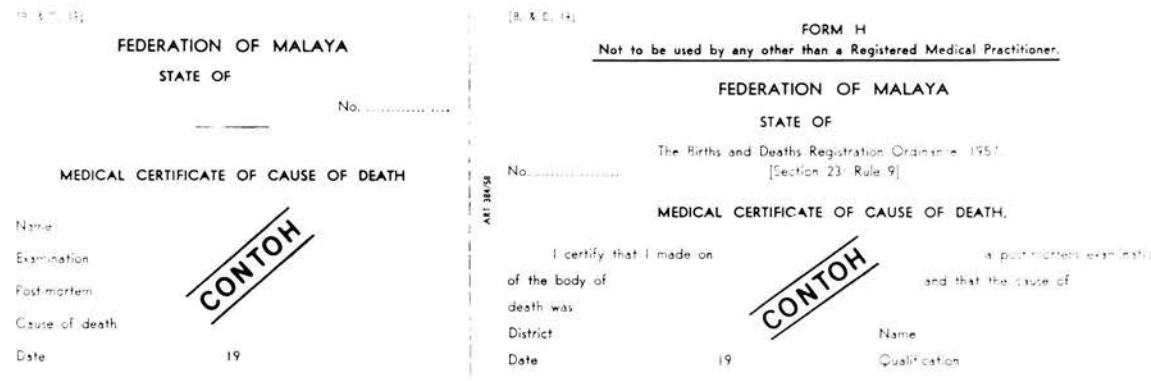
Cause of death
Primary
Secondary
Duration of illness

District Name
Date 19 qualification

In the event of the Medical Practitioner making a post-mortem examination, he must give a certificate on the form provided for that purpose.

CONTOH

Fig. 1
Medical Certificate of Cause of Death



FEDERATION OF MALAYA

STATE OF

No.....

MEDICAL CERTIFICATE OF CAUSE OF DEATH

Name
Examination
Post-mortem
Cause of death
Date 19

CONTOH

FORM H

Not to be used by any other than a Registered Medical Practitioner.

FEDERATION OF MALAYA

STATE OF

The Births and Deaths Registration Ordinance, 1957
[Section 23; Rule 9]

No.....

MEDICAL CERTIFICATE OF CAUSE OF DEATH.

I certify that I made on a post-mortem examination
of the body of and that the cause of
death was
District Name
Date 19 Qualification

CONTOH

Fig. 2
Medical Certificate of Cause of Death (for deaths with post-mortem examination)

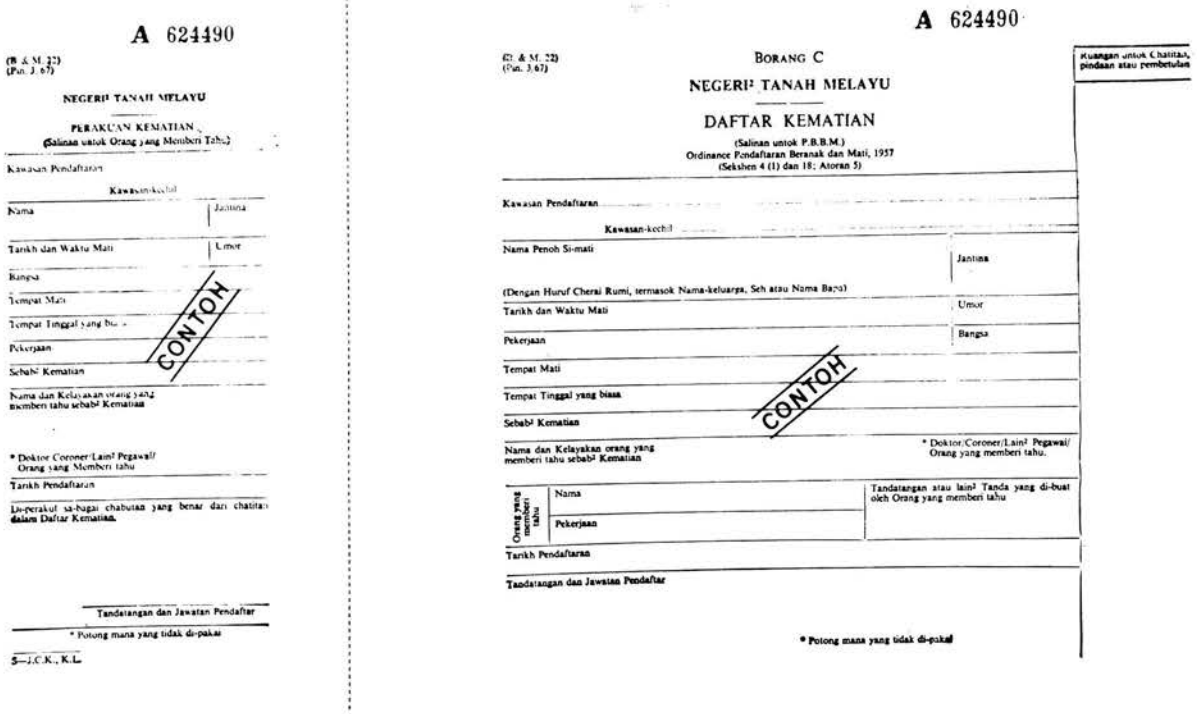
b) *Direct entry in the death register or use of other forms*

Frequently, in a hospital where the registrar of births and deaths is within the premises, a direct entry of the cause of death is made in the death register without the intermediate step of having the doctor submit a medical certificate of cause of death, or in some instances a preliminary entry is made on some other form such as the burial permit. In the death register, and also in other forms, space is limited to a single entry of cause of death under "Sebab2 Kematian" (Fig. 3). If multiple entries are made in this spacc, it necessitates the selection of the "underlying cause of death" from among them for statistical tabulation. This process of selection is carried out in the Statistics Department by non-medically qualified workers or coders. With no assistance from the medical profession, these coders cannot be expected to select the underlying cause of death correctly in spite of whatever arbitrary rules of selection that they may employ. Thus an entry of "bronchopneumonia, subdural harmorrhage" may appear in the statistics as a death due to broncho-pneumonia instead of subdural haemorrhage which is the underlying cause.

c) *The international form of medical certificate of cause of death* (Fig. 4)

This form is recommended by WHO in order to promote uniform application of the principle of tabulation based on the underlying cause of death. In this form, in Part I the immediate cause of death is put first and the preceding or antecedent causes which led to the fatality are listed in order underneath. The last cause listed in Part I is taken as the underlying cause of death.

This form allows the doctor to record multiple conditions on the certificate. The use of such a form would help the doctor, the registrar of births and deaths and the statistical clerk to sort out the part played by each condition in causing death and select the appropriate condition for tabulation.



A 624490

(B. & M. 22)
(Pin. 3. 67)

NEGERI[1] TANAH MELAYU

PERAKUAN KEMATIAN
(Salinan untuk Orang yang Memberi Tahu)

Kawasan Pendaftaran

Kawasan-kechil

Nama | Jantina

Tarikh dan Waktu Mati | Umur

Bangsa

Tempat Mati

Tempat Tinggal yang biasa

Pekerjaan

Sebab[2] Kematian

CONTOH

Nama dan Kelayakan orang yang memberi tahu sebab[2] Kematian

* Doktor/Coroner/Lain[2] Pegawai/ Orang yang Memberi tahu

Tarikh Pendaftaran

Di-perakui sa-bagai chabutan yang benar dari chatitan dalam Daftar Kematian.

Tandatangan dan Jawatan Pendaftar

* Potong mana yang tidak di-pakai

5—J.C.K., K.L.

A 624490

(B. & M. 22)
(Pin. 3.67)

BORANG C

NEGERI[1] TANAH MELAYU

DAFTAR KEMATIAN

(Salinan untuk P.B.B.M.)
Ordinance Pendaftaran Beranak dan Mati, 1957
(Seksyen 4 (1) dan 18; Aturan 5)

Ruangan untuk Chatitan, pindaan atau pembetulan

Kawasan Pendaftaran

Kawasan-kechil

Nama Penoh Si-mati | Jantina

(Dengan Huruf Cherai Rumi, termasok Nama-keluarga, Seh atau Nama Bapa)

Tarikh dan Waktu Mati | Umur

Pekerjaan | Bangsa

Tempat Mati

Tempat Tinggal yang biasa

Sebab[2] Kematian

CONTOH

Nama dan Kelayakan orang yang memberi tahu sebab[2] Kematian

* Doktor/Coroner/Lain[2] Pegawai/ Orang yang memberi tahu.

Orang yang memberi tahu: Nama | Pekerjaan

Tandatangan atau lain[2] Tanda yang di-buat oleh Orang yang memberi tahu

Tarikh Pendaftaran

Tandatangan dan Jawatan Pendaftar

* Potong mana yang tidak di-pakai

Fig. 3
The Death Register

INTERNATIONAL FORM OF MEDICAL CERTIFICATE OF CAUSE OF DEATH

CAUSE OF DEATH		Approximate interval between onset and death
I		
*Disease or condition directly leading to death**	(*a*)	. . . . .
	due to (or as a consequence of)	
Antecedent causes Morbid conditions, if any, giving rise to the above cause, stating the underlying condition last	(*b*)	. . . . .
	due to (or as a consequence of)	
	(*c*)	. . . . .
II		
Other significant conditions contributing to the death, but not related to the disease or condition causing it	. . . . .	. . . . .
	. . . . .	. . . . .

* This does not mean the mode of dying, e.g., heart failure, asthenia, etc. It means the disese, injury, or complication which caused death.

Fig. 4
International Form of Medical Certificate of Cause of Death

The use of this form is not without danger of causing further confusion in an existing system of death registration such as that used in Peninsular Malaysia. As seen earlier, limited space is provided in the death register for making a single entry, namely, "the cause of death". There are more than 1000 registrars of births and deaths in Peninsular Malaysia and except for registrars in hospitals, these are mainly made up by police officers and village headmen. They cannot be expected to select correctly for entry into the death register, the underlying cause of death from such a form particularly when it has no fixed position in the form because it depends on how many entries are made in Part I. Even less so can they be expected to be able to recognise and deal with improbable sequences, incorrect or vague entries. Another danger is that the registrar will try and "squeeze" into the limited space provided in the death register all the entries made by the doctor in the international form of the medical certificate. This generally results in illegibility but more important is that the order of copying will follow the order as listed in the form: the immediate cause being put first and the contributory cause in Part II comes as the last entry, the underlying cause usually ending up being somewhere in between. When such an entry in the death register reaches the coder's hands in the Department of Statistics, the tendency is for the first mentioned condition to be coded for tabulation since no provision is made for indicating which is the underlying cause of death in the local death register. Thus care taken in certifying the cause of death by a doctor on such an elaborate certificate, will be vitiated.

d) *Some other forms printed for private use*

These usually incorporate the locally prescribed form or the international form or may even be individually designed.

e) *A "letter" from the physician*

This method is frequently used by private practitioners. It may take the form of a simple statement of the cause of death or a lengthy description of the

medical history of the deceased with or without an indication as to the underlying cause of death. (Fig. 5)

To Whom It May Concern

(name of deceased)

Re:.....

The above named is an old case of hypertension with right hemiplegia following stroke. He is also a case of ?recurrent renal stones and has been bedridden for the past 2 years. He is also a case of ?Ca bladder. He died at home last night at.....on.....

Please do the needful.

Thank you.

(signed by doctor)

Fig. 5
Sample of letter from the doctor

This latter method requires the registrar, who in this situation is usually a police officer to decide which, among the many medical terms mentioned in the letter, should be selected as the cause of death. This may be an insurmountable task for a layman particularly if it is written in undecipherable hand writing. Thus one can understand it if under these circumstances, he ignores the doctor's letter and proceeds to ascertain the cause of death himself from the informant, the doctor's efforts then amount to nought.

Conclusion

The present system of medical certification of cause of death is ineffective and unclear to most doctors as well as various personnel involved in the whole system of registration of deaths. A system was provided in the Births and Deaths Registration Ordinance 1957, but the practice has since become obscured or deviated from the original system. If the quality of cause-of-death statistics is to improve, the system needs to be reviewed with a view to improving the accuracy of certification and registration of cause of death as well as improving the proportion of medically certified deaths.

Much can and should be done by the medical profession to improve certification practices. Attention is drawn to what Logan (1953) said: "In filling up death certificates conscientiously and carefully doctors are doing more than meeting a legal responsibility; they are providing information of direct scientific value to their colleagues, and information which will in the long run be useful to themselves."

Acknowledgement

I am grateful to Professor W. Danaraj, Head of Department of Social and Preventive Medicine, University of Malaya and Professor D.R. Peterson, Visiting Professor, Social and Preventive Medicine for encouragement and advice, Encik Haji Junid bin Haji Abdul Rahim, Registrar-General of Births and Deaths for permission to reproduce the forms in figures 1, 2 and 3, Miss D.Z. Fernandez, Senior Statistician of the Census and Demography Division, Statistics Department, and staff of her Division for cooperation and assistance, many members of the various departments involved in the death registration system for cooperation, the Department of Medical Illustration, University of Malaya, for photographs of the forms in figures 1, 2, 3 and 4, Mrs. S.M. Wong for technical assistance and Miss M.L. Yap for typing the manuscript.

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A Review of Poisoning Cases Examined by the Department of Chemistry, Malaysia from 1968 to 1972

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Introduction

THE TOXICOLOGICAL EXAMINATION OF exhibits and specimens in cases involving poisons are carried out by the laboratories of the Department of Chemistry in Petaling Jaya, Penang, Kuching, Kuala Trengganu and Johor Bahru. This review covers all cases of human poisoning for the period 1968 to 1972 and the data is on all cases received from all the States of Malaysia during this period.

Poison as mentioned in this paper means any foreign substance not normally taken by a person that would cause upset of the person's system which may or may not ultimately result in death.

Aim

A review of poisoning cases examined by the Department of Chemistry, Malaysia for the period 1963 to 1967 was published in this Journal in 1969. The aim of the present survey is to review the ca s s of poisoning examined during the period 1968 to 1972 and compare the results for the two periods.

Techniques of Analysis

The increase in the number of poisons identified in suspected poisoning cases depends partly on the development of the techniques of analysis. In the Department of Chemistry modern analytical methods were used in the following order: Paper Chromatography in 1952, Column Chromatography in 1953, U.V. Spectrophotometry in 1953, Quartz Spectrography in 1953, Ion-exchange in 1955, I.R. Spectrophotometry in 1958, X-ray diffraction in 1958, Thin layer Chromatography in 1963, Gas-Chromatography in 1967 and Atomic Absorption Spectrophotometry in 1972. The use of these analytical techniques has resulted in a far larger number of positive identifications of poisons than was previously possible.

The Range of Poisons Identified

The range of poisons identified is described in Table I. Although a wide range of poisons has been found some of which are unusual, in the majority of cases, 19 types of poisons predominate – these are discussed in detail below.

Table I

The Various Poisons Isolated from Exhibits

1. **Acids**

   Acetic Acid
   Formic Acid
   Hydrochloric Acid
   Oxalic Acid
   Sulphuric Acid

2. **Alcohols**

   Ethyl Alcohol
   Methyl Alcohol

3. **Aldehydes**

   Formaldehyde (Formalin)

4. **Alkalis**

   Ammonia
   Calcium Hydroxide
   Potassium Carbonate
   Sodium Carbonate
   Sodium Hydroxide

5. **Alkaloids**

Chloroquine
Codeine
Ephedrine
Ergometrine
Heroin
Morphine/Opium
Yohimbine

6. **Disinfectants, Antiseptics**

Acriflavine
Calcium Hypochlorite
Cresol
Dettol
Iodine
Izal
Jeyes Fluid
Lysol
Mercurochrome (Merbromin)
Phenol
Potassium Permanganate
Sodium Hypochlorite
Thymol

7. **Drugs – Others**

Acetylsalicylic Acid/Salicylic Acid
Adrenaline
Amitriptyline
Amphetamine
Benzyl Benzoate
Carbimazole
Chlorpheniramine
Chlorpropamide
Cortisone
Diphenhydramine
Hydroxyamphetamine
Imipramine
Lignocaine
Methapyrilene
Paracetamol
Penicillin
Pentazocine
Phenacetin
Phenylbutazone
Phenylephrine
Phenytoin
Prednisolone
Promazine
Promethazine
Salicylamide
Streptomycin Sulphate
Sulphadimidine
Sulphamerazine
Sulphapyridine
Tetracycline

8. **Hypnotics**

Barbiturates – Allobarbitone
Amylobarbitone
Barbitone
Butobarbitone
Cyclobarbitone
Hexobarbitone
Phenobarbitone
Pentobarbitone
Quinalbarbitone

Non-Barbiturates – Bromisovalum
Carbromal
Dichloralphenazone
Glutethumide

9. **Inorganic**

Calcium Carbide
Glass
Hydrogen Sulphide
Potassium Cyanide
Zinc Phosphide

10. **Insecticides/Weedicides/Fungicides**

See Table III

11. **Metallic**

Arsenic
Copper
Lead
Mercury
Selenium

12. **Mineral Oils**

Kerosene
Petrol

13. **Tranquillisers**

Chlordiazepoxide (Librium)
Chlorpromazine
Meprobamate
Perphenazine
Prochlorperazine (Stemetil)
Thioridazine
Trifluoperazine

14. **Miscellaneous**

Acetone
Amainta Toxins (Mushroom Poisons)
Camphor
Carbon Tetrachloride
Castor Oil
Clove Oil
Citronella Oil
Detergents
Methyl Salicylate
Naphthalene
Petroleum Ether
Pyridine
Shellac
Tuba Root.

Human Poisoning

The majority of cases in which exhibits are submitted for examination are in connection with suicide and attempted suicide. Exhibits and specimens in these cases are submitted by the medical officer through the Police. Other exhibits include clinical specimens submitted for toxicological examination.

Table II lists the most common poisons consumed by people who committed suicide or attempted to commit suicide. The figures for the period

Table II

The Most Common Poisons Consumed by People Who Committed Suicide or Attempted to Commit Suicide in Malaysia During The Period 1968 to 1972. (Data on Race, Age, Sex Included). Figures for The Period 1963 to 1967 Given in Parenthesis.

				R A C E				*A G E (I N Y E A R S)*							*S E X*	
P O I S O N	Total	Dead	Alive	Chinese	Indian	Malay	Others	10 & Below	11 – 20	21 – 30	31 – 40	41 – 50	51 – 60	60 & Over	Male	Female
Insecticides – Organophosphorus	316(207)	231(125)	85(82)	96(41)	210(163)	7(3)	3(2)	3(2)	123(79)	92(68)	40(24)	25(14)	17(12)	16(8)	148(83)	168(124)
FORMIC ACID	295(232)	220(169)	75(63)	125(91)	146(115)	21(26)	3(0)	1(2)	72(46)	85(76)	46(33)	31(20)	17(30)	43(25)	166(153)	129(79)
Arsenic	271(308)	234(186)	37(122)	86(79)	171(218)	13(11)	1(0)	4(6)	95(103)	74(108)	38(32)	28(21)	18(26)	14(12)	163(199)	108(109)
Insecticide – Organochlorine	206(115)	103(44)	103(71)	54(30)	132(77)	17(8)	3(0)	8(6)	91(42)	52(36)	25(16)	11(5)	7(7)	12(3)	96(51)	110(64)
Sodium Hydroxide/ Sodium Carbonate	144(232)	87(80)	57(152)	98(163)	40(61)	6(8)	0(0)	2(2)	35(48)	40(79)	29(30)	16(31)	9(23)	13(19)	63(97)	81(135)
Barbiturates	124(99)	45(34)	79(65)	84(77)	28(20)	6(2)	6(0)	2(0)	20(17)	55(49)	26(16)	12(8)	8(5)	1(5)	55(54)	69(45)
Weedicides/ Fungicides	82	61	21	40	33	7	2	2	24	29	12	4	8	3	46	36
Non-Barbiturate – Hypnotics	57(38)	7(5)	50(33)	44(31)	8(6)	3(1)	2(0)	0(0)	14(6)	28(25)	9(5)	2(1)	1(0)	3(1)	30(24)	27(14)
Acetyl Salicyclic Acid/Salicyclic Acid	47(23)	31(13)	16(10)	32(13)	7(7)	5(3)	3(0)	5(0)	15(6)	13(7)	9(6)	2(0)	1(2)	2(2)	23(13)	24(10)
Phenols	46	18	28	21	21	1	1	4	17	13	0	2	4	6	23	23
Methyl Salicyclate	37(21)	25(12)	12(9)	18(13)	15(7)	4(1)	0(0)	1(3)	12(6)	12(6)	6(0)	3(2)	1(2)	2(2)	13(12)	24(9)
Sulphuric Acid	27(61)	18(31)	9(30)	11(24)	11(25)	5(12)	0(0)	1(2)	2(8)	6(22)	2(10)	6(6)	7(6)	3(7)	12(44)	15(17)
Methyl Alcohol	24	17	7	3	12	0	9	0	6	7	5	2	1	3	10	14
Tranquillisers	24	8	16	18	3	2	1	0	6	11	5	1	1	0	14	10
Opium Alkaloids	22(18)	10(15)	12(3)	16(17)	2(1)	2(0)	2(0)	4(2)	4(3)	5(4)	4(3)	2(2)	0(2)	3(2)	15(11)	7(7)
Detergents	14	2	12	11	3	0	0	0	8	3	1	1	1	0	1	13
Chloroquine	13	12	1	2	5	2	4	2	2	5	3	0	0	1	4	9
Ammonia	(32)	(8)	(24)	(12)	(19)	(1)		(1)	(7)	(8)	(7)	(2)	(4)	(3)	(11)	(21)
Hydrochloric Acid	(10)	(8)	(2)	(5)	(2)	(3)		(0)	(1)	(3)	(1)	(0)	(4)	(1)	(9)	(1)
TOTAL	1749(1396)	1129(730)	620(666)	759(596)	847(721)	101(79)	42(0)	39(26)	546(371)	530(491)	260(183)	148(112)	101(123)	125(90)	882(761)	867(635)

1963 to 1967 are given in parenthesis. The figures include data on race, age and sex.

Table III lists all the organo-pesticides consumed by people who committed suicide or attempted to commit suicide. Data on their relative percentage occurrence is also given.

Table III

List of Consumed Organo-pesticides 1968 – 1972

Insecticides: Organophosphorous	**Percentage**
Malathion	73.1
Parathion	5.3
Gusathion	5.0
Diazinion	5.0
Diazinion	2.9
DDVP	1.7
Dipterex	1.7
Tamaron	1.4
Dimethoate	0.6
Bidrin	0.3
Sumuthion	0.3
Phenthoate	0.3
Unidentified Organophosphorous Compound	7.4
Insecticides: Organochlorine	
Dieldrin	24.5
BHC	21.2
Thiodan	20.8
DDT	20.0
Endrin	9.0
Aldrin	1.6
Telodrin	0.5
Unidentified Organochlorine Compound	2.4
Insecticides: Others	
Pyrethrum	61.2
Carbamate	16.7
Nicotine	16.7
Dimethylphthalate (Insect repellant)	5.4
Weedicides/Fungicides	
Paraquat	68.2
2-4D	15.9
2-4-5 T	4.6
Pentachlorophenol	4.6
2-2 Dichloropropionic Acid (Dalapon)	3.4
Captan	1.1
Weedazol	1.1
Diuron	1.1

The Most Commonly Consumed Poisons

1. **Organo-pesticides**

   (i) *Insecticides* – As we stated in the earlier paper the incidence of poisoning by insecticides is on the increase and during the period of review the organophosphorous insecticides have been the most frequently consumed poison. The organochlorine insecticides are also frequently consumed (fourth on the list). These insecticides are readily available to the public and are therefore chosen by those who intend to commit suicide.

   From Table III of the organophosphorous insecticides malathion (73.1%) is the most frequently consumed. Parathion (5.3%) an extremely potent poison is the next most frequently consumed although its importation is prohibited.

   Of the organochlorine insecticides, dieldrin (24.5%) is the most frequently consumed whilst BHC (21.2%), thiodab (20.8%), DDT (20.0%) follows closely behind.

   (ii) *Weedicides/Fungicides* – The increased use of weedicides and fungicides in estates and vegetable gardens has made available these chemicals as a source for those who want to commit suicide. From Table III, paraquat (68.2%) has been the most frequently consumed. In nearly all such cases the result of ingestion has been fatal.

   In general, the frequency of the consumed organopesticides depends largely on their availability.

2. **Acids** – Formic acid which is used as a coagulant of rubber latex in estates is used frequently (2nd highest on the list) for suicide purposes. It is easily available in rubber estates and is thus used by rubber tappers and estate labourers most of whom are Indians. Sulphuric acid is also used by would be suicides.

3. **Arsenic** – Arsenic consumed as a poison has decreased slightly. The reason for this is that the use of sodium arsenite as a weedicide has decreased in recent years and many estates have switched to other weedicides.

4. **Alkali** – Caustic soda is another commonly consumed poison. It is usually taken by those who live in towns where the poison is more readily available. There has been a significant decrease in the number of persons who consumed this poison in the period (1968 – 1972) when compared to the earlier period (1963 – 1967). This could be due to more efficient implementation of the Poisons Ordinance 1961 which restricts its sale to the general public. This poison is usually taken by the lower income group of Chinese.

5. **Hypnotics** – There has been an increase in the consumption of hypnotics such as barbiturates, non-barbiturate hypnotics and tranquillisers. Most of these cases involve those in the middle and upper income groups.

6. **Others** – The other common poisons found include acetyl salicylic acid, phenols, methyl salicylate, methyl alcohol, opium alkaloids, detergents and chloroquine.

The Incidence of Suicide

The majority of poisoning cases examined by this Department are in connection with suicide cases.

Figure 1 gives details of the distribution of the most commonly consumed poisons. A study of these figures show that there has been an increase in the cases in which insecticides have been used while there has been a decrease in the use of arsenic. The decrease in the use of arsenic has been offset by an increase in the use of weedicides. There has also been a significant increase in the use of formic acid and a significant reduction in the use of caustic soda (sodium hydroxide) and sulphuric acid. There have been an increase in the use of barbiturates and other hypnotics.

Figure 2 gives the number of deaths and survivals according to the type of poisons taken. It is noted that in cases where organophosphorus insecticides, formic acid and arsenic were consumed, the number of deaths were significantly more than survivals in both the review periods. In the cases where barbiturates, non-barbiturate hypnotics and tranquillisers were taken there were more survivals than deaths in both the review periods. In the case with organochlorine insecticides there were more survivals than deaths for the review period 1963 – 1967 but there were equal numbers of deaths and survivals for the review period 1968 – 1972. In the case of caustic soda (sodium hydroxide) there were more survivals in the earlier review period while there were more deaths in the present review period. There were more deaths when weedicides/fungicides were taken.

The three main factors affecting death or survival are:

1. The availability of the poisons in the concentrated or technically pure forms for example, sodium arsenite, malathion, formic acid and paraquat when consumed they would more than often result in death.

2. The availability of medical attention. The urban suicide cases have the advantage of immediate and effective medical attention and their chances of survical are higher whereas certain types of medical facilities are not speedily available to the rural suicide cases. This is illustrated in both the review periods where there are more deaths than survivals in arsenic, formic acid, malathion and paraquat poisoning cases and more survivals than deaths in tranquilliser, barbiturate and non-barbiturate hypnotic poisoning cases. The former being consumed more by the rural population whereas the latter being consumed more by the urban population.

3. The mode of action of the poison after it has been ingested. Corrosives if ingested would more than often result in death as on contact they would puncture the alimentary canal. This is in contrast to the consumption of non-corrosive poisons where they act only after they have been absorbed into the blood stream.

The distribution of suicides according to race is given in Figure 3. In the previous paper covering the period 1963 – 1967 it was noted that the largest number of suicide cases were to be found among the Indian (51.6%) who constitute the smallest percentage of the population (9.0%) while the smallest percentage of suicides was among the Malays (5.7%) who constitute the largest proportion of the population (46.8%). The Chinese accounted for 42.7% of the suicides. They make up 34.1% of the population. In the present survey the percentages of suicides was 48.4% Indians, 43.3% Chinese, 5.8% Malays and 2.4% others. The figures for the two review periods are almost similar* thus indicating that the pattern of suicides among the three main races in this country remain the same over the ten year period 1963 to 1972. The type of poison taken and the availability may have a bearing on the consumption of these poisons. For instance insecticides, acids, arsenic and weedicides are used in rubber estates where the majority of workers are Indians.

Figure 4 gives the suicides according to age. There has been a shift in the age group which is most prone towards suicide. In the present survey it is noted that the 11 – 20 years age group is the most prone (546 cases) while the 21 – 30 years old group is a very close second (530 cases). In the previous survey the 21 – 30 years age group (491 cases) were the highest group while the 11 – 20 years age group (371 cases) were the second.

FIGURE 1

MOST COMMONLY CONSUMED POISONS

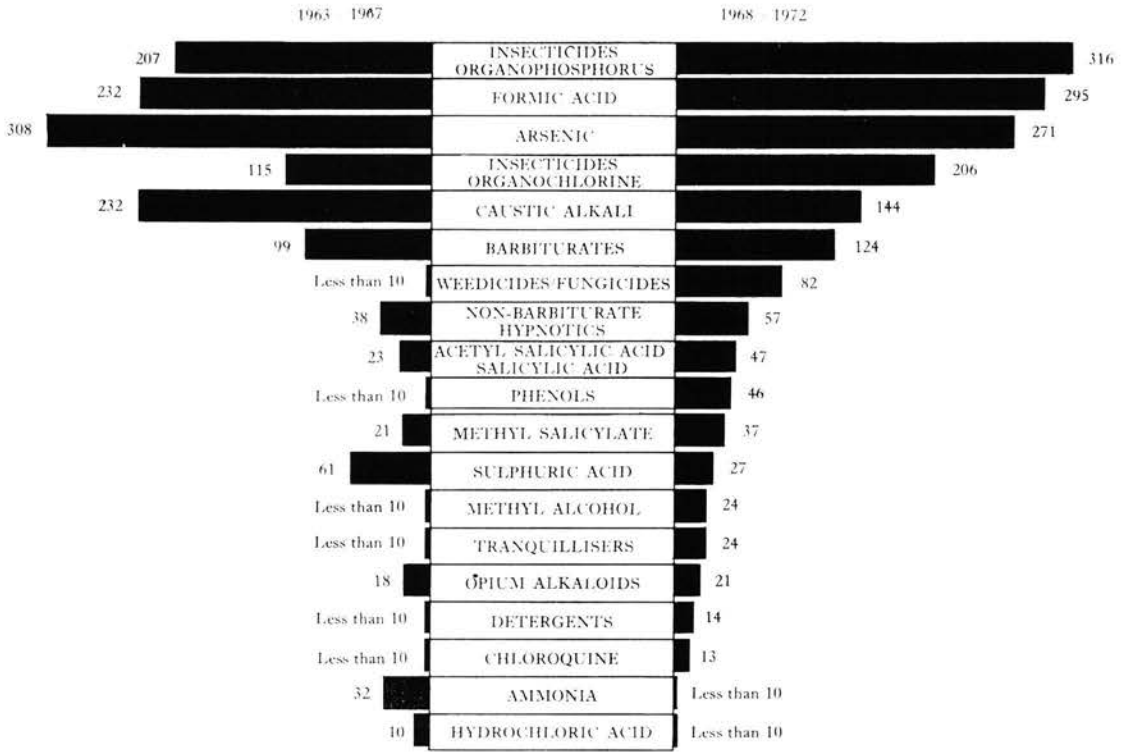

FIGURE 2

NUMBER OF DEATHS AND SURVIVALS IN SUICIDE CASES

ACCORDING TO THE POISON CONSUMED

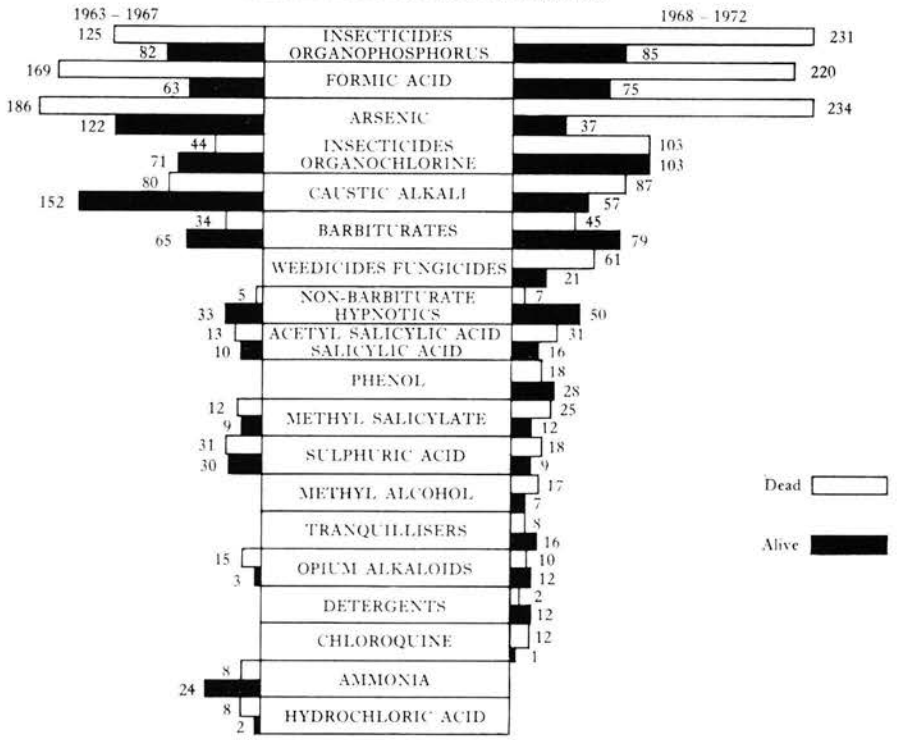

FIGURE 3

COMMON POISONS FOUND IN SUICIDE CASES

DISTRIBUTION BY RACE

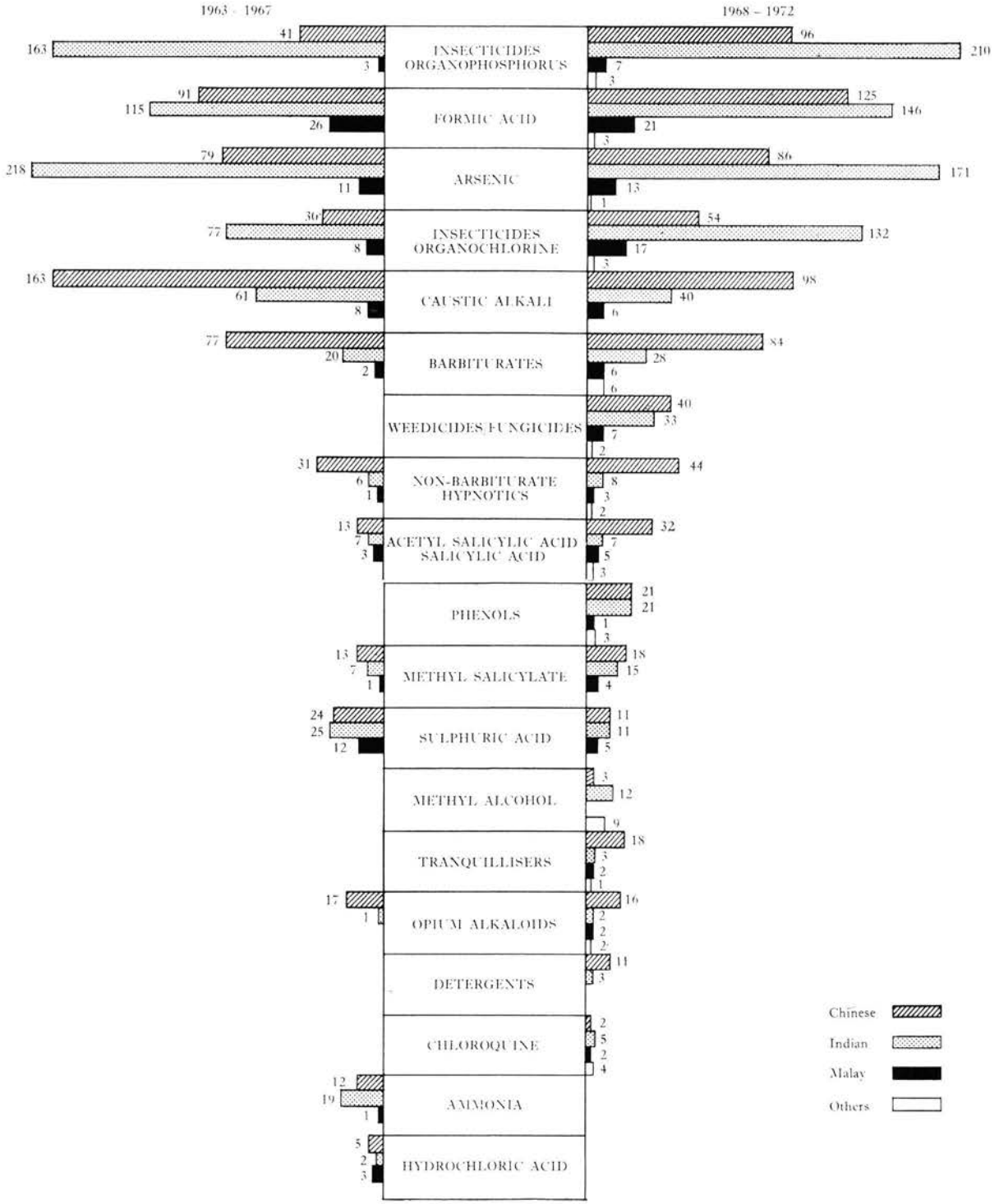

FIGURE 4

POISONS FOUND IN SUICIDE CASES

DISTRIBUTION BY AGE

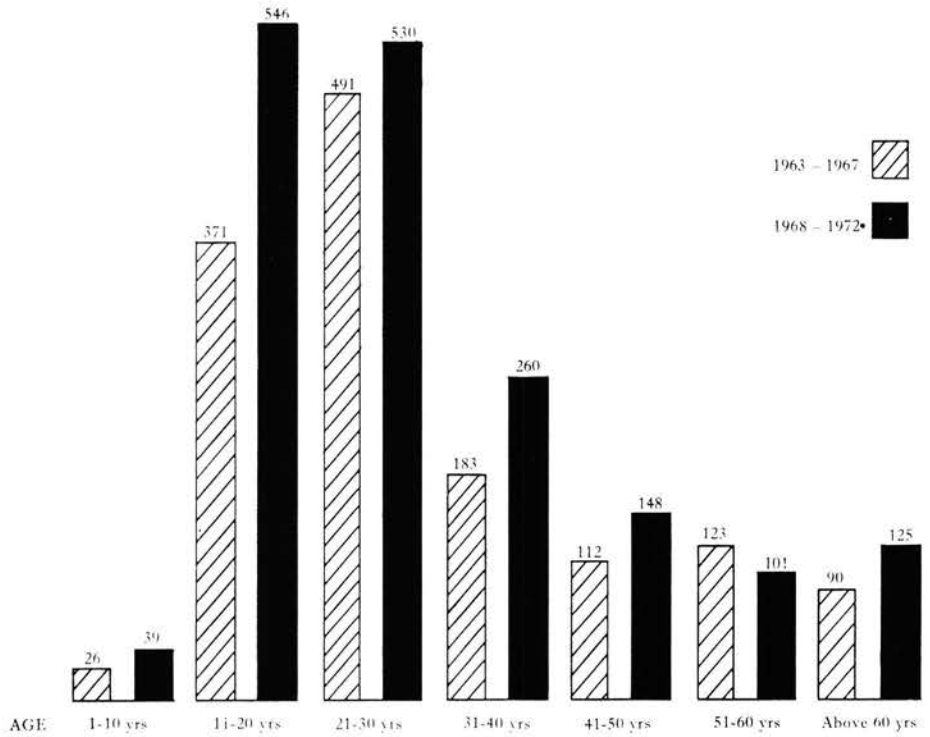

FIGURE 5

COMMON POISONS FOUND IN SUICIDE CASES

DISTRIBUTION BY SEX

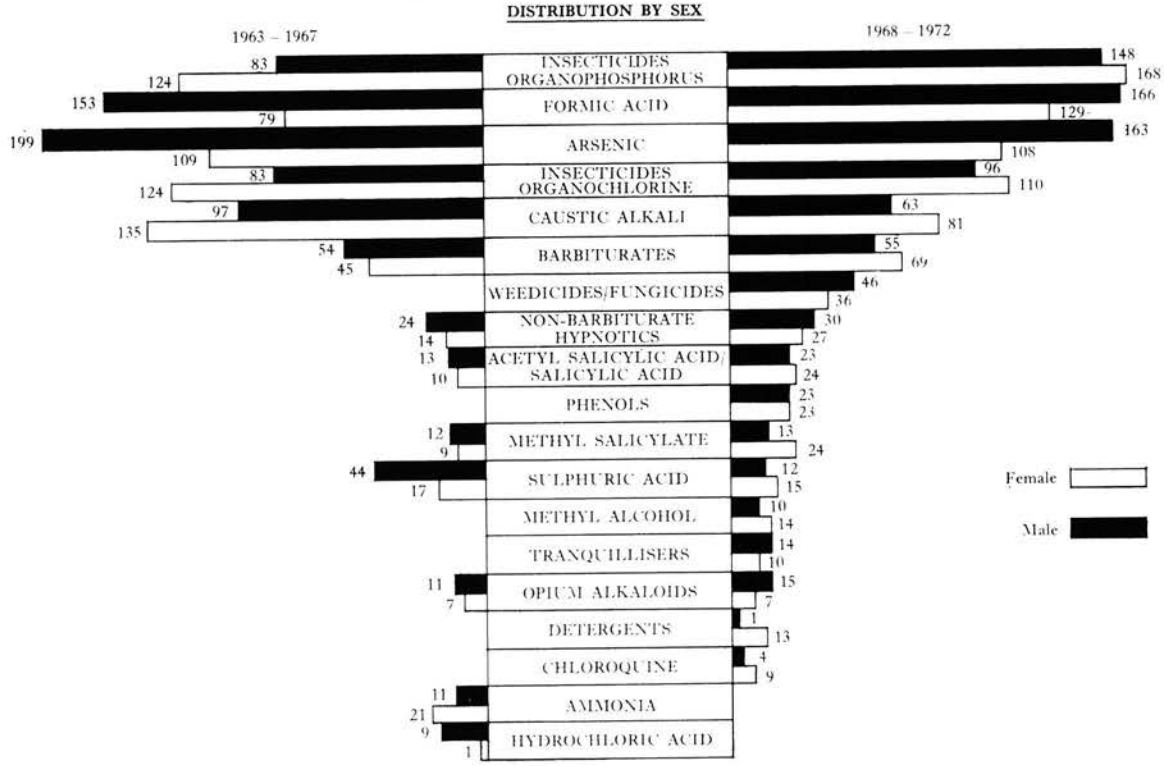

Figure 5 gives the suicides according to sex. The figures for number of cases of male and female are very close to each other indicating that both sexes are equally prone towards suicide. The previous survey indicated that males were slightly more prone than females.

*It is to be noted that the presentstudy covers the whole of Malaysia while the previous study covered only West Malaysia. This will account for the small difference in the figures obtained for the two separate studies.

Conclusion

The results of the present study and the previous one are almost similar with slight variations. These variations are due to the increased availability of some poisons such as weedicides and the reduced availability of some poisons such as caustic soda (sodium hydroxide). This review confirms the earlier review that the Indians have the highest rate of suicides in the country followed by the Chinese. The Malays very rarely commit suicide or attempt to do so. It is interesting to note that whilst the number of cases in the 21 – 30 years age group has increased very slightly, the number of cases in the 11 – 20 years age group has increased very significantly over the first review period. Perhaps this could possibly be attributed to the social changes in our present society and the absence of adequate parental supervision both over their children and the storage of poisonous substances. Most of the people who attempted suicide are in the lower income group. They are mainly rubber tappers, labourers, factory workers and domestic servants.

The lower income group of illiterate people generally consume poisons such as insecticides, acids, weedicides, arsenic and alkalis. In contrast the literate class of people usually takes to the more sophisticated drugs such as hypnotics.

The availability of poisons is also a contributing factor to the incidence of suicide.

Acknowledgement

We are grateful to the Director General of Chemistry, Dr. Surinder Singh J.S.M., for the interest shown in this study and for permission to publish these findings; to the Deputy Director General of Chemistry, Dr. Ong Kim Chye, K.M.N., for his advice and encouragement; to Mr. Kirat Singh, Mr. Yeo Hock Siew and Mr. Peter Chin Pit Ted for their contribution of data from our Branch laboratories in Johore Bahru, Kuala Trengganu and Kuching respectively.

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Electronystagmography (ENG.) as an aid to Diagnosis of Intracranial Lesions

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Introduction

EMIL DUBOIS – Reymond described the corneo-retinal potential difference in 1849. In the human retina, the electrical processes that are always taking place, even in darkness, cause it to be negatively charged against the cornea. Hence, the eye may be considered as a dipole, the electrical axis of which coincides with the optical axis. ENG, which was first described by Schott in 1922, utilizes this principle to record the changes in electrical fields produced by the eye movements by means of skin electrodes placed at the outer canthi of the eyes. Although it has been used extensively as a valuable clinical tool by the neuro-otologists in Europe, USA and UK for the investigation of disorders of the vestibular system, it has only been introduced into Malaysia recently. We report two interesting ENG records of central vertigo.

Case 1

T.S.Y., 36 years old Chinese male was seen in April 1975 with six weeks history of bitemporal and occipital headaches, worst in the right temporal region. This was continuous and throbbing in nature; it was associated with bouts of giddiness, nausea and vomiting. He had no hearing loss, tinnitus or otorrhoea. There was no past history of head injuries or loss of consciousness.

Examination revealed no significant abnormalities of the ears, nose and throat. Tuning fork testing suggested essentially normal hearing in both ears; pure tone audiogram confirmed this. His blood pressure was normal. Neurological examination revealed a minimum ataxia with tendency to fall to the right. Cranial nerves functions appeared to be intact. No papilloedema was detected. There was, however, spontaneous horizontal third degree nystagmus to the right and spontaneous vertical nystagmus on looking upwards.

The spontaneous nystagmus was recorded in ENG; it disappeared in darkness and upon closing of his eyes (Fig. 1). Optokinetic stimulation did not abolished the original spontaneous nystagmus (Fig. 2). These findings indicated a central vertigo.

X-ray internal auditory meati and chest were normal.

Lumbar puncture was performed; the C.S.F. pressure was normal, protein 41 mg% and sugar 74 mg%.

EEG showed marked focal abnormalities affecting the fronto-temporal regions of the right cerebral hemisphere. The finding on this tracing was compatible with the presence of a focal destructive process such as a cerebral tumour.

Brain Scan (Fig. 3) and right carotid angiogram (Fig. 4) supported the diagnosis of space occupying lesion in the right parieto-temporal regions. On referral to Neuro Surgical Unit, a right parietal craniotomy confirmed the diagnosis and a malignant astrocytoma was removed.

Case 2

C.L.H., a 25 year old Chinese girl was first seen in March 1974. She reported that she has been having episodes of severe giddiness which

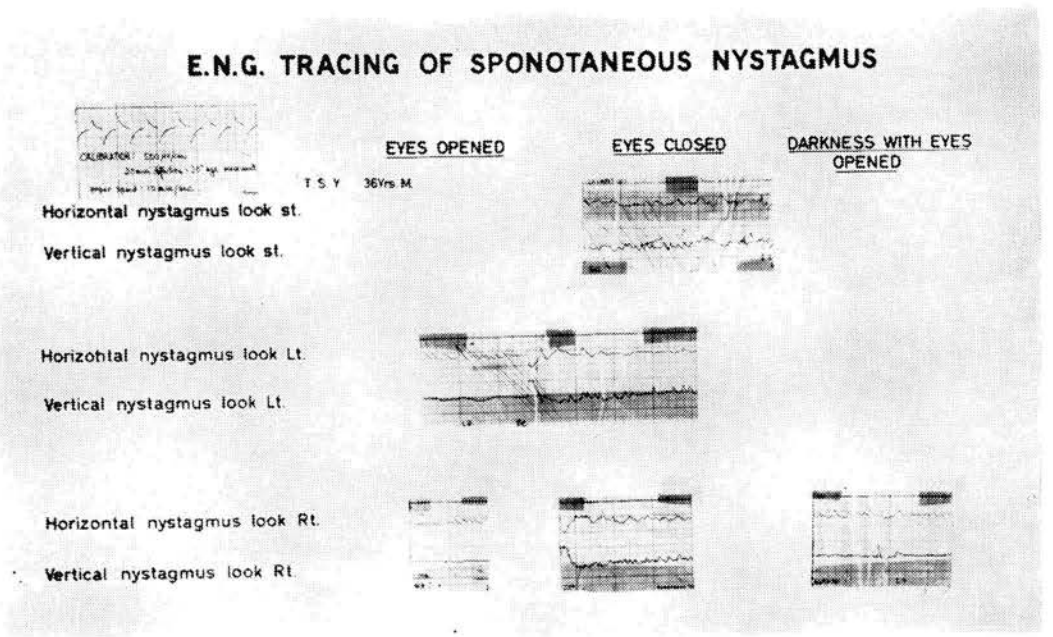

Fig. 1, Case 1

Electronystagmogram, T.S.Y.

There is third degree spontaneous horizontal nystagmus to the right and vertical nystagmus upwards. This disappears completely on eye closure. This is compatible with a central lesion.

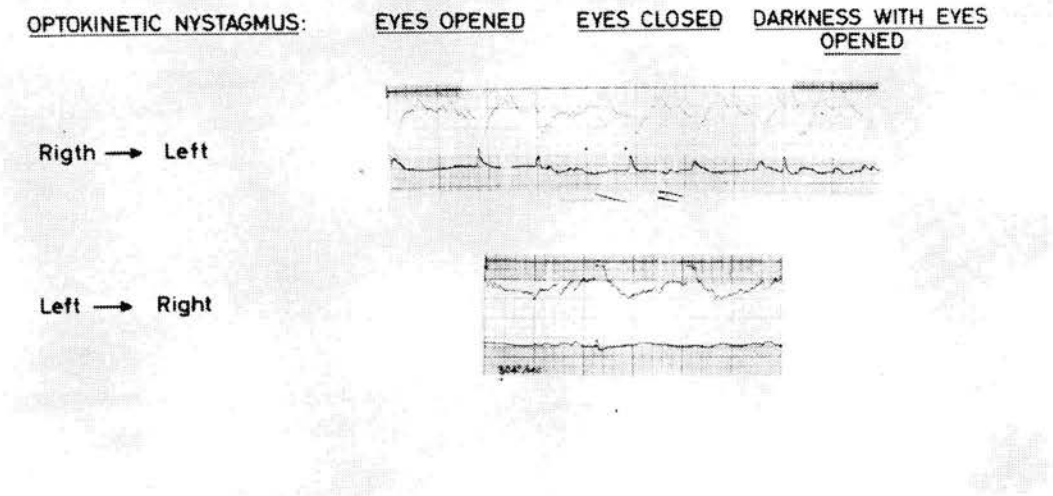

Fig. 2, Case 1

Optokinetic Nystagmus, T.S.Y.

The optokinetic nystagmus to the right is irreversible. This indicates a lesion proximal to the vestibular nucleus.

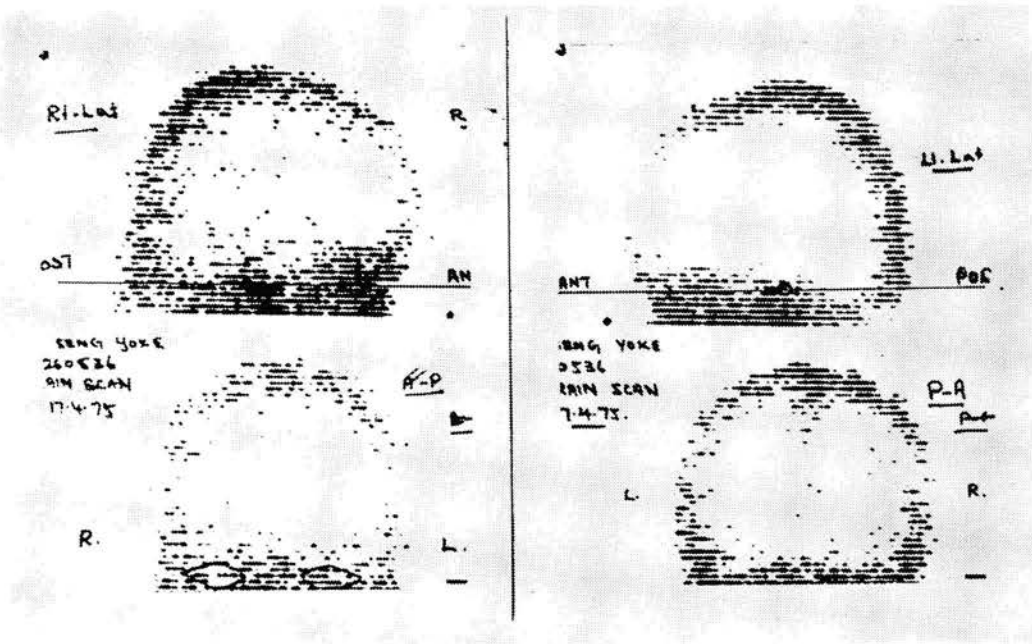

Fig. 3, Case 1
Brian Scan, T.S.Y.
There is an area of abnormal increase uptake of radiactivity in the temporo-parietal region on the right side which appears to extend to the cerebellopontine region on the same side.

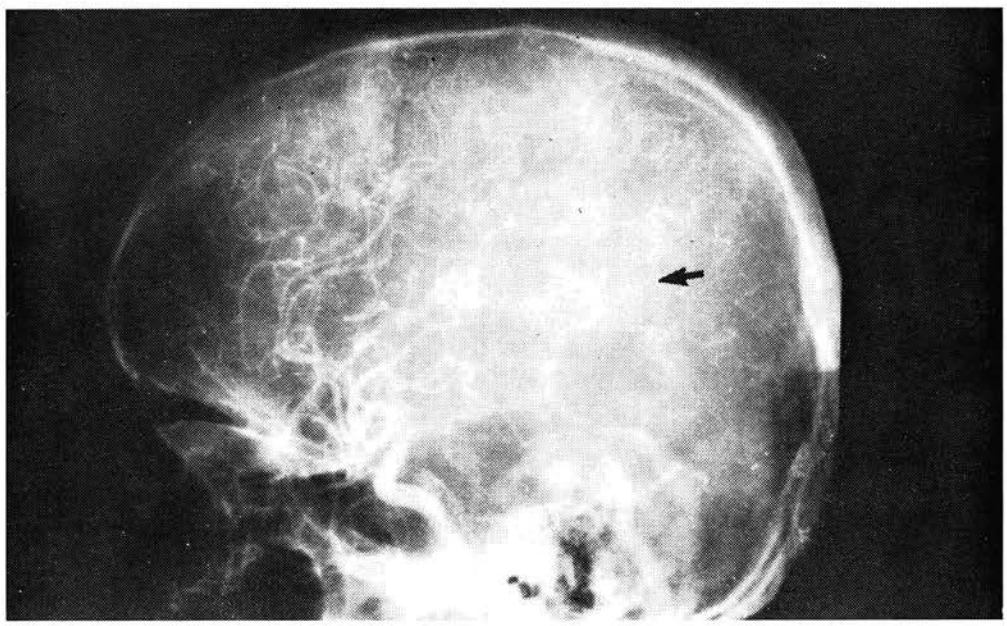

Fig. 4, Case 1
Angiogram (R), T.S.Y.
The branches of the middle cerebral artery are spread out displaced around a mass in the temporo-parietal region. The pericallosal branch of the right anterior cerebral artery is displaced upwards. A definite area of abnormal circulation in the right tempero parietal region seen.

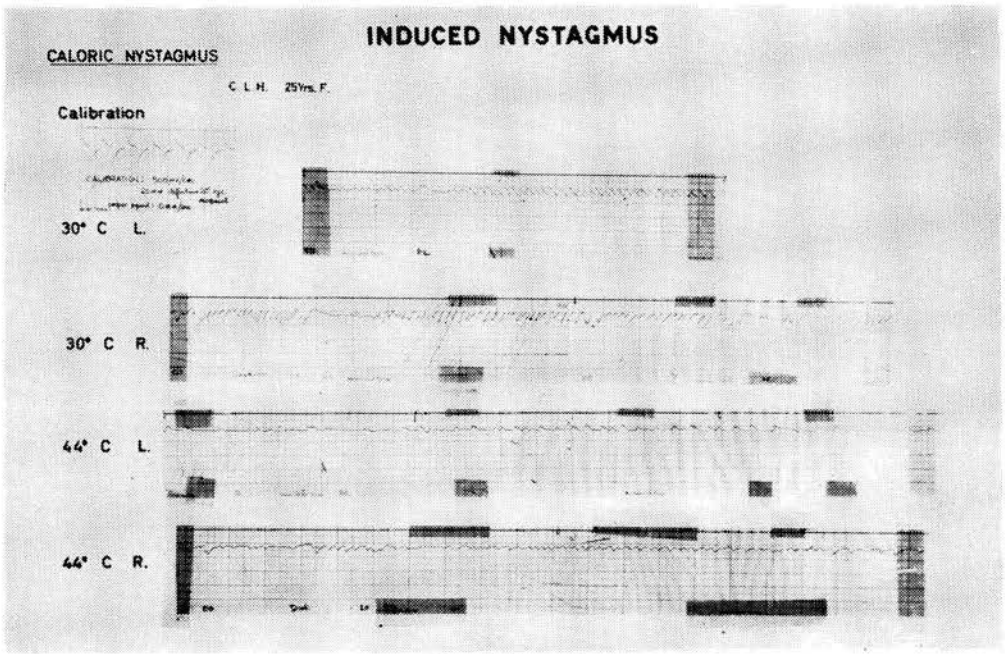

Fig. 5, Case 2
Electronystagmogram, C.L.H.

The induced nystagmus with caloric stimulation of the labrinth increases on eye closure (EC), thus indicating a peripheral lesion.
There is canal paresis on the left side, with directional preponderence to the right. This indicates a lesion probably in the cerebellum with pressure on the vestibular nucleus.

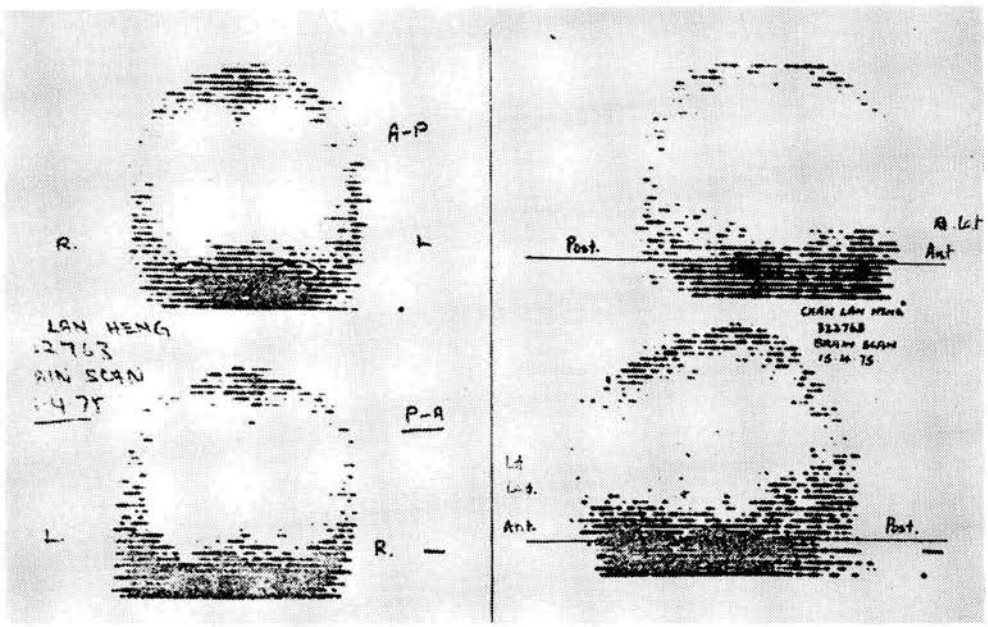

Fig. 6, Case 2
Brain Scan, C.L.H.

The Brian Scan shows a hot posterior fossa in the lateral view, more on the right than left. However, the P.A. taken earlier shows a relatively clear posterior fossa. There is obviously some delay in the uptake of radiactivity in the lesion. These findings suggest presence of extensive tumour in the posterior fossa which partially extends across the nidline from right to left.

was aggravated by lying on her left side. This was associated with vomiting and unsteadiness of gait. Some one month prior to being seen, she developed a severe occipital headache on and off; this was worst in the morning and upon bending forwards.

Examination revealed no significant abnormalities in the ears, nose and throat. Hearing was essentially normal bilaterally on tuning fork testings and pure tone audiogram. Cranial nerves functions were intact and there was no other neurological deficit except some truncal ataxia, more evident on the right side. She had no papilloedema. Her blood pressure was normal.

X-ray skull, cervical spine and internal auditory meati were normal. VDRL was non-reactive.

There was no spontaneous or positional nystagmus recorded on ENG. Caloric induced nystagmus was recorded on ENG: it showed bilateral peripheral lesions (Fig. 5). Because she had bilateral normal hearing, this suggested a lesion involving both the vestibular nuclei at the brain stem. Brian Scan (Fig. 6) supported the diagnosis of posterior fossa lesion.

Posterior craniotomy was performed by a neuro-surgical team and a large cystic astrocytoma was removed from the posterior cranial fossa, situated on the right cerebellum.

Discussion

Vertigo, the symptom of hallucination of movements, is often a difficult one to evaluate. It is, of course, necessary to differentiate a peripheral vertigo from a central one. This problem has been confronting the otolaryngologists and other clinicians for years. The importance of correlating the otological, neurological, vascular and anatomical findings in each case to reach a reasonable conclusion must be emphasised. ENG has a definite role in the evaluation of patient presenting with vertigo.

One of the great advantages of ENG is its ability to record the nystagmus, spontaneous or induced, in darkness and upon closing of the eyes. This eliminates optic fixation. In central vertigo, the nystagmus characteristically disappeared under these conditions as shown in case one; the reverse is true in peripheral vertigo (Hood 1968). Central nystagmus has been known to suppress the optokinetic nystagmus to one side (Ballantyne 1971). These ENG findings, together with the long duration of vertigo and its associated headache supported the diagnosis of central vertigo in case one.

The second case illustrates the importance of correlating the ENG findings with the clinical features and the anatomical knowledge of the vestibular system. Although it showed a bilateral peripheral lesions, her hearing was normal. This would mean that there is a lesion involving the vestibular nuclei at the main stem, e.g., posterior cranial fossa lesion. Again the associated headache and long duration of vertigo supported the diagnosis.

Summary

ENG is a relatively new investigation in Malaysia. Its value in aiding the diagnosis of central vertigo is briefly discussed in reference to the two proven cases of intracranial lesions.

Acknowledgement

Our thanks are due to the Medical Illustration Unit, Faculty of Medicine, University of Malaya for the help in providing the photographs and Miss A.M. Tan for typing.

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Ocular Complications in Longstanding Leprosy Patients at the Tampoi Leprosarium, Johore, West Malaysia

by Dr. (Mrs.) Jenny P. Deva
MBBS (OSMANIA.HYBD.) D.O.(IRELAND)

THE TAMPOI LEPROSARIUM was opened in October 1937. The total inmates were then 550. At the time of the survey however in October and November 1972, the total number of inmates was 296.

The Leprosarium is situated about 5 miles from the General Hospital in Johore Bahru.

Area Served by Leprosarium

Different states are served by this Leprosarium situated in the south of Malaya. The northern parts of Malaya are served by another Leprosarium situated in Sungei Buloh.

Johor State itself has the maximum number attending the Tampoi Leprosarium. After that come Malacca, Pahang, Negri Sembilan and Selangor – all these comparatively less in number.

Within Johor itself – the maximum number of patients come from Johor Bahru itself – then in decreasing numbers from Muar, Batu Pahat and Pontian. Very few patients come from the east coast of Johor state-areas of Kota Tinggi and Mersing.

Scope and Method of Survey:

Eye examinations were made with the help of a corneal loupe and Ophthalmoscope. Such cases as had to be seen by *slit* lamp or for confirmation by the Eye Specialist, Mr. S. Selvarajah were seen in the Eye-unit, General Hospital, Johor Bahru.

All the cases whether Lepromatous, Tuberculoid or Borderline were examined and their ocular lesions recorded. The lesions and findings are similar to those of Weerekoon's article 'Ocular Leprosy in West Malaysia' in the British Journal of Ophthalmology, Vol. 56 No. 2 February 1972. To quote him; "It is admitted that Active cases, mainly those involving the iris and sclera, were not numerous, but longstanding ocular involvement of every possible kind was rather common".

Only 239 out of 296 were examined. The numbers according to sex and ethnic origin were as follows:–

Male	165	Chinese	184	Lepromatous	52
Female	74	Malay	42	Tuberculoid	94
		Indian	13	Borderline	93
	239		239		239

Incidence of Eye Lesions:

To quote again, the opening sentences from 'The Eye in Leprosy' by D.P. Choyce in Cochrane's book on Leprosy, aptly fit in here.

> "The eyes are frequently involved in Leprosy either by the presence of bacilli in the eye, or secondary to involvement of Vth, or VIIth nerves, or by sensitization of the ocular tissues to leprous processes elsewhere in the body".

The incidence differs greatly with different authorities. However, in the group of inmates

examined in this Leprosarium – the ocular complications were apparently higher among the Lepromatous and Borderline cases in comparison with Tuberculoid group. In the Tuberculoid group, VIIth nerve involvement with paralysis of orbicularis muscle causing lagophthalmos and exposure keratitis was quite common.

Summary of Literature: (By D.P. Choyce 'The Eyes in Leprosy')

There are essentially two types of Leprosy or Hansen's Disease. One in infective or Lepromatous and the other Non-infective or Tuberculoid. Intermediate between these two is the Borderline group. Ocular involvement of the Eyes may occur in three ways:–

1) Direct spread of Leprous lesions from the lids, the face, and the nose and nasolaerimal apparatus to the eye itself.
2) Eye lesions secondary to lesions of Vth. and VIIth. nerves.
3) Direct infections of the eyeball with Leprosy bacilli.

1) **Direct Spread of Leprous Lesions:–**

This mode of spread is rare and ocular adnexal lesions might be present in the absence of an affected eye.

The following lesions may be seen:–

a) Gross lepromatous masses in the lids
b) Entropion lid may result and
c) Trichiasis resulting in Keratitis and Ulcer cornea
d) Madarosis
e) Dacrocystitis

2) **Eye Lesions Secondary to Vth and VIIth Nerve**

a) Vth. Nerve involvement may lead to corneal and conjunctival anaesthesia.
b) VIIth. Nerve involvement leads to lagophthalmos. Exposure Keratitis results if the Facial Palsy is marked.

3) **Direct Infection of Eyeball by Leprosy Bacilli**

How Leprosy bacilli reach the eye is still a disputable topic. Two views are held:

a) Majority favours the Nerval route – via the vth Nerve.
b) Others favour a Herxheimer type – sensitivity reaction of the deeper tissue like the iris.
c) Others think of a blood-borne infection.

Ocular Affection Can Present As Follows:–

I. **Conjunctivae and Episclera:**

Nodules may present commonly in the interpalpebral region. These may be quite large, smooth, reddish and painless.

II. **Cornea**

a) Corneal Nerves may appear unduely large and beaded.
b) Localised discrete opacities or cornea may appear covered by milky, chalky deposits.
c) Pannus formation – usually in superior limbus first and later circumferential.
d) Sclerosing keratitis may result from (c).

III. **Sclera**

Diffuse Scleritis may present but usually with Keratitis and Iridocyclitis.

IV. **Iris and Ciliary Involvement**

Very common and presents in 4 forms.

a) Miliary Lepromata or Iris Pearls – which are aggregations of Leprae bacilli and appear as tiny white spots – adjoining the pupillary margin.
b) Nodular Lepromata – are rarer, occurring in any part of the iris – are yellowish, globular and flattened.
c) Chronic Plastic Iridocyclitis
This is insidious in onset and is the most common cause of blindness in ocular leprosy. Later complications like Posterior Synechiae. and complicated cataracts can occur.
d) Acute Diffuse Plastic Iridocyclitis – This may occur suddenly.

V. **Posterior Segment Lesions:**

This is of low incidence

There are 2 types of Fundal lesions:

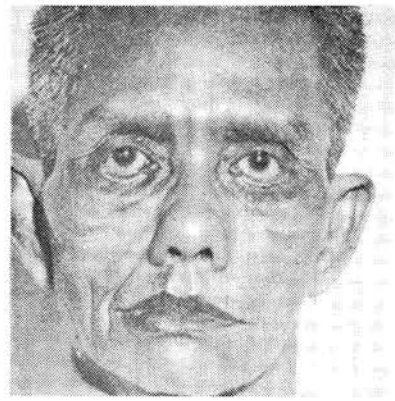
a) White, waxy, highly refractile deposits may occur at periphery of choroid and retina. Later there is retinal destruction and vascular fibrosis and sheathing result.
b) Discrete, circular, waxy and occasionally pedunculated nodules on retina.

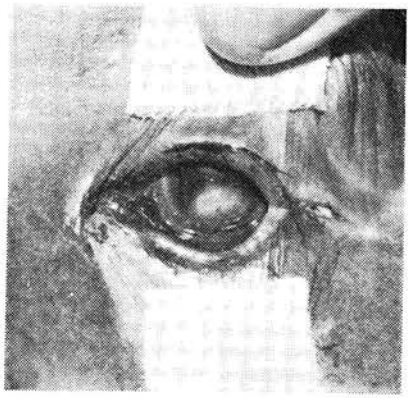
Ocular lessions are usually bilateral, but one eye may be affected earlier and more severely than its fellow.

Illustrated Case-Studies

Case 1

A Malay male aged 59 years, Tuberculoid leprosy. Visual acuity was 6/6. He had bilateral Facial palsy with marked lagophthalmos. The exposed conjuntiva showed increased vascularization and cornea showed Exposure Keratitis.



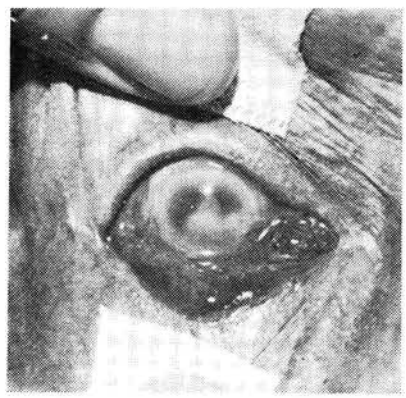


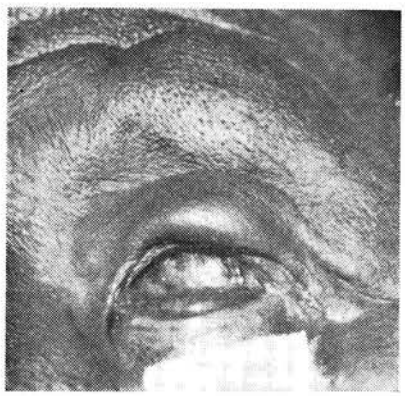
Case 2

A Chinese female aged 57 years. Borderline. Visual acuity 6/6, 6/6. She had a partially healed ulcer with a leucoma in the lower lateral quadrant of the cornea. A lateral tarsorrhaphy had been done for her.

Case 3

A Malay male aged 65 years. Borderline. Visual acuity was 6/24, 6/24. He had madarosis as well as entropion upper left eyelid and bilateral early Ectropion of lower lids. The whole conjunctiva of the right eye showed congestion and was hypertrophied. The cornea also showed a macula in the lower half of it.



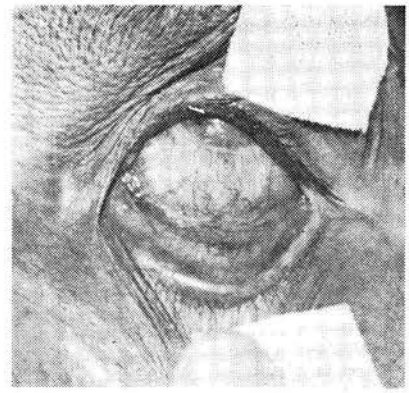


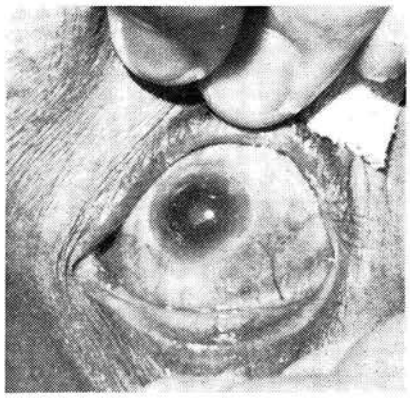
Case 4

A Chinese male aged 45 years. Lepromatous. Visual acuity 6/6, 6/9. He had a fairly large sized Lepromatous nodule on the left upper eyelid resulting in Entropion lid and trichiasis. This caused recurrent chronic conjunctivitis in that eye.

Case 5

A Malay Female aged 64 years. Borderline. Visual acuity 6/6, 6/9. She also had bilateral lagophthalmos. This was to illustrate the tortuous vessels present in the exposed parts of the conjunctiva. She also had Exposure Keratitis.



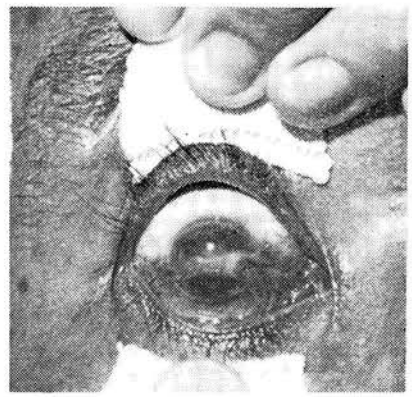


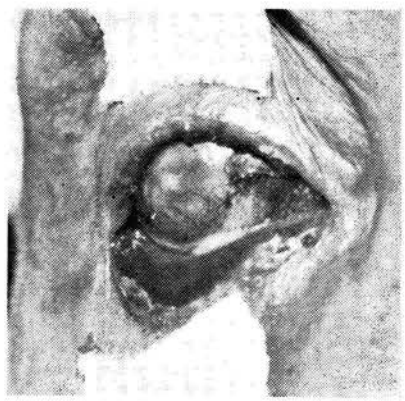
Case 6

An Indian Male aged 53 years. Lepromatous. Visual acuity 6/6, 6/9. He had diffuse hyperemic and yellowish lesions on lateral and medial bulber conjunctiva in the left eye. Episcleritis.

Case 7

A Chinese Female aged 99 years. Tuberculoid. Visual acuity 6/15, PL. She had bilateral lagophthalmos. Left eye had an ulcer in the centre and again pterygial-like vessels were seen.



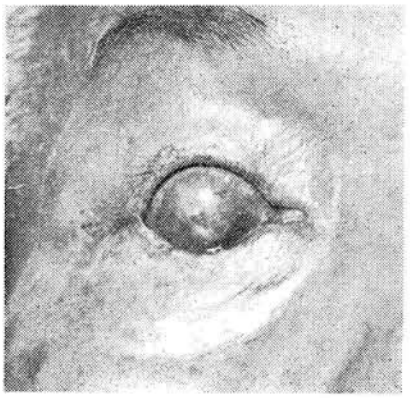


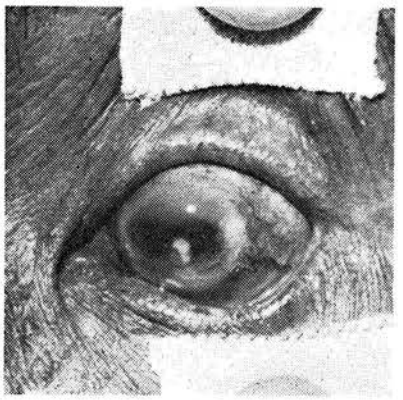
Case 8

A Chinese Male aged 68 years. Tuberculoid. Visual acuity No Vision. CF. The right eye had marked ectropion lid, the conjunctiva was congested. Tortuous vessels were seen. There was an ulcer cornea and surrounding keratitis. The pupil was fixed and exudates were present in the pupillary region.

Case 9

A Chinese Male aged 51 years. Borderline. Visual acuity CF: PL. There were exudates and posterior Synechiae in the eye while the rest appeared relatively normal.





Case 10

A Chinese Male aged 72 years. Tuberculoid. Visual acuity HM: 6/9. Right Facial Palsy with lagophthalmos corrected by Tarsorrhaphy. Old Iritis and ulcer cornea gave rise to adherent leucoma with vascularisation of cornea.

Leprosy Lesions:

	Lepromatous	*Borderline*	*Tuberculoid*	*Total*
Absence of Lashes	5	7	3	15
Entropion	1	—	—	1
Lid Nodules	2	—	—	2
Lid Erythema	1	—	—	1
Seventh Nerve Involved	—	16	22	38
Exposure Keratitis	1	6	9	16
Corneal Vascularisation	2	—	—	2
Adherent Leucoma	1	3	—	4
Corneal Macula or Leucoma	1	1	—	2
Chronic Conjunctivitis	1	4	6	11
Active Iritis	—	1	—	1
Phthisis Bulbae	—	3	3	6
Complicated Cataracts	1	1	—	2
Non-Leprous Lesions				
Cataract	2	4	8	14
Pterygium or Pterygical-like vessels	1	8	7	16
Tortuous vessels from periphery of conj,	12	10	5	27
Secondary Glaucoma	—	—	1	1
Diabetic retinopathy	—	—	1	1

Findings

Adnexal Lesions:

Absence of lashes: A total of 15 cases had madarosis.

Entropion: One case of entropion lid due to a single big leprous nodule on upper eyelid was seen, while the other had bilateral multiple nodules on upper eyelids of about 3 mm diameter.

VIIth nerve involvement with partial or complete paralysis resulted in atonic ectropion or lagophthalmos. This in turn led to Exposure Keratitis. One case of Lid Erythema was seen. Anaesthetic patches on lids were not seen.

Cornea:

16 cases only had Exposure Keratitis. Corneal leucoma or Adherent leucoma totalled 6. In one case, there was pannus formation around the upper limbus.

Uvea:

Uveal involvement is common in the Lepromatous and Borderline cases and is also the cause of blindness.

Chronic Plastic Iridocyclitis or the effects of old Iritis probably was quite often seen in both lepromatous and borderline cases.

One case of *Active uveitis* was seen. There were exudates on the iris and posterior synechiae had started forming but no Keratic precipitates were seen.

Phthisis bulbae was seen in borderline and tuberculoid cases.

Posterior Segment Lesions – No Leprous lesions were seen.

Non-Leprous Conditions

Non-leprotic conditions like cataract were present in a few cases. Tottous vessels growing from palpebral to bulbar conjunctiva was quite often seen among Lepromatous and Borderline cases.

A leash of vessels resembling that in pterygium was seen in a few cases. Intercurrent infection of the conjunctiva in cases with ectropion and exposure was common too.

Incidence of Blindness

The criterion of blindness was taken to be vision of 3/60 or less than that. There were 12 blind female patients out of a total of 73. In the male population there were 28 blind out of the total of 164.

The causes of blindness were as follows:–

	Male	*Female*	*Total*
Cataracts	17	9	26
Phthisis Bulbae	4	2	6
Old Iridocyclitis	6	2	8
Glaucoma	1	–	1
Surgical Anopthalmos	1	–	1

From this it can be seen that cataracts are the main cause of blindness. However, 14 of the cases are due to some form of uveal involvement or other. 7 female out of 12 and 14 out of 28 had binocular blindness.

Ethnic and Sex Incidence

The number of male patients to female patients with ocular lesions was slightly more being 35: 27, though the total population was in the ratio of 2.2: 1.

The number according to ethnic origin was as follows:–

	Female	*Male*
Chinese	24	29
Indians	1	2
Malays	2	4
	27	35

Summary

From this survey of longstanding cases of Hansen's Disease at the Tampoi Leprosarium it can be seen that ocular involvement is quite common and varied. The incidence in the Lepromatous and Borderline cases was slightly higher than in Tuberculoid cases. Amongst Tuberculoid cases the commonest conditions were secondary to VIIth nerve involvement.

The illustrated cases serve to show the variety in involvement of the eye from its adnexae to its intraocular structures.

The findings from this survey give a clear picture of how the eyes are involved in Leprosy either directly or indirectly or secondary to Vth or VIIth nerve involvement. It also illustrates the importance of eye examination in Leprosy patients to prevent a possible preventable blindness which may be the sequelae of intraocular leprous infection too.

Non-Leprous ocular complications also occur in these patients and these are amenable to treatment.

It was noted too, blindness in these patients were due to leprous-induced as well as non-leprous conditions. Ocular complications in the male population seemed to be slightly higher than that in the female population.

All in all, it can be said that Ocular Leprosy can be quite varied in presentation, and if treated or detected early, can be made to respond to treatment – before the course of it becomes uncontrollable leading to complicated cataracts or total blindness.

Acknowledgement

Thanks are due to Mr. S. Selvarajah (FRCS, Edin.) Ophthalmologist, General Hospital Johore Bahru for his kind advice.

Thanks are also to Dr. K. Rajagopalan, Dermatologist, General Hospital Kuala Lumpur, who was Supervisor of Tampoi Leprosarium then.

Eosinophilic Meningoencephalitis Caused by the Rat Lung Worm, Angiostrongylus Cantonensis with Special Reference to A. Malaysiensis in Malaysia

by *Lim Boo Liat*

Division of Medical Ecology,
Institute for Medical Research,
Kuala Lumpur,
Malaysia.

Introduction

ANGIOSTRONGYLUS CANTONENSIS (Chen, 1935), a metastrongyle nematode (Protostrongylidae, Nematoda) found in the lungs of rats in Canton, China was described as *Pulmonema cantonensis*. Matsumoto (1937) found this worm in rats in Taiwan, and in the same year Yokogawa (1937) described it as *Hematostrongylus ratti*. Dougherty (1946) treated the genus *Pulmonema* as synonymous with *Angiostrongylus* (Kamenskii, 1905) and since then the worm is known as *A. cantonensis*.

Geographical Distribution

A. cantonensis which is found in wild rats (definitive hosts) and molluscs (intermediate hosts) is widely distributed.

a. *Southeast Asia*:– Philippines (Nishimura and Yogore, 1965); Vietnam (Do and Hendricks, 1974); Indonesia (Kwo and Kwo, 1968); Thailand (Harinasuta *et. al.* 1964; Crooks *et. al.* 1968); Malaysia (Schacher and Cheong 1960; Lim *et. al.* 1965; Lim and Heyneman, 1965; Lim, 1967, 1970; Lim and Ungku Omar-Ahmad, 1969).

b. *Other countries*:– East Africa (Brygoo and Chabaud, 1964, Alicata, 1965); India (Parmeter and Chowdhury, 1966); Queensland, Australia (Mackerras and Sanders, 1955); Ryukyu Islands, Japan (Nishimura *et. al.* 1964); Taiwan (Kuntz and Myers, 1946); Pacific Tropics (Alicata 1963a; Wallace and Rosen, 1965).

Angiostrongylus cantonensis in Man

Nomura and Lin (1945) reported the first human infection in Taiwan where the worm was found in the cerebro-spinal fluid of a patient having eosinophilic meningoencephalitis. Sever alcases of this disease were reported later (Hsieh, 1967; Chiu *et. al.* 1968). Rosen *et. al.* (1962) reported adult nematodes occurring in the brain of a man in Hawaii, and they were confirmed to be *A. cantonensis* (Chitwood, 1961). In Vietnam a fatal case of eosinophilic meningoencephalitis was reported in a girl of 18 years at Haiphong by Jindrak and Alicata (1965). From serial histological sections of the brain, the morphological characters of the nematodes are believed to be that of young adults of *A. cantonensis*. Tangchai *et. al.* 1967, reported *Angiostrongylus* probably *cantonensis* in the brain of a Thai woman who died of eosinophilic meningoencephalitis. In Malaysia two cases with worms found in the CSF were reported by Watts (1969) and Bisseru (1972).

Several cases of ocular angiostrongyliasis in Thailand were also reported (Promminderoj *et. al.* 1962; Ketsuwan and Pradatsundarsar, 1965, 1966).

Clinical and Symptomatic Cases of Eosinophilic Meningoencephalitis

An epidemic of this disease occurred in Ponape, Eastern Carolines (Bailey, 1948). Further incidences were reported in the Pacific Tropics (Franco *et. al.* 1960; Allison, 1962), Vietnam (Sison *et. al.*). Indonesia (Smit, 1962), Thailand (Khwanmitra *et. al.* 1957; Punyadasni and Punyagupta, 1961; Tantibehduangur, 1963; Behjaponge, 1964; Punyagupta, 1965) and in Malaysia (Watts, 1969; Bisseru, 1972).

The epidemiology of this disease suggests that direct ingestion of certain food of animal origin was involved in the transmission of the parasite to man. In Thailand, Punyadasni and Punyagupta (1961) and Punyagupta (1965) discovered that eosinophilic meningoencephalitic patients had ingested pickled snails, *Pila ampullacea*. Naturally infected *Pila scutata* in Malaysia when consumed, could transmit the same disease (Lim and Krishnansamy, 1970). In the Pacific Tropics certain infected fresh water crustaceans (prawns), fish, land crabs, when eaten, transmitted the infective larvae of the parasite to man (Bailey 1948; Alicata and Brown, 1962; Rosen *et. al.* 1967; Franco *et. al.* 1960; Alicata 1965a). The African snail *Achatina fulica,* commonly eaten in certain parts of Taiwan (Formosa) has been implicated in several cases of cerebro-angiostrongyliasis (Hsieh, 1967). Heyneman and Lim (1967) found that fresh vegetables in Malaysia may be involved in the transmission of these parasites to man.

The parasite seldom reaches maturity in man, an accidental host, and in all but one positive case, the parasite were found only in the cerebrum, cerebellum or spinal cord. The exceptional case was a 5-year old female in South Taiwan who died of the disease; immature worms were recovered from the brain and spinal cord, but mature worms were found in the lungs (Chin *et. al.* 1968).

Clinical Manifestations of *A. Cantonensis*

The most typical symptoms of the disease start about two weeks after infection with an abrupt or slowly increasing headache, neck and back stiffness, photophobia, nausea and vomiting (Bailey 1948). Sometimes, a generalised or focal hyperesthesis of skin or muscles appears with signs of paralysis of one or more nerves. The temperature may be slightly elevated. After one or two weeks duration, the symptoms slowly disappear.

The following symptoms are listed in accordance with frequency of their occurrence (Alicata and Jindrak, 1970).

a. Headache with a throbbing syndrome is the most constant symptom of angiostrongyliasis.

b. In most instances a headache is accompanied by nuchal and dorsal stiffness and pain.

c. Photophobia often preceded or accompanied by blurring of vision.

d. Vertigo, loss of balance on standing or sitting.

e. Nausea, often followed by vomitting, accompanies other meningeal symptoms.

f. Parenthesiae consisting of sensations of burning, tingling, pain, numbness, commonly occur on the face, shoulders, forearm and trunk, sometimes over half of the body.

g. Diplopia has been found in some cases.

h. Defective hearing, troubles of deglutition and in articulation of speech have been found in some cases (Schollhammer *et. al.* 1966).

i. Chills, malaise, anorexia, general aches ean pains are manifestations of a more severe course of the disease.

Duration of the illness ranges from two to thirty-one days, but it may extend over several months (Bailey, 1948).

Angiostrongylus malaysiensis

Lim *et. al.* (1965) studied extensively the natural infections in field and house rats and various species of intermediate molluscan hosts with this parasite in different habitats throughout the country. In their studies of the adult worms slight difference were found in morphology between the Malaysian strain of *A. cantonensis* and the parasite in the original description by Chen (1935) and by Mackerras and Sanders (1955). Evidence of strain specificity among three geographical strains of *A. cantonensis,* namely the Thai, Hawaiian and Malaysian strains has been observed by Heyneman and Lim (1967) and by Lim and Heyneman (1968). These studies showed that previously infected rats developed no marked protection against heterologous strains, and that there was a high probability that the host was protected against a challenge by the homologous strain. Cross and Fresh (1969) demonstrated that the Malaysian strain could cause a different pathology in animals from that caused by the Thai and Hawaiian strains. Subsequently, the Malaysian strain, *A. cantonensis* was redescribed as a new species, *A. malaysiensis* by Bhaibulaya and Cross (1971). In view of the redescription of the parasite, Lim (1973) reexamined the *Angiostrongylus* adult worms which were previously studied by Lim *et. al.* (1965) and agreed with Bhaibulaya and Cross (1971) that the worm is a new species, *A. malaysiensis*. However, Lim (1974) also found forest rats naturally infected with *A. malaysiensis* and he postulated that the parasite is indigenous to Malaysia.

Lim *et. al.* (1965), Lim and Heyneman (1965) and Lim (1967) found that *A. cantonensis* (= *A. malaysiensis*) is a widespread parasite of domestic, rural and forest rats. It is transmitted by various

land snails and slugs (Lim *et. al.* 1965; Lim and Heyneman 1965; Lim, 1970; Bisseru, 1971). Fresh water snails have also been found to be susceptible intermediate hosts (Lim *et. al.* 1965; Lim and Heyneman, 1965). The worms develop in the rats, and mature in the pulmonary arteries after migrating through the brain (Lim *et. al.* 1965).

Malaysian Cases

The first five cases of eosinophilic meningoencephalitis in Malaysia were reported from Sarawak (Watts, 1969). The clinical picture was that of a subacute meningitis with eosinophilic pleocytosis. All five patients suffered headache, muscle pains, fever, vomiting, diplopia, neck stiffness, papilloedema and cranial nerve palsies. The duration of illness was from 23-24 days. Larvae supposedly identified as *A. cantonensis* were recovered from two of the five cases. All the cases were treated with Hetrazan (diethycarbamazine) in a dosage of 6 mgms/kgm body weight daily for 21 days.

None of the cases reported ate raw molluscs or crustaceans. In one case a child of eleven months old was occasionally given unpeeled banana to eat. The African snail *Achatina fulica,* intermediate host of the parasite, was found in large numbers on the fruit and leaves of banana trees, and it was suspected that this case was infected from the contaminated skins of bananas. Studies of the intermediate hosts of the parasite in Sarawak by Lim (1970), shows that other land molluscs, a species of land snail, *Macrochlamys resplendens,* land slugs, *Microparmarion malayanus,* and *Laevicaulis alte,* and a species of freshwater molluscs, *Pila scutata,* are abundant. The molluscs except *P. scutata* are also commonly found in banana plantations (Lim, 1970). *M. malayanus* in particular, is found always attached to banana trees and leaves, and this snail has been established to shed larvae on lettuce leaves (Heyneman and Lim, 1967).

The sixth Malaysian case of eosinofphilic meningoencephalitis was observed in Kuala Lumpur, Peninsular Malaysia (Bisseru *et. al.* 1972). The patient was found to show all the symptoms of the disease, and two larval nematodes were recovered from the CSF, one of them alive. Unfortunately no illustration of the two larval nematodes was given, but they have been allegedly identified by the authors as late third stage larvae of *A. cantonensis* corresponding to about the fifth post-infective day from the cerebrum of laboratory-bred white rats infected with the third stage infective larvae of the parasite. Measurements of the two worms were 0.52 mm long by 0.01 mm wide and 0.71 mm long by 0.01 mm wide. The mode of infection by the parasite in this case was suggested by the history of the patient having eaten half cooked prawns, shellfish, raw lettuce, tomatoes and other salad greens contaminated by larvae.

In the Kuala Lumpur case, larvae reported as late third stage were recovered 17 days after the patient was known to have eaten a meal of half-cooked shellfish, prawns and raw vegetables Bisseru *et. al.* (1972). In monkeys *(Macaca mulatta)* fed with infective larvae of *A. cantonensis* 5th stage larvae developed in the brains 17 days after infection Weinstein *et. al.* (1973); these were found to be comparable to 5th stage larvae recovered from man after an infection of unknown duration Rosen *et. al.* (1962). Experimental study of local macaques *(M. fascicularis)* fed with infective larvae recovered from naturally infected slugs, *M. malayanus,* showed that some of the worms developed to 5th stage or sub-adult stage in the brains from 11 to 19 days after infection, but most of the other worms recovered were stunted Lim (1970). The normal worms consisted of nine 11 days, two 15 days, and four 19 days old. The mean measurement for the 11 days old worms was 1.94 mm (0.90-2.80) long and 0.05 mm (0.03-0.07) wide; for 15 days old, 2.29 mm (1.11-3.48) long and 0.07 mm (0.04-0.09) wide and for 19 days old 4.79 mm (3.57-5.88) long and 0.12 mm (0.08-0.14) wide. Mean measurement of 30 five days old worms recovered from experimental infected white rats was 0.64 mm (0.45-0.80) long and 0.01 mm (0.01-0.02) wide.

Epidemiologic evidence in these six instances of eosinophilic meningoencephalitis in Sarawak, and Kuala Lumpur suggests that ingestion of contaminated food with larvae of the parasite was the probable route of infection. Positive evidence for aetiological role of the parasite in three cases (Watts 1969; Bisseru 1971) was based on the finding of larvae in the cerebrospinal fluid. Since the larvae recovered from these cases were not available for further re-examination and as such one could question the authenticity of these cases.

Conclusion

Six cases of human angiostrongyliasis have been reported in Malaysia up to the present time. Larvae, presumably *A. cantonensis,* were recovered in three of the six cases; the remaining four diagnoses were based on clinical signs and symptoms.

Angiostrongylus malaysiensis is widely distributed in Malaysia) in a number of land molluscs and rat host species (Lim *et. al.* 1965; Lim and Heyneman, 1965). Fortunately none of the land molluscs are consumable. Only two species of fresh water molluscs, *Pila scutata* and *Bellamyia ingallsiana,* were found to be edible (Lim and Krishnansamy,

1970). Of these *P. scutata* is found to be eaten by various communities in this country (Lim *te. al.* 1965; Lim 1970; Lim and Ungku Omar-Ahmad, 1969); thus there is a potential risk of human infection. The infection could also be acquired by eating foods, particularly raw vegetables, which are contaminated with the parasite shed by the land slug, *M. malayanus* and the African snail, *A. fulica* (Heyneman and Lim, 1967; Watts, 1969).

The freshwater snail, *P. scutata* is common in ricefields, fish ponds, and abandoned tin-miting pools. The land slug, *M. malayanus* and the African snail, *A. fulica* are abundant in vegetable gardens in the rural areas. It could appear that rural folks are more likely to come in contact with the parasite than people in the urban areas. Since the evidence for eosinophilic meningoencephalitis in Malaysia is inconclusive, a systematic survey of the rural folk for symptoms and signs of this disease – with special attention also to dietary habits – would be worthwhile.

Acknowledgements

My gratitude to the Director, Institute for Medical Research, Kuala Lumpur, Malaysia for permission to publish this paper.

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Homocystinuria – A Case Report

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Introduction:

HOMOCYSTINURIA is an inborn error of methionine metabolism, first described in 1962 by Carson and Neill[1] as a result of a survey of institutionalized mentally retarded children using urine chromatography. Mudd[2] (1964) pointed out that the defect was in a deficiency of the enzyme cystathionine synthetase which mediates the conversion of homocysteine to cystathionine (Figure 1). This he confirmed by demonstrating the deficiency of the enzyme activity in the liver of such patients.

The enzyme deficiency results in an accumulation of homocysteine. This is converted to homocystine which overflows into the urine[3]. Blood and urine levels of methionine are also increased but are usually not high enough to be detectable.

Homocystinuria is heritable in an autosomal recessive manner. Up to 1970, 150 cases have been reported in the literature[4]. The incidence among the mentally retarded is 0.3% in Ireland (Carson, 1963)[5] and 0.02% in the United States (Spaeth and Barber, 1967)[6]. Most cases have been reported among Caucasians though reports have also appeared from Japan, India[4] and Thailand[7]. We are not aware of any previously reported case in Malaysia and Singapore.

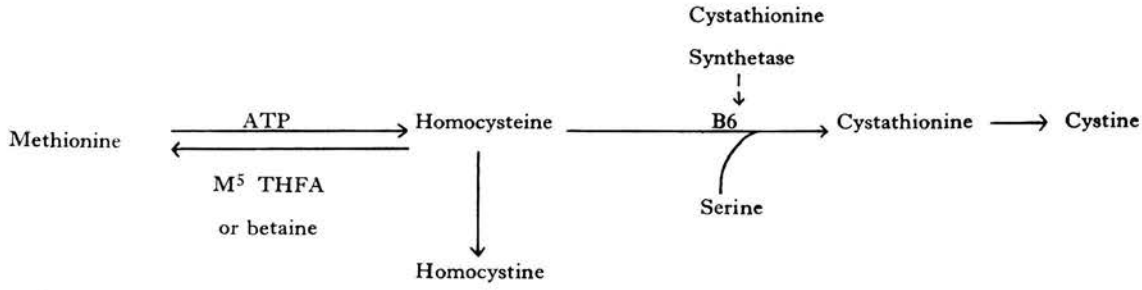
Case report:

A 9 year-old Chinese boy was first seen at the University Hospital, Kuala Lumpur on 17/12/74 for progressive deterioration of vision of 3 years' duration. He was variously diagnosed as having "dislocated lenses" and "enophthalmitis".

He was born after a full term normal delivery with a birth weight of 7 lbs. His developmental milestones were delayed-viz. sat up at 1 year, walked at 3 years and could say a few words with meaning only at 5 years. He was also hampered by deteriorating vision in school which he was forced to leave a year before admission to hospital.

He is the second child in a family of five. His parents were not related and there was no family

Figure I: Methionine Metabolism in Mamalian Tissues



M^5THFA = N^5 methyltetrahydrofolic acid.
B6 = Pyridoxal phosphate.
ATP = Adenosine triphosphate.

history of similar illness, mental retardation, unexplained deaths or abortions. He had no past history of thrombosis.

Physical Examination showed the Marfan habitus (Fig. 2) – tall and thin with the height on the 50th percentile of the growth charts; arm span (139 cm) greater than height (133 cm) upper segment to lower segment ratio (64/69) 0.92 and arachnodactyly (Fig. 3). Bone deformities were striking – prominent thoracic kyphoscoliosis (Fig. 4), pectus excavatum (Fig. 5) and mild genu valgum. His fingers could not be fully extended because of contractures (Fig. 6) and there was limitation of abduction at the shoulder joints due to a varus deformity of the head of the humerus (Fig. 7).

Examination of his eyes was hampered by the marked (Fig. 8) photophobia. Divergent squint was present with blue sclerae and interstitial keratitis. There was a corneal opacity on the left eye in addition to the bilateral vitreous opacity. No ectopia lentis could be detected and the Consultant ophthalmologist was of the opinion that he had endophthalmitis.

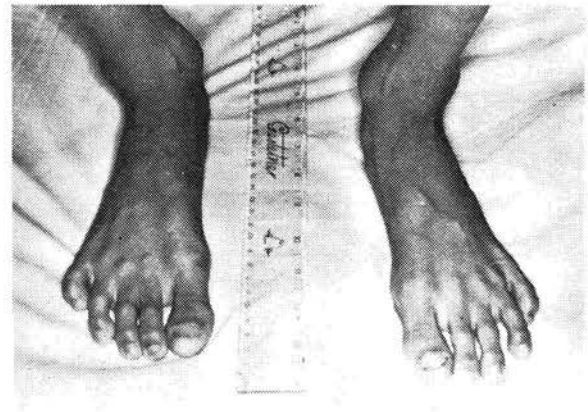


Fig. 3 – Arachnodactyly.

He was severely mentally retarded – could say a few words but was unable to speak in sentences. All peripheral pulses were palpable and there was no bruit heard. No skin manifestations of homocystinuria could be detected.

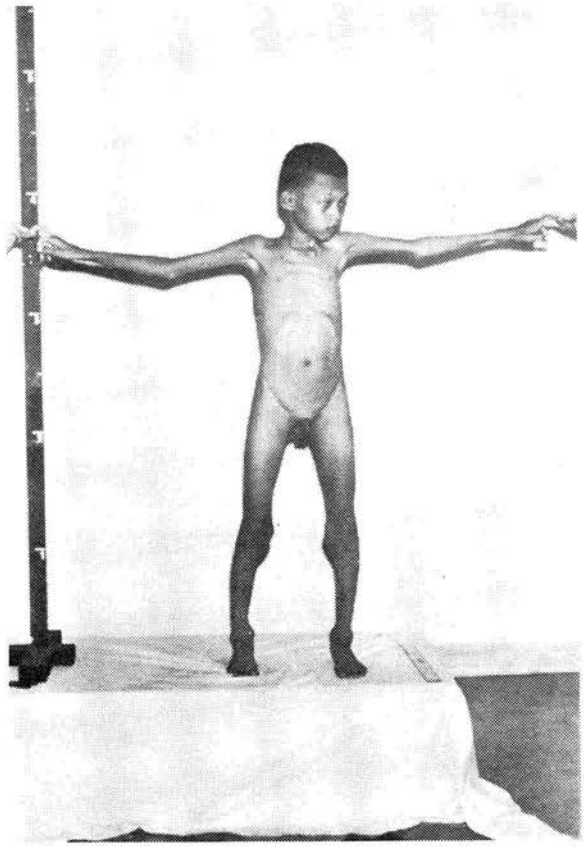


Fig. 2 – Shows the Marfan habitus; the arm span is greater than the height.

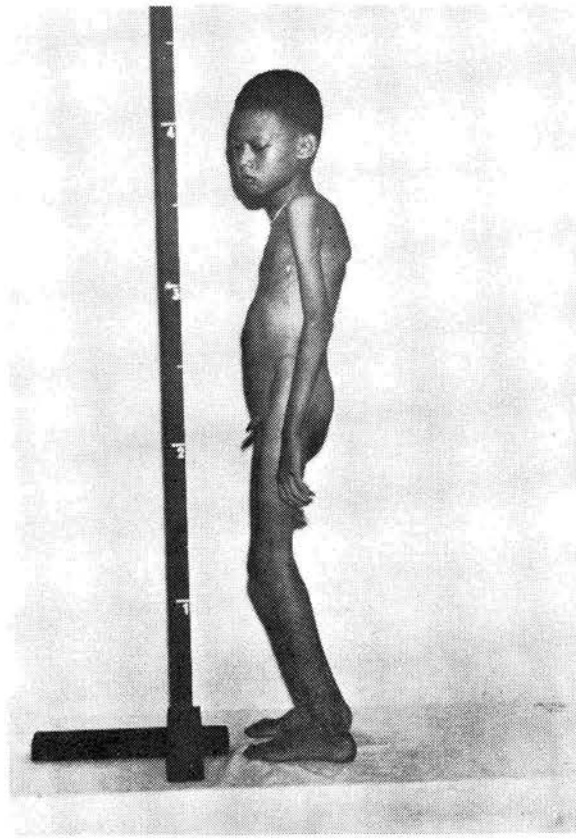


Fig. 4 – Thoracic kyphoscliosis.

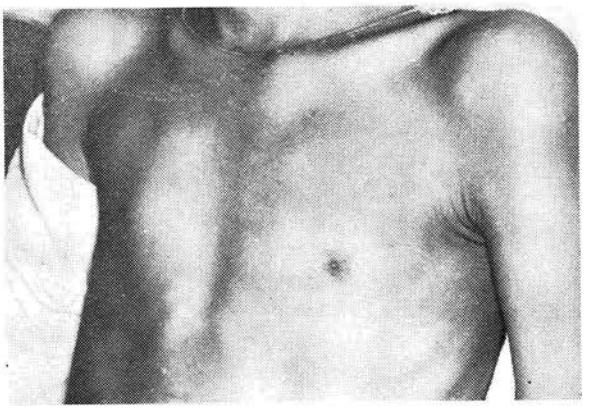


Fig. 5 – Pectus excavatum.

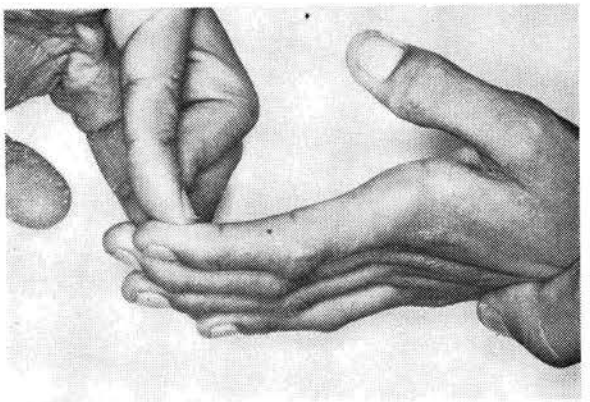


Fig –6 Shows contractures at the proximal interphalargeal joints of the fingers thus causing limitation in extension.

Laboratory Studies:

Routine blood counts, urine examination, electro cardiograph and liver function tests were normal. The platelets showed a slight reduction in adhesiveness.

The cyanide nitroprusside test was strongly positive on 3 occasions. One dimensional urine chromatography in butanol: acetic acid: water (12:3:5 v/v)[8] showed a densely staining spot corresponding to the region of homocystine marker (Fig. 9). Methionine was also detected. Blood chromatography gave similar results. Further resolution using high voltage electrophoresis in acetic acid: formic acid: water (4.6:1:32.8 v/v)[23], pH 2.0, revealed strong reaction at the spot corresponding to standard homocystine (Fig. 10). The homocystine marker was obtained from homocystine thiolactone by atmospheric oxidation in the presence of ferric chloride.

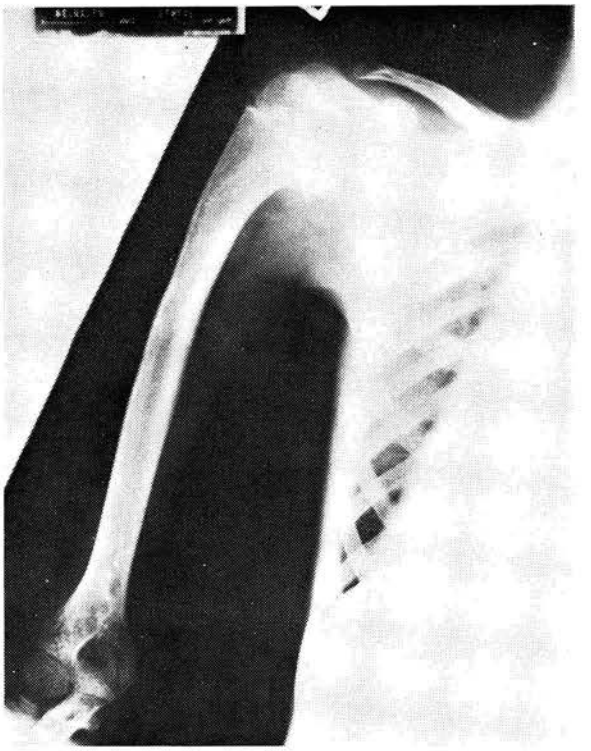


Fig. 7 – X-Ray shows a varus deformity of the head of the left humerus.

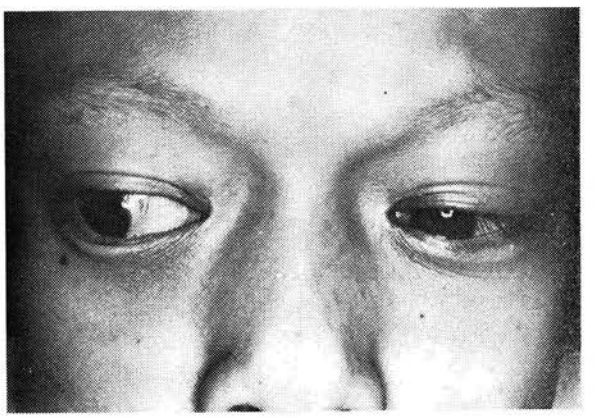


Fig. 8 – Shows the divergent squint and a ring of blue sclera in the right eye.

X-rays of the spine showed osteoporosis and kyphoscoliosis. The metacarpal index of 10.8 was in the Marfan range (Parish, 1966)[9]. X-rays revealed a varus deformity of the head of both humeri (Fig. 7). Serum folate level was 8 pg/ml.

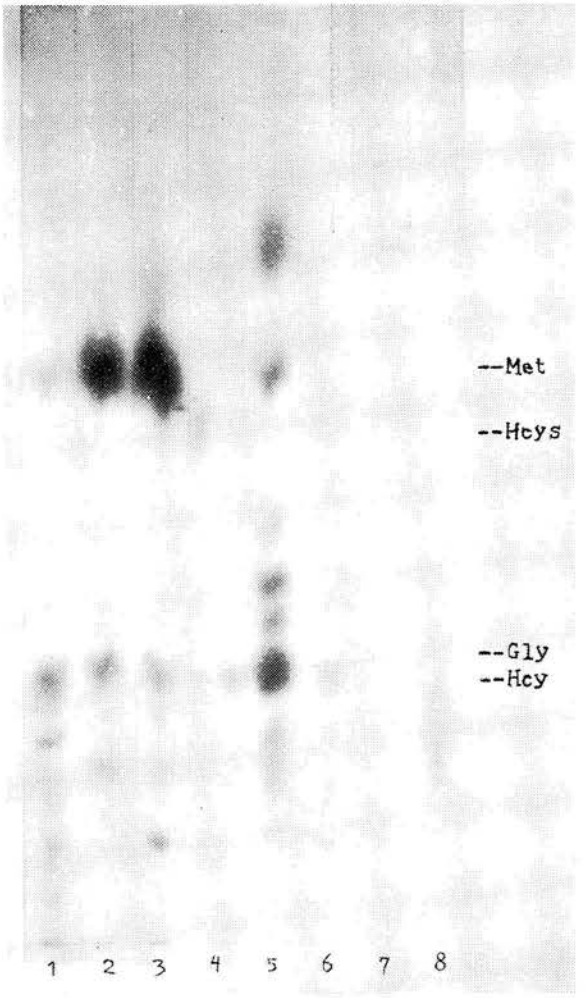


Fig. 9 – One Dimensional Paper Chromatography of Amino Acids from the Urine of the Patient and the Parents.

1. **Urine of Father (23.12.1974)**
2. **Urine of Mother (23.12.1974)**
3. **Urine of Patient (23.12.1974)**
4. **Standard-Mixture of 20 amino acids**
5. **Standard-Mixture of homocysteine and homocystine**
6. **Urine of Father (30.12.1974) after Methionine Loading**
7. **Urine of Mother (30.12.1974) after Methionine Loading**
8. **Urine of Patient (30.12.1974)**

Met. = methionine; Hcys. = homocysteine; Gly. = glycine; Hcy. = homocystine

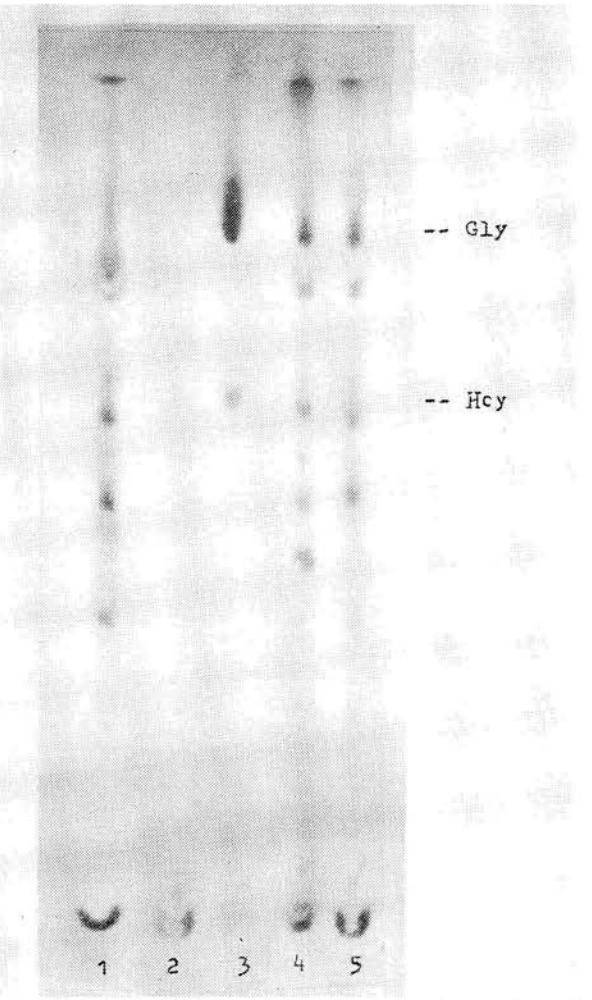


Fig. 10 – High Voltage Electrophoretic Seperation of the Amino Acids from the Urine of the Patient and the Parents.

1. **Urine of Father (23.12.1974)**
2. **Urine of Mother (23.12.1974)**
3. **Mixture of Homocystine and Glycine**
4. **Urine of Patient (23.12.1974)**
5. **Normal Urine to which Homocystine was added**

Gly. = glycine; Hcy. = homocystine.

Family studies were restricted to the phenotypically unaffected parents as the other siblings were not available. A methionine load (100 mg/kg) was given to the parents and 2 hours later, blood and urine samples were collected for the following tests (Table I).

Treatment and Progress:

Large doses of Pyridoxal phosphate (600 mg daily) was given. Two weeks after therapy, the cyanide-nitroprusside test and urine chromatography still showed presence of homocystine. The serum folate level remained at 8 pg/ml. Clinically, the child remained unchanged.

Table I

Biochemical Tests on the Urine Samples of the Patient and his Parents

	Cyanide Nitroprusside Test	*URINE* Chromatography	HVE** Confirmation
1) *Mother:* *BEFORE* methionine loading	Faint reaction	Negative	Negative
AFTER *methionine loading	†	†	†
2) *Father:* *BEFORE* methionine loading	†	†	†
AFTER *methionine loading	†	†	†

*: methionine was given in a dose of 100 mg/Kg body weight and urine was tested 2 hours later.
†: indicates presence of homocystine.
**: HVE: High-voltage electrophoresis.

Discussion:

The diagnosis of homocystinuria was suspected on the basis of the Marfan-like features, mental retardation and the history of "dislocated lenses".

Ectopia lentis occurs in the majority of homocystinurics. Cross and Jensen (1973)[10], in a review of 42 biochemically proven cases noted that 38 (90%) had symmetrically dislocated lenses. It is difficult to determine the time of onset of dislocation as serial examinations from birth were not performed in most series. In McKusick's series of 83 cases[11], dislocated lens was detected at 3 years of age in one child while in two others it did not occur till the ages of 24 and 28 years – the latter were mildly affected cases with minimal skeletal manifestations, unlike the patient described here. Other less well-known ocular abnormalities reported include strabismus, blue sclerae, glaucoma with or without pupillary entrapment of the dislocated lenses, buphthalmos, staphyloma, retinal detachment and optic atrophy. Cross et al (1973)[10] found 5 with strabismus and two with blue sclerae in their 42 cases. Both these features are present in the patient reported here. The striking eye changes in the patient described i.e. corneal opacity, vitreous opacity, bilateral endophthalmitis and interstitial keratitis are atypical of homocystinuria and to the best of our knowledge, have not been described.

The skeletal abnormalities, namely the Marfan habitus, kyphoscoliosis, pectus excavatum and osteoporosis are well established features of homocystinuria. The contractures of the fingers in this disorder contrast sharply against the joint laxity of the fingers seen in Marfan's Syndrome. In addition, the varus deformity of the head of the humeri is a distinctive feature of the disease.

Mental retardation, the other conspicuous finding in this patient, probably began early in life, as evidenced by the delayed developmental milestones. Though present in the majority of homocystinurics, it is not an invariable feature and intelligence may even be superior. Other nervous system manifestations described include seizures and psychoses.

Thromboembolic phenomena are commonly described in homocystinuria, especially following surgical procedures. In addition, angiographic studies are contradicted because of the risk of thrombosis. These patients are also prone to myocardial infarction, renal vascular hypertension, pulmonary and cerebral thrombosis.

No cutaneous manifestations were observed in this child. Those that have been described in homocystinuria include malar flush, livedo reticularis and light-coloured hair.

The differential diagnosis rests chiefly with Marfan Syndrome. Table II after McKusick[11] lists the contrasting features.

The cyanide-nitroprusside test, strongly positive in the patient described, is based on the reduction of cystine or homocystine in the presence of sodium cyanide to cysteine or homocysteine which then reacts with nitroprusside to give a violet colour. It is not specific for homocystinuria.

The diagnosis was established by urine and blood chromatography. Urine chromatography revealed dense staining spots corresponding to homocystine. Further resolution on high voltage electrophoresis confirmed the presence of homocystine in the patient, as well as in the parents.

Table II

Differentiating features of Homocystinuria and Marfans Syndrome (after McKusik, 1972)[11]

	Homocystinuria	Marfan Syndrome
1. Inheritance	Recessive	Dominant
2. Skeletal abnormalities	Osteoporosis, fractures, arachnodactyly	Arachnodactyly and loose-jointedness more striking.
3. Pectus excavatum or Carinatum	Frequent	Frequent
4. *Ectopia lentis*	Develops progressively with downward displacement.	Usually congenital and displaced upward
5. *Vascular disease*	Dilation with thrombosis in medium sized arteries and veins.	Dilation and/or dissection of aorta.
6. *Skin*	Malar flush, livedo reticularis	Striae distensae.
7. *Mental retardation*	Frequent	Absent

Facilities for the essay of cystathionine synthetase were not available.

Detection of heterozygote carriers of this disorder is often hampered by the lack of facilities for enzyme assay. It has been shown that such carriers have approximately half the normal cystathionine synthetase activity in liver biopsy specimens (Finkelstein et al, 1964)[12]. Methionine loading tests, based on the reduced ability of carriers to metabolise methionine have been used in the detection of heterozygotes but many workers have not found them useful (Brenton et al, 1965[13]; Kennedy et al, 1965[14], Laster, 1965[15], Dunn et al, 1966[16]). However, Sardhawala et al, 1974[17] found that a study of sulphur-containing amino acids in plasma and urine after L-methionine loading is of value in the detection of heterozygotes for homocystinuria. The presence of homocystine in the urine of the parents after methionine loading, as confirmed by high voltage electrophoresis is significant and may indicate that parents are carriers of this disease.

Vitamin B6, a co-factor for cystathionine synthetase, is currently used in the treatment of homocystinuria on the basis that it increases residual cystathionine synthetase activity. Mudd (1970)[18] and Barber (1969)[19] treated homocystinuria with high doses of vitamin B6 and subsequently found homocystine not detectable in the urine. The disease is a heterogenous one and not all patients so treated will respond. It is not possible to predict which case will respond, but in general, mildly affected cases show a better response than the more severely affected ones. In the reported case here, the eye and mental changes, being already well-established, are unlikely to respond to any form of treatment. It is hoped that with treatment such complications, as thrombosis, may be prevented. One important point to note is that during treatment with pyridoxine, folate depletion may occur which may reduce the response to pyridoxine (Wilcken et al, 1973)[20]. It is thus important to ensure that adequate folate levels are maintained during treatment and when indicated, folate supplements given.

In addition, a low methionine diet has been used in the treatment of homocystinuria. The rationale is to reduce the concentration of metabolites proximal to the site of enzymic block i.e. methionine and to supplement the diet with cystine which is deficient as a result of the enzymic block. The efficacy of a low-methionine, high cystine diet has been reported (Komrower, 1966[21]; Perry, 1968[22]) in patients who have been treated from early infancy. Perry (1968)[22] gave the diet from birth to an affected sibling of a severely affected case of homocystinuria. Regular follow-up till the age of 6 years showed that the child was developing normally. Such a diet was not given to this patient as the disease is advanced and unlikely to respond to this form of treatment which is expensive and has to be supervised for prolonged periods.

Prognosis is very variable. Deaths have been reported as early 1 year as late as 89 years[11]. Morbidity may be considerable from thrombo-embolic phenomena, visual changes and intellectual deficit.

Summary:

A case of homocystinuria is presented and the clinical features, laboratory studies, treatment and prognosis discussed. We believed this is the first case reported in the Malaysian and Singapore literature.

Acknowledgements:

We are most grateful to Professor M.J. Robinson for the encouragement and invaluable criticisms and to Mr. R. Daly for typing the manuscript.

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Direct Infusion of Coconut Water

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Abstract

The use of coconut water as a form of infusion therapy has been limited to the under-privileged countries. It has been so utilised mainly as a cheap and readily available source of fluid containing the requisite electrolytes. Hitherto, infusion of the water was carried out only after considerable prior treatment. This paper describes a method of direct infusion of the water from the fruit into the patient and presents the clinical impression of its use in 15 surgical cases treated in areas with no available facilities.

Introduction:

THIS PAPER describes a highly interesting and as yet unrecorded method of direct infusion of water from the fruit into vein without any preliminary preparation. Clinical experience suggest it to be an adequate substitutive therapy in unprivileged areas where any form of ancillary clinical help, diagnostic or therapeutic are not available.

Materials and Methods:

A review of the literature reveal its use hitherto be limited in cases with chlorodiarrhoeas, nutritional oedemas, and deficiency diseases[3,5,6]. This series comprise of 15 post-operative cases (Table I), where clinical ion deficiencies were suspected. All patients suffering from undue weakness, apathy, fatigue, anorexia and intestinal ileus approximately 36 hours post-operative were suspected of ionic deficiency.

Preoperatively, all the cases were found to be grossly underweight and malnourished. Mild to moderate degree of dehydration was found to coexist in 13 of the cases. Clinically, this was assessed by dryness of the mucosa, laxity of skin and by the tension of the eyeball. Replacement of fluid by infusion with 5% dextrose on normal saline were commenced in all these cases before surgery. Nasogastric suction was instituted post operatively in all cases.

Table I
Case Material

Cl. Diagnosis	Operation	No.
Gastric Ulcer	Gastrectomy	1
Pylorio stenosis from duodenal ulcer	Vagotomy with byepass	7
Tuberculosis of ileum	Intestinal resection	2
Intestinal fibrosis	Release of obstruction bands	2
Intestinal obstruction	Laporotomy with resection	2
Multiple injury	Disarticulation knee	1
	Total	15

Of the cases with pyloric stenosis, visible left to right epigastric peristaltic waves were easily discerinible in five cases. These cases with three others with intestinal obstruction had associated recurrent bouts of vomiting.

All but one were male subjects.

Four abdominal surgeries and one knee disarticulation were done under infiltration anaesthesia.

The case materials are obtained from Bon-Hooghly Hospital, W. Bengal, India and from district hospital, Raub, Malaysia.

Facilities for biochemical estimation of serum electrolytes were sadly absent from these hospitals. Hence they were not performed in any of the cases. All cases received only a single infusion (590 mls. approx) into the cubital vein. Intradermal hypersensitivity test were not performed nor did any of them receive an antihistamine cover[3]. Subsequent replacement was done by using normal saline or 5% dextrose infusions, the only available product.

Technique:

Commercially available young green coconuts between the ages of 5-6 months were chosen. All the coconuts used were of the commonly available variety Cocos Nucifera. No deliberate attempt at selection was made though fruits with suspected cracks were rejected for fear of infection. Strips of husk are raised on either sides of the fruits, as is done by the local vendor, and tied into a knot. This is reinforced with strapping and the loop used for suspension. The surface of the coconut is sterilised with surgical spirit or tincture of iodine and with a knife similarly treated slices of husk are removed until the reselient inner shell is exposed. Using a large gauge sterile needle, a preliminary puncture is made and some of the fluid emerging under pressure is allowed to escape.

The needle is then withdrawn, the infusion needle inserted in its place and infusion commenced.

Results:

Pyrexia: Transient pyrexia rising upto 100.4F was recorded in six cases. As this was observed to abate shortly after discontinuing the infusion all subsequent infusion were allowed to run in completely with no adverse effects.

Painful Vein: – In three of the initial cases intense pain along the infusion vein was noted. A correlation between the rate of infusion and severity of pain was detected. The pain disappeared when infusion rate was regulated to between 40 and 60 drops/min. At or above 90 drops/min. the symptom recurred.

Blocked infusion:- In two initial cases, the infusion needle within the fruit was found to be blocked with particulate matters encountered, during the puncture. The preliminary puncture with a needle of a slightly larger gauge was found to circumvent this difficulty.

One of the two fruits collected from the same tree spontenously burst with mild explosion when attempting the preliminary puncture. From the remnant of the fluid no evidence of fermentation could be detected. No explanation can be offered at the moment.

Clinical Response:- The high concentration of K ion raises the possibility of Potassium intoxication. Hence, this therapy was commenced only when the 24 hour urinary output was 1000 mls. or more. No harmful effects occurred.

A diuretic effect, as evidenced by an increase in the 24 hour urinary output by 150 to 350 mls. following the infusion, was noted in seven of the cases and the ecuritic diuretic[3] effect as may be feared following the infusion of a fluid with high concentration of potassium was not observed in any of the cases.

In assessing the value of this therapy in 9 cases (60%), clinically beneficial effect as indicated by feeling a sense of well being, reduction in abdominal distension and return of peristalsis within 24 hours of receiving this treatment, was gained. The remaining 6 cases did not show any appreciable clinical changes. Perhaps, the presence of adequate number of trained nursing personnel may have helped to obtain more complete data.

Table II

Composition of Coconut Water in West Malaysia

Volume	—	590 ml.
PH	—	4.8
Specific gravity	—	1.019
Calcium	—	13.1 mEq/L
Magnesium	—	4.7 mEq/L
Sodium	—	4.0 mEq/L
Chloride	—	41.0 mEq/L
Potassium	—	35.1 mEq/L
Sugar (Total)	—	2.8 gm/100 ml
Inorganic phosphates	—	4.0 mg/100 ml
Protein	—	0.269 gm/100 ml

Comment:

It is of interest to remember that a coconut closely simulates an egg. From a coconut fruit grows the future coconut tree. It seem therefore reasonable to believe that nature must put into

coconut water substances vital for generation of life. The close affinity of the chemical constituents of the coconut water to the intracellular fluid in man[4] testify to this.

The biological effects of coconut water has been studied in considerable detail both experimentally[6] and in patients[3,5,6,7]. The high concentration of potassium, physiologically balanced by a comparably high concentration of magnesium[3,6,7] together with the added presence of carbohydrate in the form of glucose and fructose[3,7] protein in the form of amino acids[5,6] Vitamin B[6] and mannitol[3] have sporadically prompted physicians in the less privileged countries within the tropical and subtropical belt[3,7] to utilise this fluid as a form of therapy. It has been so used, orally[6], hypodermically[6] and by intravenous route[3,4,6,7]. For intravenous purposes, the water is collected aseptically by suction[6] or decantation[4,7] then filtered for particulate matters through layers of sterile gauze,[3,4,7] sterilised in autoclave[3] and treated with penicillin prior to infusion[3]. No such prior treatment was necessary in this series.

The favourable clinical response to coconut water therapy as opposed to those of glucose saline and synthetic coconut water infusion is well recorded[1] and its utilisation as a readily available source for K ion has been advocated[2]. In veterinary practice this has proved to be a basis of an effective yet economical mode of therapy[8,9].

The increasing awareness of the effect of parental replacement of 'salt and water' in the successful management of patients, presents additional problems of adequate laboratory facilities and financial expenditure to the profession among the less privileged societies. A wider acceptance of this therapy may help curtail some of these demands without compromising the basic tenents of infusion therapy.

A similar acceptance of direct coconut water infusion in time of emergencies as with the uprecendented cylones of East Bengal (1970) and the recurrent typhoons of the Philippines, can well provide a safe and adequate substitute for the more sophisticated and expensive form of infusion therapy.

It is submitted that the result of the study now provide a basis for a research protocal, designed to collect data for the study of various parameters, to help put this on a more scientific footing.

Summary

A technique of direct infusion of coconut water is described. The overall impression of its use has been encouraging. A plea for its wider adoption is made.

It is believed that a similar trial with direct infusion has not been reported before.

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Double Contrast Barium Investigation

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THE TRADITIONAL barium meal and enema are common methods of investigation of gastro-intestinal symptoms. Diagnosis depended upon irregularities (tangential and "en face") or filling defects in the filled organ assisted by some air contrast or compressive coning. Observer error and low diagnostic accuracy especially in acute haemorrhage (assessed by endoscopy) should stimulate us to carry out routine double contrast examinations as briefly described below.

Barium Meal

Barium Sulphate is kept in the patient's mouth and then gulped to distend the oesophagus. Besides

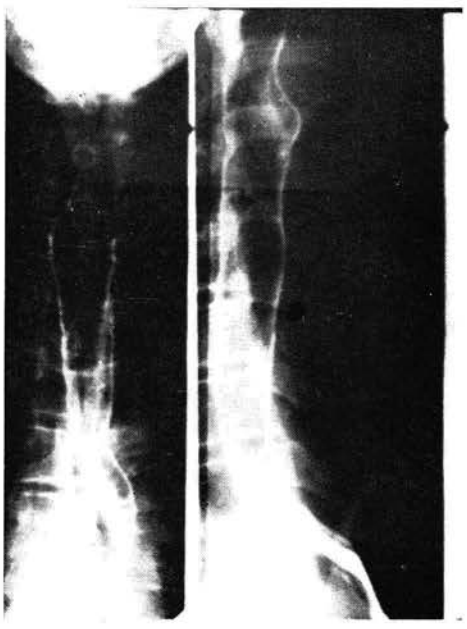

Fig. 1
Double Contrast Oesophagus

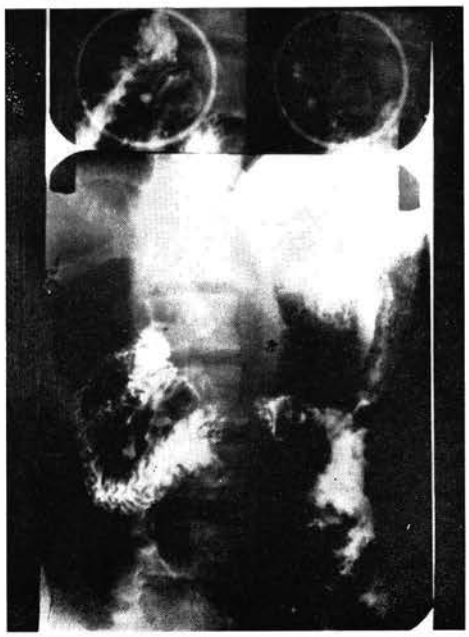

Fig. 2
Cone Views showing Duodenal Bulb Ulcer Crater with radiating folds ("fingers") pointing to it.

PA and Lateral views of the upper oesophagus, erect oblique views taken during the brief moment when the Barium is at the lower end of the oesophagus, shows the upper two thirds distended with gas.

The patient is turned prone and the table tilted to horizontal position with the pad under the abdomen to obtain a view of the anterior wall of the

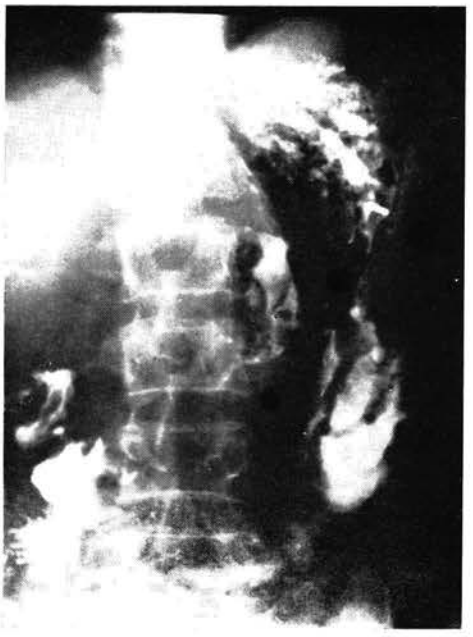

Fig. 3
Supine PA showing Giant Gastric Ulcer Lesser Curve.

Fig. 4
Further Views of Malignant Gastic Ulcer Greater Curve and benign ulcer posterior wall of stomach. Left – Erect P.A. Right – L.A.O.

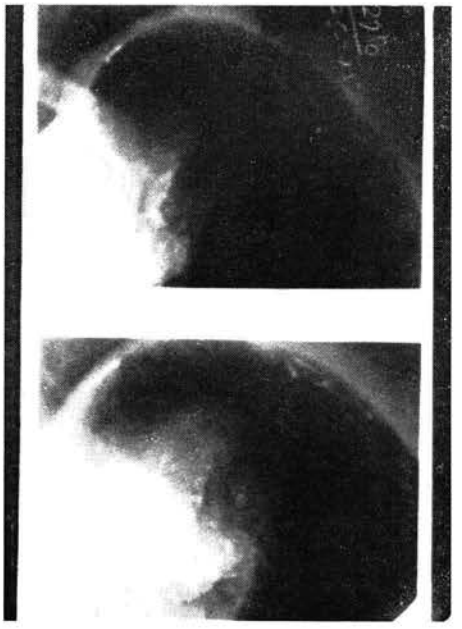

Fig. 5
Carcinoma Fundus.

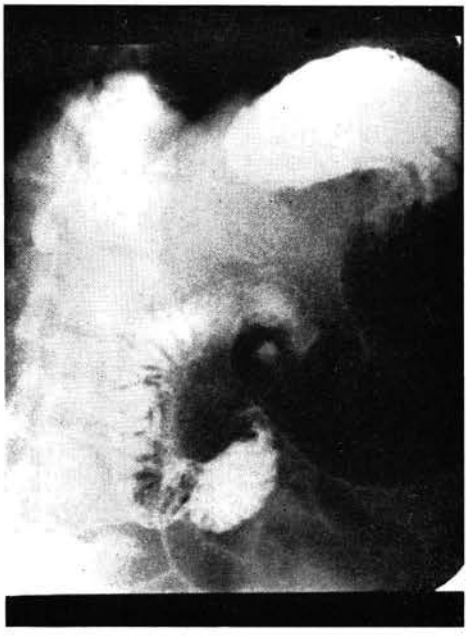

Fig. 6
Tubeless Hypotonic Duodenogram.

stomach. Coca-cola or efferverscent powder/tablets are given and the patient turned supine over the left side (reduces barium entry into duodenum)-added Siloxane helps reduce gas bubles but is not essential.

The patient is moved side to side to coat the stomach surface with barium before AP (for posterior wall of stomach), RAO & LAO films are taken.

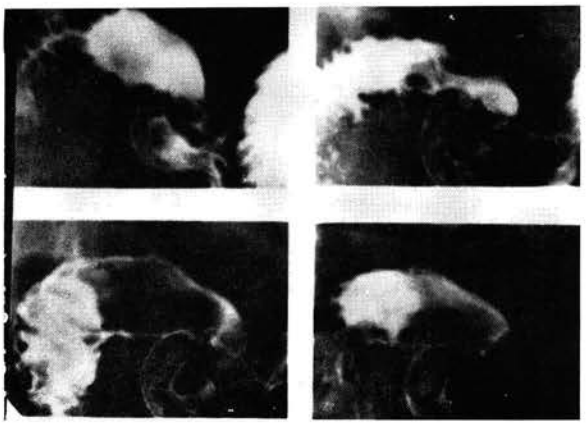

Fig. 7
"Fingers" (lines) pointing to healed (scarred) pyloric canal of perforated gastric ulcer.

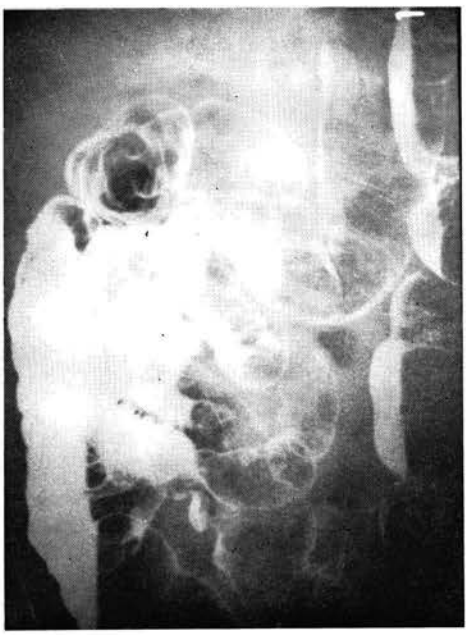

Fig. 8
Ba-enema – Decubitus View in Multiple Polyps of Colon.

The table is brought erect or semi erect for double contrast views of the fundus.

Finally cone compression serial pictures of the duodenum are taken. If pancreatic or distal duodenal disease is suspected, atropine, buscopan, or Glucagon (not available yet) should be given intravenously just before the examination to obtain a modified tubeless hypotonic duodenogram.

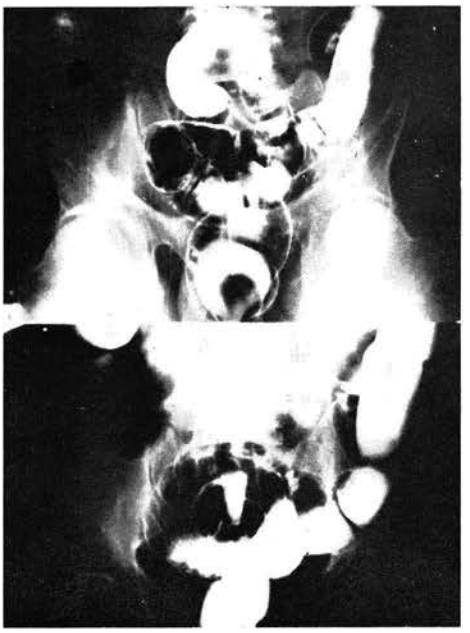

Fig. 9
Ba-enema – Normal
Supine and Prone 45° angled film.

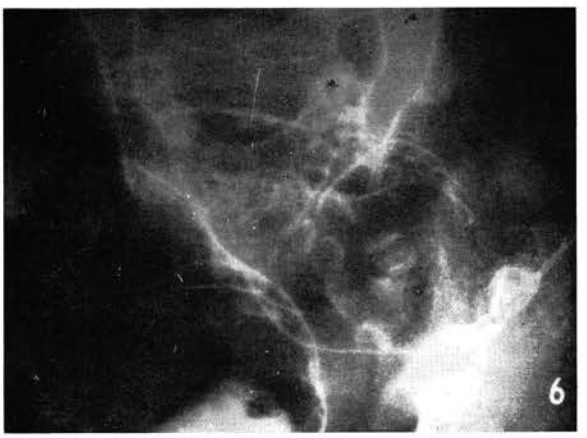

Fig. 10
Close up view of multiple polyps of colon.

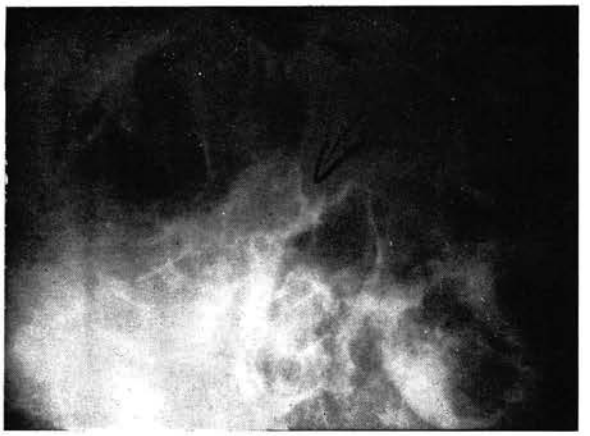

Fig. 11
Close up of Cauliflower like growth and stricture of sigmoid colon not obstructed by adjacent barium filled loops in supine 45° angled film.

Barium Enema (modified Malmo technique)

The patient should be well prepared to clear the bowel of faecal material. After a plain x'ray of the abdomen, barium is introduced through a wide-bore catheter per rectum. After barium has reached the proximal transverse colon, the rectum is drained and air slowly injected with a Higginson syringe while the patient rotates 360 degrees.

Although screening and undercouch films may be done, the following films are taken with the over-couch tube:–

1) Supine/Prone with 45° tube tilt for rectosigmoid region and caecum.

2) Left and right erect obliques for flexures.

3) Left lateral for rectum.

4) AP & PA decubitus films using horizontal beam for ascending and descending colon.

5) AP or PA for transverse colon.

Discussion

The advantages of double contrast barium investigations are:–

1) Mucosal surface shown and therefore even small lesions are visualised and they correspond to mascroscopic and endoscopic appearances.

2) Suture irregularities can be differentiated from ulcer niches.

3) Guide lines point straight accusing fingers at benign ulcers of stomach and duodenal bulb. In cases of Gastric malignant ulcers the guide lines do not run straight, are irregularly thickened and show sudden amputation.

4) Bleeding ulcer craters do not fill with barium but "larval flow" patterns run away from the ulcer.

5) Gastric rugal hypertrophy can be distinguished from carcinoma.

6) Areas of intrinsic rigidity and deformity can easily be seen and distinguished from extrinsic pressure defects.

7) Translucent colon allows lesions to be visualised even though it is overlaid by other segments of colon.

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Acknowledgement

I wish to thank the Director General of Medical and Health Services of Malaysia, Tan Sri Datuk (Dr.) Abdul Majid Ismail for permission to publish this article and my Radiographers who took the excellent radiographs and especially Mr. Mohd Amin bin Deta for typing this paper and Mr. Francis Leong Foo Sen for taking the photographs.

A Case of Cardiac Arrest Following Orel 250mg. Mefenamic Acid

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Introduction

ANAPHYLACTIC or anaphylactoid reactions can occur with any drug, whether given orally, by intravenous, intramuscular, subcutaneous or intradermal injection, or by local instillation to the mouth, nose or eyes, and in the case of a hypersensitive patient, even local application to the skin. A case of cardiac arrest, successfully resuscitated with external cardiac massage and insertion of a pharyngeal airway, is reported. A search of the literature and of the reports of clinical trials with mefenamic acid, has shown that no anaphylactic or anaphylactoid reactions have ever been reported following oral mefenamic acid (ref.1,5,6,9 & 10), and it is believed that this is the first case of its kind in the world.

Case History

L.N., a 66-year-old Chinese male, living in Ipoh but working in Kuala Lumpur, presented at about 9.50 in the morning on the 24th. March 1975, with a history of epigastric pain and pain in both shoulder joints and legs of one week's duration. On examination, his blood pressure was 140/90 mm Hg., his abdomen was soft with no liver or spleen palpable, but his epigastrium was slightly tender. There were no rhonchi or crepitations in his chest, although he said he had a slight cough. His temperature was normal and his urine was free of albumin and sugar. There was no inflammation in his shoulder and knee joints, although crepitus was present in his knee joints. When asked whether he was allergic to any drugs, he produced a note from his previous doctor dated the 20th. March 1975, which stated that he was sensitive to "PHENSEDYL" May and Baker (Promethazine 3.6 mg., Codeine phosphate 9 mg. and Ephedrine 7.2 mg. per 3.6 mls.), "NOVAPYRIN" T. W. Wu (Sulpyrin J.P., Metamizole, Sodium Methylaminoantipyrine methane sulphonate), and "BUTAZOLIDIN" Geigy (Phenylbutazone). He also said that he was suffering from "gastric" before. A provisional diagnosis of arthritis of the shoulder and knee joints and gastritis was made and the patient was prescribed "TITRALAC" Riker (Calcium carbonate 420 mg., Glycine 180 mg. per tablet), "STROCAIN" Eisai (Oxethazaine 5 mg., Polymigel 244 mg. per tablet), and "PONSTAN" Parke Davis (Mefenamic acid 250 mg. per capsule), one each orally four hourly, four times a day. He took the tablets and capsule at approximately 10 a.m., and was told to lie on a couch for one hour. At 11.15 a.m., he was re-examined and as he had no complaints and no itchiness, he was allowed to go home. On reaching the bus station, he developed itchiness in both hands and he returned at 11.30 a.m., complaining of itchiness in both hands and was scratching them. Within two minutes after examining him, he was given orally one tablet "INCIDAL" Bayer (Mebhydrolin napadisylate 50 mg.), one tablet "PIRITON" Glaxo (Chlorpheniramine maleate 4 mg.), and four tablets of "DELCORLON" Synco (Prednisolone 5 mg. per tablet), and was told to stay back for two hours. He was lying on a couch and was reviewed every five minutes. At 11.45 a.m., he complained of severe itch all over his head with uncontrollable scratching and also started to cough. At his wife's insistence for injections, he was called to the injection room and corticosteroid and antihistamine injections were prepared. Before he could come to the injection room and before he could be given the injections, his wife called out that her husband was not responding to her calls. He

was examined and found to be clinically dead with no heart beat, no pulse, no respiration and he was cold and cyanosed. Immediate external cardiac massage was done and an adult size pharyngeal airway ("LIFE-SAVER" Lepetit) was inserted, after the left index finger was put into his mouth and his tongue pulled forward and some phlegm removed. After approximately one minute, he gave a groan and after a further two minutes, he was able to cough and his heart beat and respiration returned. This was kept up for a further five minutes. At 12.10 p.m., he was able to get up assisted by two persons and was able to hold on to his pharyngeal airway, and at 12.20 p.m., he was able to walk to a chair and remove his pharyngeal airway. Investigations later showed that his electrocardiogram, which was done at 1.30 p.m., to be normal with no evidence of ischaemia or myocardial infarct. A chest X-Ray was not done. His urine was clear. His Hb. was 8.6 G.%, and his WCC was 12,200/cumm., with polymorphs 83% and Lymphocytes 17%. Over the next 48 hours, he was kept under observation and complete rest in bed. He was given orally "Piriton" 4 mg. three times a day, Magnesium Trisilicate half an ounce three times a day, and "Actal" Winthrop (Sodium polyhydroxy aluminium monocarbonate hexitol complex 360 mg. per tablet), two tablets as required. No analgesics were given even for his arthritic pains. He was seen in town a week later and he said he had no complaints except that he nearly lost his life.

It was later learnt from his previous doctor, that on the 20th. March 1975, he was given IMI "BUTAZOLIDIN" Geigy, 600 mg. phenylbutazone or 3 cc., and he had collapsed in a restaurant less than 15 minutes later. When examined, he was unconscious and soon after a rash appeared all over his face and body. He was given IMI Adrenalin 1/1000 w/v (1 mg./cc.), 0.5 cc. at first and another 0.5 cc. slowly later, and also IMI "Kenacort A" Squibb (Triamcinolone acetonide) 40 mg. or 1 cc. Besides "Phensedyl", "Novapyrin", and "Butazolidin", he was also sensitive to chloramphenicol, as he was the previous doctor's patient for some time.

Classification of Analgesic, Antipyretic and Anti-inflammatory Agents

A broad classification is given below. Not all drugs have the above properties. There are some that are mainly anti-inflammatory, e.g. the anti-inflammatory enzymes, corticosteroids and indomethacin. Others are mainly analgesic, e.g. morphine and some of its derivatives, glafenine, or have anti-inflammatory and analgesic but little antipyretic properties. Still others, e.g. the antimalarials of the chloroquine (4-aminoquinolines) group, D-penicillamine, gold salts and the immunosuppressive drugs, in rheumatoid arthritis, and the alkaloids from the autumn crocus, viz. colchicine and demecolcine, in gout, do not themselves have analgesic and antipyretic properties. Their mode of action is still debatable. Gold does have a definite action on collagen and synovial membrane, immunological reactions and enzymatic systems. Chloroquine has anti-inflammatory effects (ref. 4, pg. 12.35), while colchicine and demecolcine probably act by interrupting the inflammatory cycle (ref. 4, pg. 12.38). If rheumatoid arthritis is considered as an inflammatory process resulting from an immune reaction, there is a possibility that immunosuppressive agents could have a role in its management, as "they can inhibit the function of immunologically committed cells as well as inhibit cells with a rapid proliferative rate, but they have no definite immunological commitment. The same applies to D-penicillamine. and the response is better in cases where the serum copper level is high" (ref. Professor J. F. Silva:- The General Management of Rheumatoid Arthritis. Medical Progress, May 1975, Vol. 2, No. 5, pg. 12).

There are two main groups of analgesic, antipyretic and anti-inflammatory agents, viz.

(I) the steroidal hormonal group, e.g.

(a) the corticosteroids, e.g.

(i) Betamethasone ("Betnelan" Glaxo, "Celestone" Schering U.S.A.),

(ii) Cortisone ("Cortone" Merck Sharp and Dohme),

(iii) Dexamethasone ("Decadron" Merck Sharp and Dohme, "Deltafluorene" Lepetit, "Oradexon" Organon),

(iv) Fludrocortisone,

(v) Fluocortolone ("Ultralanum" Schering AG),

(vi) Hydrocortisone (cortisol, "Solu-Cortef" Upjohn),

(vii) Methyl prednisolone ("Medrol" Upjohn, "Urbason" Hoechst),

(viii) Paramethasone ("Metilar" Syntex),

(ix) Prednisolone ("Deltacortril" Pfizer, "Juvasolon" Dolder, "Nisolone" Lepetit, "Precortisyl" Roussel, "Scherisolone" Schering AG),

(x) Prednisone, and

(xi) Triamcinolone ("Kenacort" Squibb, "Ledercort" Lederle).

(b) the corticotrophins, e.g.

(i) Adrenocorticotrophic Hormone (ACTH, corticotrophin, "Acthar Gel" Armour, "Cortrophin-Zn" Organon),

(ii) Tetracosactrin, and

(iii) Tetracosactrin Zinc (tetracosactide adsorbed on zinc phosphate, "Synacthen Depot" Ciba-Geigy).

(II) the non-steroidal group. This is divided into two sub-groups, viz.

(1) the opiate and opioid group, viz. the opium alkaloids and their synthetic derivatives. They belong chemically to two separate groups (ref. 3, pg. 122),

(a) PHENANTHRENE derivatives and other related drugs, e.g.

(i) Dextropropoxyphene ("Doloxene" Eli Lilly),

(ii) Diamorphine (Heroin),

(iii) Dihydrocodeine ("DF 118" Glaxo-Allenburys),

(iv) Fentanyl ("Fentanyl" Janssen),

(v) Levallorphan ("Lorfan"),

(vi) Meperidine ("Pethidine" Burroughs Wellcome),

(vii) Methadone ("Physeptone" Burroughs Wellcome),

(viii) Methylmorphine (Codeine),

(ix) Morphine,

(x) Nalorphine ("Lethidrone" Burroughs Wellcome),

(xi) Pentazocine ("Fortral" Winthrop, Australia, "Talwin" Winthrop/Sterling Drug),

(xii) Phenazocine ("Narphen"), and

(xiii) Thebaine.

Some of these, e.g. dextropropoxyphene and pentazocine, are said to have less dependence potential.

(b) ISOQUINOLINE derivatives, e.g.

(i) Papaverine, and

(ii) Narcotine (Noscapine).

These derivatives exert no analgesic or narcotic action.

(11) the non-opiate and non-opioid group. This includes:–

(a) Aniline derivatives, e.g.

(i) Acetyl derivative of aniline (acetanilide, "Antifebrin"),

(ii) N-acetyl-p-aminophenol (acetaminophen, paracetamol, "Calpol" Calmic, "Datril' Bristol-Myers, "Dumin" Dumex, "Milidon" Malayan Pharmaceutical Factory, "Panadol" Winthrop, "Tabalgin" Berk Pharmaceuticals Ltd.),

(iii) p-ethyl derivative of acetanilide (acetophenetidin, phenacetin).

(b) Anthranilic acid derivatives or the fenamates, e.g.

(i) Aluminium N-(3'-trifluoromethylphenyl) anthranilate ((Aluminium flufenamate, "Opyrin" Taisho Pharmaceutical Co., Ltd., Tokyo, Japan)),

(ii) Meclofenamic acid (Parke Davis),

(iii) N-(alpha, alpha, alpha-trifluoro-m-tolyl) anthranilic acid (Flufenamic acid, "Arlef" Parke Davis)), and

(iv) N-(2,3-xylyl) anthranilic acid ((Mefenamic acid, "Ponstan" Parke Davis)).

(c) Anti-inflammatory enzymes, e.g.

(i) Chymotrypsin ("Chymar" Armour, "Deanase D.C." Consolidated Chemicals Ltd., "Kimopsin" Eisai),

(ii) Chymotrypsin and trypsin ("Chymoral" Armour),

(iii) Lysozyme chloride ("Neuzym" Eisai),

(iv) Prolase ("Papase" Warner-Lambert),

(v) Proctase and pancreatin ("Proctase P" Meiji Seika),

(vi) Seaprose S ("Jeoase" Suzuken, "Kyorinase" Kyorin), and

(vii) Serratio-peptidase ("Danzen" Takeda).

(d) 1,2,4-Benzotriazine derivative, e.g. 3-dimethylamino-7-methyl-1,2-(n-propylmalonyl)-1,2-dihydro-1,2,4-benzotriazine dihydrate (Azapropazone, "Prolixan 300" Siegfried Ltd., Switzerland).

(e) Carboxylic acid derivatives, e.g.

(i) Diacetylpyrocatechol carboxylic acid ("Movirene" Union Chemique Belge), and

(ii) 2-Phenylquinoline-4-carboxylic acid (Phenylcinchoninic acid, Cinchophen, Quinophan).

(f) 7-chloroquinoline derivative, e.g. Glycerylaminophenaquine (Glafenine, "Glifanan" Roussel). Exclusively an analgesic, without antipyretic, anti-inflammatory or hypnotic properties, though concomitant anti-inflammatory and antipyretic activity is observed with very high doses, well above therapeutic levels (ref. "Glifanan" brochure pg. 3 and 6, 184-69 EXA).

(g) Indole derivative, e.g. 1-(p-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic acid (Indomethacin, "Confortid" Dumex, "Indocid" Merck Sharp and Dohme).

(h) Nicotinic acid derivative, e.g. Trifluoromethyl-3-phenylamino-2-nicotinic acid (Niflumic acid, "Niflucid" Squibb).

(i) Phenothiazine derivative with dimethylaminopropyl side-chain, e.g. Methotrimeprazine ("Veractil"). It is a potent analgesic and sedative (ref. 4, pg. 12.32; 14.9).

(j) Phenylacetic acid derivatives, e.g.

(i) 4-allyloxy-3-chlorophenylacetic acid (Alclofenac, "Prinalgin" Berk), and

(ii) Sodium-[0-[(2,6-dichlorophenyl)-amino]-phenyl]-acetate (Diclofenac Sodium, "Voltaren" Geigy).

(k) Propionic acid derivatives, e.g.

(i) DL-2-(3-phenoxyphenyl)-propionic acid (Fenoprofen, "Fenopron" Dista Products Ltd.),

(ii) 2-(2-fluro-4-biphenyl)-propionic acid (Flurbiprofen, "Froben" Boots Company Ltd.). It is 10 to 15 times more potent than ibuprofen.

(iii) 2-(4-isobutylphenyl)-propionic acid (Ibuprofen, "Brufen" Boots Company Ltd.),

(iv) 2-(3-benzoylphenyl)-propionic acid (Ketoprofen, "Orudis" May and Baker Ltd.), and

(v) D-2-(6'-methoxy-2'-naphthyl)-propionic acid (Naproxen, "Naprosyn" Syntex Pharmaceuticals Ltd.).

(l) Pyrazolone derivatives, e.g.

(i) Antipyrine and its derivatives, e.g.

(a) Amidopyrine (Aminophenazone, aminopyrine, dimethylamino-antipyrine, dimethylaminophenazone, pyramidon),

(b) Antipyrine (Phenazone),

(c) Antipyrine salicylate (Phenazone salicylate, salipyrin),

(d) Isopropylantipyrine (Isopropylphenazone, isopyrin, propyphenazone) and

(e) Methylaminoantipyrine-methane sodium sulfonate (Analgin, dipyrone, metamizol, metamizole, noramidopyrine methane sodium sulfonate, novamine sulfone, phenyldimethyl-pyrazolone-methylamino-methane-sodium sulphonate, "Bonpyrin" Takeda, "Conmel" Winthrop, "Himapyrine" Himalaya Medical Hall, "Novalgin" Hoechst, "Novapyrin" T. W. Wu, "Pyralgin" Siegfried, "Sulpyrin" Chugai, Grace Pharmaceutical Co., "Tanapiron" Tanabe Seiyaku). The magnesium salt of dipyrone is "Magnopyrol" Siegfried.

(ii) Pyrazolidine derivatives, e.g.

(a) Butylmalonic acid mono-(1,2-diphenylhydrazide) calcium semihydrate ((Bumadizone, "Eumotol" Byk Gulden)),

(b) 4-Butyl-1,2-diphenyl-ketopyrazolidine-3,5-dione ((Ketophenylbutazone, "Ketazon" Kyowa Hakko Kogya Co.)),

(c) 4-Butyl-1-phenyl-pyrazolidine-3,5-dione ((Monophenylbutazone, "Mobutazon" Benzon, Denmark)),

(d) 2,3-Dimethyl-4-nicotinamido-1-phenyl-5-pyrazolone ((Nifenazone, "Thylin" West-Silten Pharmaceuticals)),

(e) 1-Phenyl-2-(p-hydroxyphenyl)-3,5-di-oxo-4-n-butylpyrazolidine monohydrate ((Oxyphenbutazone, "Tanderil" Geigy)), and

(f) 4-Butyl-1,2-diphenylpyrazolidine-3,5-dione ((Diphenylbutazone, phenylbutazone, "Butazolidin" Geigy)).

(m) Pyrimidine derivative, e.g. 5-n-butyl-1-cyclohexyl-2,4,6-trioxoperhydropyrimidine (Bucolome, "Butymidin" Takeda).

(n) Salicylic acid derivatives, e.g.

(i) Acetylsalicylic acid ("Aspirin" Bayer, "Aspro" Nicholas, "Levius" Farmitalia, "Palaprin Forte" – aloxiprin – Nicholas, "Paynocil" Bencard),

(ii) Salicylamide ("Salamide" Hamilton Laboratories, Adelaide, "Salimed" Medo-Chemicals), and

(iii) Sodium salicylate.

(o) Thienopyridine derivative, e.g. 2-amino-3-ethoxycarbonyl-6-benzyl-4,5,6,7-tetrahydrothieno (2,3-c) pyridine hydrochloride (Tinoridine hydrochloride, "Nonflamin" Takeda).

(p) Others, e.g.

(i) 4-aminoquinolines (amodiaquine "Camoquin" Parke Davis, chloroquine, hydroxychloroquine "Plaquenil" Winthrop),

(ii) D-penicillamine,

(iii) Gold salts (Sodium aurothiomalate), and

(iv) Immunosuppressive drugs, e.g.
(a) Azathioprine ("Imuran" Burroughs Wellcome),

(b) Chlorambucil ("Leukeran" Burroughs Wellcome),

(c) Cyclophosphamide ("Endoxan" Asta-Werke AG), and others.

Combinations of the two main groups are also available, e.g.

(i) "Delta-Butazolidin" Geigy (Phenylbutazone 50 mg. and Prednisolone 1.25 mg.), and

(ii) "Realin" Geigy (Oxyphen-butazone 100 mg. and Prednisolone 2.5 mg.),

so also are combinations of the two subgroups of the main group II, e.g.

(i) "Algaphan" Boehringer Mannheim (D-propoxyphene 25 mg. and aminophenazone 300 mg.),

(ii) "Codopar-118" Glaxo-Allenburys (Dihydrocodeine tartrate 10 mg. and paracetamol 500 mg.),

(iii) "Dologesic-32" Eli Lilly (D-propoxyphene 32.5 mg. and paracetamol 325 mg.),

(iv) "Doloxene Compound" Eli Lilly (D-propoxyphene 32 mg. or 65 mg., aspirin 227 mg., phenacetin 162 mg., and caffeine 32.4 mg.),

(v) "Safapryn-Co" Pfizer (enteric-coated core aspirin with paracetamol and codeine phosphate), and

(vi) "Veganin" Warner-Lambert (Acetylsalicylic acid 250 mg., phenacetin 250 mg. and codeine phosphate 10 mg.),

or of combinations of members of subgroup 11, of main group II, sometimes with caffeine, e.g.

(i) A.P.C. (Acetylsalicylic acid 225 mg., phenacetin 150 mg., and caffeine 30 mg.),

(ii) "Irgapyrin" Geigy (Phenylbutazone 125 mg. and amidopyrine 125 mg.),

(iii) "Mopyrine" Malayan Pharmaceutical Factory (Amidopyrine 125 mg. and monophenylbutazone 125 mg.),

(iv) "Safapryn" Pfizer (enteric-coated core acetylsalicylic acid 300 mg. and paracetamol 250 mg.),

(v) "Tomanil" Byk Gulden (Isopyrin hydrochloride 200 mg. and phenylbutazone 100 mg.),

and others.

Discussion

The antacids, "Titralac" and "Strocain", are extremely unlikely to cause anaphylactic or anaphylactoid reactions as very few side-effects to calcium carbonate, glycine and polymigel (Al_2O_3. $2CaCO_3$. $MgCO_3$. XH_2O), have ever been reported (ref. 2, 11). Glycine is an amino acid and as such is a constituent of the normal diet, and calcium carbonate is also a very unreactive substance. Besides, the patient did not react to sodium polyhydroxy aluminium monocarbonate hexitol complex ("Actal" Winthrop) and magnesium trisilicate, when he took these orally over the next 48 hours. As to the local mucosal surface anaesthetic agent, oxethazaine, N,N-bis-(N-methyl-omega-phenyl-tertiary-butyl-acetamido)-beta-hydroxyethylamine, the amount 5 mg. in one tablet of "Strocain" would be too little to be absorbed enough into the blood stream to produce the cardiac arrest in this patient. In combination with polymigel, a co-precipitate of aluminium, calcium and magnesium present in "Strocain", its absorption rate is prolonged.

Oxethazaine is an amide anaesthetic and is insoluble in water but soluble in dilute acids. It is unique in that as a weak base it is relatively non-ionised in acid solutions. The potency of a local anaesthetic appears to depend on the availability of the un-ionised free base (ref. 15, F 8143, pg. 2 and 3). Oxethazaine antagonizes the action of acetylcholine (slight antiacetylcholine action), histamine (potent antihistaminic action), physostigmine, serotonin, and barium sulfate on smooth muscle (ref. 2, 15), and these anticholinergic, antihistaminic and anti-serotonin actions can be shown in vitro but not in vivo. No effects on the central nervous system or on respiration have been observed. In studies for acute toxic effect, 32 mg. oxethazaine administered to normal volunteers at four-hourly intervals, four times in the day, produced no significant changes in blood pressure or pulse taken at hourly intervals for twelve hours, and comparison of the initial and final electrocardiograms showed no change (ref. 15, F 8143, pg. 3 and 5). It therefore has a wide safety margin because of its low toxicity and its least absorption rate. When administered orally, oxethazaine produces a peak blood level approximately

four hours after administration and then declines. Its oral LD 50 in mice is approximately 400 mg. of base per kg., and when suspended in alumina gel as a vehicle, the oral LD 50 in mice is 1012 mg. of base per kg. When oxethazaine is suspended in acacia, the oral LD 50 in mice is 1800 mg. of base per kg., while the intraperitoneal LD 50 in mice is 118 mg. of base per kg. A dose of 10 or 20 mg. of oxethazaine respectively in a human weighing 50 kg. is only 0.2 or 0.4 mg. per kg. of body weight (ref. 15, P. 441705). Oxethazaine as present in "Strocain", is therefore only 0.0833 mg. per kg. body weight in this patient as his weight was approximately 60 kg. It is generally believed that oxethazaine permeates the lipid of peripheral nerves and that it anaesthetizes the vagus nerve ending, when present in the stomach (ref. 16, pg. 11), and it is scarcely absorbed through the digestive system as only 1% of oxethazaine in aqueous solution is absorbed from the gastro-intestinal tract, and if oxethazaine is given with an alumina gel, an insignificant 0.4% is absorbed. The very little oxethazaine that is absorbed, is so rapidly and thoroughly decomposed and detoxicated that it is hardly detected in the blood or urine. Side-effects of oxethazaine are usually mild and transient, and include dryness of the mouth, nausea, soreness of the tongue, and one case of glossitis of the hypersensitive type and one observed case of skin eruption. Dizziness, drowsiness, and faintness have been reported following more than 120 mg. of oxethazaine per day (ref. 15, P. 441705). Side-effects following "Strocain" are rarely reported and include anorexia, constipation, and diarrhoea.

Mefenamic acid, which is N-(2,3-xylyl) anthranilic acid (Figure 4), is slowly absorbed from the small intestine following oral medication. Peak blood levels are attained two to three hours after dosage. Blood levels resulting from oral administration of mefenamic acid are not necessarily proportional to the size of the dose beyond a certain range. Single dose of one Gm. each of mefenamic acid (four capsules of 250 mg. each) produces peak plasma levels of 7 to 10 micrograms per millilitre within two to three hours following oral administration. The levels decline sharply to values between one and two micrograms at six hours following dosage and then gradually taper off to mere traces of drug at 24 hours. Plasma levels for free and total drug are nearly identical, indicating that mefenamic acid occurs mainly in the unconjugated form (ref. 6, pg. 24, 25 and 27). Side-effects of mefenamic acid that have been reported include brisk diarrhoea (occurring in some 10 to 20 per cent of patients on long-term continuous dosage of 2,000 mg. or more daily), constipation, depression (ref. 1), dizziness, dyspepsia, gastric irritation, gastric upset, haemolytic anaemia (ref. 5), leucopenia, and maculopapular rash leading to mild exfoliative dermatitis if medication is continued (ref. 6, pg. 2).

Though mefenamic acid is not related to other analgesic and anti-inflammatory agents, e.g. acetylsalicylic acid, ibuprofen, indomethacin, metamizol, paracetamol, pentazocine and phenylbutazone, outside the group of fenamates, it contains the basic benzol ring structure (Figure 1), in its composition, like the other analgesic and anti-inflammatory agents. It is of interest that this patient is also sensitive to chloramphenicol (Figure 2), which is D-threo-(-)-1-p-nitrophenyl-2-dichloro-acetamido-1,3-propanediol, and to codeine (Figure 3), the methyl derivative of morphine, as they both have this benzol ring structure.

From the above, it could be said that the cardiac arrest in this patient was due to mefenamic acid, probably to the benzol ring structure. Thus a patient who is sensitive to certain analgesic and anti-inflammatory agents, might develop severe reactions to a different and unrelated analgesic and anti-inflammatory agent, whose basic structure is essentially the same.

Pros and Cons of Immediate Injections in the Treatment of Drug Reactions

It might be argued why adrenalin, corticosteroid, anti-histamine, calcium gluconate or even an intravenous drip, were not given when this patient returned with itchiness one and a half hours after oral medication.

The cons are viz.

1. the bias and prejudices of patients regarding injections in private medical practice especially among the Chinese population, and the previous adverse reaction to an injection in this patient, although to an unrelated drug.

2. the side-effects of adrenalin viz. increased heart rate, the much increased excitability and conductivity of the heart, the rise of systolic and fall of diastolic blood pressure, and the stimulation of the central nervous system with feelings of fear and anxiety, increased respiration and tremor (ref. 4, pg. 17.4), considering the age of the patient and his questionable blood pressure.

3. the patient was given oral medication and he did not react to it until one and a half hours later and he did not present with urticaria or collapse, but with itchiness, and it was considered that he should be given orally anti-histamines and corticosteroid and watched over a period of two hours. Supposedly, if the patient had been given adrenalin,

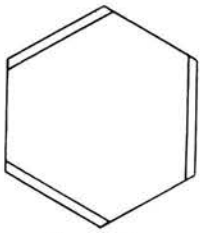

Figure 1.
Benzol Ring

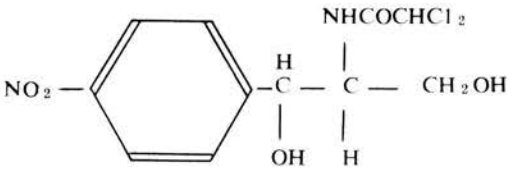

Figure 2.
Chloramphenicol

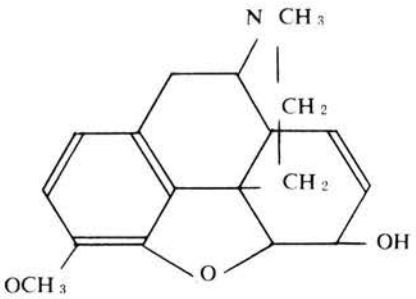

Figure 3.
Codeine

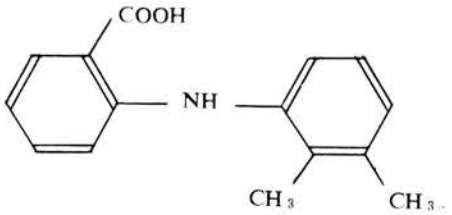

Figure 4.
Mefenamic Acid ("Ponstan")

corticosteroid and anti-histamines and then suffered a cardiac arrest and could not be resuscitated, only a doctor who had such an unfortunate experience would know the severe repercussions on his practice and good name, and it would "be remembered for a long time that Dr. X killed a patient with an injection. Sad but true." (ref. 13, Donal R. O'Holohan:– Collapse as a medical emergency pg. 237).

The pros are viz.

1. that immediate adrenalin, corticosteroid and anti-histamine injections given as soon as he presented with the itch, would have prevented the cardiac arrest approximately twenty minutes later.

2. that medico-legally, a doctor would be able to argue that he had given the necessary injections, even if the patient failed to be resuscitated.

No doubt, immediate injections and even an intravenous drip to counteract the allergy and shock should be given if there is immediate or delayed anaphylactoid reactions following injection or oral medication of any drug, but it is not considered necessary if there is only itchiness as the presenting symptom, and scratching as the presenting sign. There can certainly be a spirited debate regarding the relative merits of alternate courses of management in this patient. "Even if such an alternative course was established to have been preferable, this does not of itself indicate that a doctor would be liable medico-legally because the law does not require a doctor to be correct, all that is required is that a doctor acts reasonably according to his qualifications and experience." (ref. 8)

Summary and Conclusion

A case of cardiac arrest, successfully resuscitated with external cardiac massage and insertion of a pharyngeal airway, following one capsule orally of 250 mg. mefenamic acid is recorded. This case also served to remind doctors that even well-proven and well-tried drugs might produce anaphylactoid reactions, even though such reactions had never been reported before. "No drug is entirely harmless or non-toxic to the partaker and treatment is essentially a balance between its baneful and useful effects..... It is certainly essential to be vigilant in the surveillance of drug reactions and to document the yet unknown side-effects of drugs" (ref. 12, Dr. Leong Vie Chung:– Hospital Monitoring of Adverse Drug Reactions, pg. XXXIV). It is also to inform doctors, especially private medical practitioners, that in the case of a medical emergency, they are all alone in their resuscitative efforts, as usually onlookers are too spell-bound to be able to

do much, as was in this case where there were nearly twenty onlookers who would not even help to lift up the patient's chin when requested. It is also intended to help doctors, especially private medical practitioners, who are faced with such a dilemma, to make a decision in their choice of treatment, and not to be implicated medico-legally later.

A plea is made to those who have sensitivities to join the Medic Alert Foundation, West Malaysia, and to wear the Medic Alert "Warning" emblems, and to doctors who have patients with sensitivities, to give to them the full list of drugs they are sensitive to and to warn them that should they consult another medical practitioner, they must produce the warning note.

Acknowledgement

I wish to record my appreciation and thanks to The Medical Protection Society, London, for permission to quote the medico-legal aspects of this case, to Eisai (Malaysia) Sdn. Bhd., Petaling Jaya, and Eisai Co., Ltd., Tokyo, Japan, for reports on "Strocain", to John Wyeth & Brother Limited, Maidenhead, Berkshire, England, and Wyeth International Ltd., Philadelphia, U.S.A., for information on oxethazaine printed in Wyeth pamphlet P. 441705 and Wyeth technical booklet F 8143, to Warner-Lambert International – Warner-Lambert is the head of the Corporation which includes Parke Davis – Asian Management Center, Hong Kong, for information on mefenamic acid printed in "Ponstan Basic Medical Literature, INT-L-104-5-E-66", to the patient's previous doctor for information on his medication on the 20th. March 1975, and to the many pharmaceutical companies and representatives that provided the literature and information about their analgesic and anti-inflammatory agents. My sincere thanks also to Miss Liew Wooi Yee, and to my wife, Sabina, for typing the manuscript and drawing the diagrams.

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Med. J. Malaysia Vol. XXX No. 3 March, 1976

Ectopic Nasal Tooth

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Introduction

CASES OF rhinolith in the nostril are not infrequently seen in an E.N.T. clinic. It usually represents foreign body which may be inserted into the nose many years before and forgotten; or the child with a foreign body in the nose may be too frightened to tell anyone and will forget about it until adulthood when it will be encrusted with a deposition of layers of calcium and magnesium salts forming a chalky brown material, the rhinolith. It then presents as a case of annoying unilateral, chronic, fetid, blood stained nasal discharge in a young adult (Ballantyne 1971).

Endogenous materials, like bones and cartilages, which have been left behind in the nasal cavities after surgery or trauma, may rarely act as nuclei on which layers of calcium and magnesium salts are deposited (Paparella 1973). Supernumerary teeth which have erupted in the floor of the nose and have acted as nuclei for the rhinolith are very rare. Endicott (1934), Rao (1953), Hiranandari and Melgini (1968), Kohli and Verma (1970) have reported cases of aberrant supernumerary teeth which have erupted in the floor of the nose. An additional case is being reported.

Case Report

History

Y.S.K., a 39 year old Chinese male, has complaint of right nasal discharge for 1-2 years duration. It was blood stained and foul smelling. On further questioning, he also has occasional anosmia and nasal obstruction, but there was no other E.N.T. complaints. There was no history of insertion of foreign body in the nose, nor nasal surgery and trauma in the past, no past history of difficult dental extraction.

Examination

The only significant abnormality detected was, on anterior rhinoscopy, there was a dark-brown, hard object on the floor of the right nostril, measuring about 1 cm. in diameter. It was covered with mucopus, gritty on probing and immobile. The rest of the E.N.T. examination revealed nothing abnormal.

A provisional diagnosis of rhinolith in the right nostril was made and this was further confirmed by radiography of the sinuses showing a faintly radio-opaque mass in the right nostril.

Treatment

The patient's nose was examined under General Anaesthesia. Attempts to remove the rhinolith resulted in breaking of the calcified deposits around the nucleus which was a piece of hard, bone-like material arising from the floor of the right nostril. The right canine tooth was found to be missing.

On sublabial incision and after elevating the muco-periosteal flap, there was a deficiency of bony cover over the right canine ridge; it was enlarged by Hajeck's punch forceps. The body of the canine tooth was found lying in it with the root projecting in the floor of the right nostril. The canine was extracted (see photograph). The right maxillary sinus was not open.

Photograph of extracted ectopic canine tooth with pieces of broken rhinolith deposits; the part of tooth above the arrows erupted in the floor of the right nasal tooth.

Post operative recovery was uneventful and the patient was free of nasal complaints when last reviewed 4 months after the operation.

Discussion

Unilateral nasal discharge, especially of long duration usually calls upon the diagnosis of foreign body until proved otherwise. Diagnosis of rhinolith is relatively easy provided a nasal speculum and good illumination are used. The dark brown mass covered with mucopus, which is gritty on probing is diagnostic Radiography is helpful in the diagnosis as the calcium deposits usually rendered it radio-opaque.

Treatment is its removal, preferably under General Anaesthesia, as the rhinolith is usually firmly attached to its surrounding tissue. Occasionally a large rhinolith needs to be removed piece-meal. Caldwell Luc or lateral rhinotomy approach may rarely be needed to remove very large rhinolith. In this case, the deposits of rhinolith is removed piece-meal whereas the ectopic tooth is removed via a sublabial incision and removal of canine ridge.

Summary

An unusual case of rhinolith with the root of the ectopic canine tooth as nucleus is presented. Unilateral nasal discharge usually denotes a foreign body in the nostril is emphasised, its treatment briefly discussed.

Acknowledgements

I wish to thank Miss A.M. Tan for typing the manuscript and the staff of the Department of Medical Illustration the photograph.

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Glottic and Subglottic stenosis following intubation during surgery

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Case Report
Glottic and Subglottic Stenosis Following Intubation During Surgery

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Summary
AN ADULT PATIENT developed glottic and subglottic stenosis following intubation during surgery. Prolonged mucosal ischaemia followed by infection in the region of the rigid laryngeal box was probably responsible.

A thirty-nine year old emaciated female Indian patient with gastric outlet obstruction of three months duration was initially managed by intrevenous drip and nasogastric suction for ten days. Initial investigations showed haemoglobin concentration 3.5 gm%, PCV of 14, serum sodium 120 meq/L, serum potassium 2.6 meq/L and chloride 90 meq/L. After blood transfusion, plasma transfusion etc, her general condition improved to a haemoglobin concentration 10.7 gm%, PCV 37, serum sodium 131 meq/L, potassium 3.4 meq/L and chloride 100 meq/L.

After premedication with atropine 0.3 mg, promethazine 12.5 mg, pethidine 40 mg, she was induced with oxygen, nitrous oxide, 4 mg pancuronium and intubated with a size 7.5 mm cuffed red rubber Rush endotracheal tube. The degree of inflation of the cuff was not recorded or remembered.

Ten minutes after onset of surgery, the blood pressure fell from 100 mmHg systolic to 40 – 50 mmHg with a thready and irregular pulse. The hypotension lasted 40 minutes. Blood pressure was restored by administration of whole blood 450 ml, hydrocortisone 200 mg, Rheomacrodex in Normal saline 250 ml, 75 ml of 7.5% sodium bicarbonate and 5 ml 5% calcium chloride. A second episode of hypotension lasting 25 minutes during the third hour of surgery and it responded to administration of 500 mg hydrocortisone, 450 ml blood, 200 ml of frozen plasma and 25 ml of 7.5% sodium bicarbonate.

The duration of surgery and anaesthetic was four hours. The recovery period in the recovery ward and the immediate post-operative course was uneventful. Histopathology showed a benign gastric ulcer.

One month following the operation, she complained of difficult and noisy respiration followed by recurrent episodes of upper respiratory tract infection.

Laryngogram and tomogram of the larynx showed a normal valleculae and cuneiform fossa. The vestibule was narrowed, measuring 1 cm in length, with loss of differentiation between the true and false vocal cords. The subglottic space was narrowed for a distance of 1 cm. The stenosis was mainly posterior, but also extended around the larynx to the front.

Direct laryngoscopy showed fibrosis in the inter-arytenoid region with the right vocal cord fixed and involved in the subglottic fibrosis.

Subsequent management was by tracheostomy (for respiratory distress due to upper respiratory infection) and Kenacort* injection of the stenotic area of the larynx under anaesthesia. Tracheostomy was allowed to close and there was no significant respiratory obstruction.

Discussion

The patient developed glottic and subglottic stenosis from the combined damaging effects of prolonged ischaemia of the rigid laryngeal box and cricoid ring from a relatively overinflated cuff and probably short endotracheal tube, episodes of prolonged hypotension during surgery, infection and poor reparative response of the patient to the effects of mucosal ischaemia.

It is advised that such ill patients should have the cuff just inflated or readjusted during anaesthesia such that a minor leak occurs. A pharyngeal pack acting as a sponge will be a useful adjunct.

Case Report of Neonatal Ascites (Urinary) Due to Obstructive Uropathy

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Introduction

URINE is the common cause of neonatal ascites (see Fig. I) and the underlying pathology is obstructive uropathy often due to posterior urethral valve in a male infant.

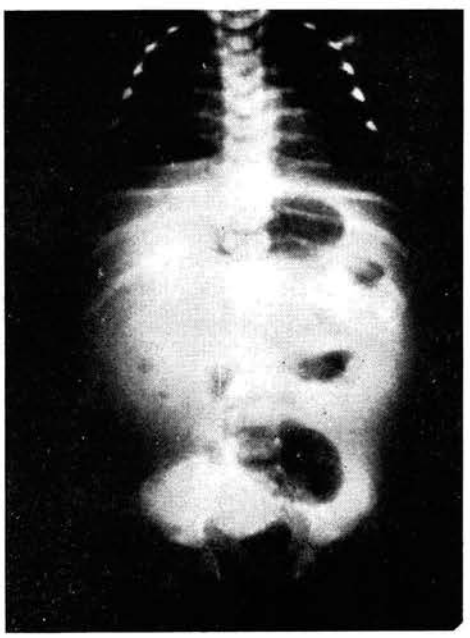

Fig. I

Ascites on Supine X'ray Abdomen: Bulging Flanks and Difuse Opacification with central (Floating) gas-filled bowel. Loss of psoas shadows.

Case Report

T.L.C., one month old male Chinese baby with history of diarrhoea one week. No improvement on treatment by General Practitioner and out patient department.

On admission (29.3.75), bowels not opened, distension of abdomen, vomiting on and off, unable to take feeds.

On Examination

Dehydrated, Drowsy, afebrile. Abdomen – Distended, non-tender, tympanitic on percussion, Vague mass Right hypochodrium. Significant Ascites present. Bowel sounds negative. P.R – no abnormality detected, Flatus tube – poor result.

Treatment

Intravenous balance solution started. 5.4.75 I.M. Penbritin and Cloxacillin 125 mg. 6 hourly commenced due to fever. Less ascites and improvement after catheterisation of bladder.

Referred to General Hospital, Kuala Lumpur for surgery.

Investigations

Peritoneal tap – 400 c.c straw coloured fluid obtained. Protein 0.8g%.
Smear showed moderate pus cells but no organisms/AFB.
Ba-enema – no evidence of Hirschsprung disease.
Bl. urea – 28 mg %
Serum electrolytes: Na-115 meg/litre
K -6.0 ,, ,,
Cl -76 ,, ,,

IVU – see figures 2 to 4.

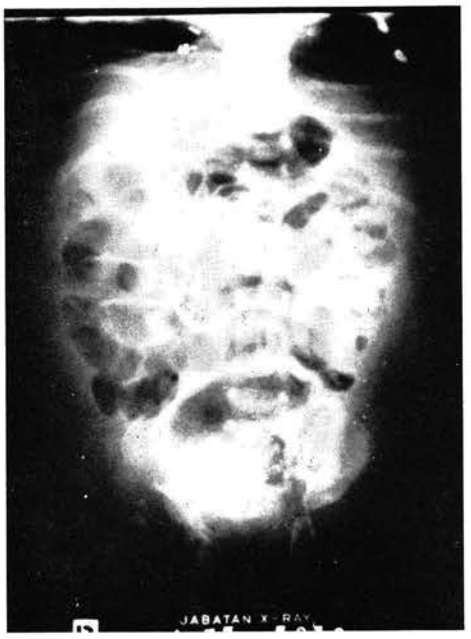

Fig. 2
Bilateral Hydronephrosis on I.V.U. 20 minute film.

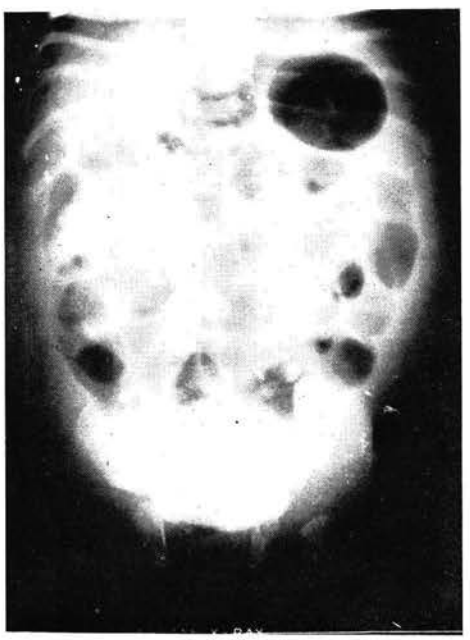

Fig. 3
45 minute film I.V.U. (R) Perirenal extravasation of contrast.

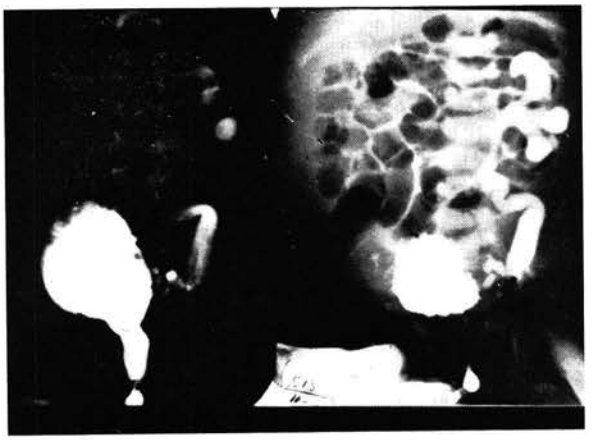

Fig. 4
Micturating Cystourethrogram. Posterior valve causing proximal urethral Dilatation. Trabeculated bladder. Reflux up (L) ureter.

Discussion

This case and recent reports show that extravasation occurs in upper urinary tract probably from the calyceal fornix unlike previous belief that transudates occur through walls of distended urinary tract. Extravasation appeared as an opaque perirenal halo in delayed films and there was no periureteral extension. Only part of the ascites is urine from peritoneal rupture the rest being peritoneal exudate.

Besides posterior urethral valves in male infants other rare causes of neonatal urinary tract obstruction with urinary ascites are pelviureteric obstruction, ectopic ureterocoeles, and urethral obstruction in females by hydrocolpos and sacrococcygeal teratomas.

Williams et al (1973) ablate the posterior urethral valve which is a single "Spinaker sail" by dorsal diathermy under radiological screening.

Acknowledgements

I wish to thank the Director General of Medical and Health Services of Malaysia, Tan Sri Datuk (Dr.) Abdul Majid Ismail for permission to publish this case report, the Medical Unit for supplying the clinical data and my Radiographers who took the excellent radiographs and especially Mr. Mohd Amin bin Deta for typing this paper and Mr. Francis Leong Foo Sen for taking the photographs.

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Book Reviews

SEVENTY-FIVE YEARS OF MEDICAL RESEARCH IN MALAYSIA. Edited by K. Ramanathan *et al. Stud. Inst. Med. Res. Malaysia.* **No. 32. pp. 372. 1976**

THIS VOLUME brought out in connection with the Diamond Jubilee Celebrations of the Institute for Medical Research, Malaysia, is the work mainly of the present staff. Forty-three contributors have tried to cover the work of the I.M.R. over the last 75 years and they necessarily repeat some of the ground covered in the "Fifty Years of Medical Research in Malaya" edited by J.W. Field *et al* in 1951. The new material, however, brings out the changing emphasis in the work of the I.M.R. in recent years in keeping with the changing pattern of diseases and the need for undertaking training of technicians and others.

The volume is dedicated to Dr. Ungku Omar-Ahmad, the Director of the Institute from 1965 to 1969 who was strongly convinced that "the role of the I.M.R. should be expanded to be viable enough to accommodate not only medical research but also teaching and other activities to meet national needs".

In addition to chapters devoted to different research fields there is a section which spells out the services rendered by I.M.R. so that the maximum use could be made of them by the people. There is also a very interesting section devoted to Personal Glimpses and Reminesences. The volume is well illustrated with pencil sketches by Yap Loy Fong and colour photos by Seow Chin Loong including those of the three Commemorative Stamps issued in connection with the I.M.R. Diamond Jubilee Celebrations.

This book is said to have been brought forth at short notice and doubtless accounts for some of the minor errors which will be corrected in a revised version. It is regrettable that there are no references in the book to published work which would have greatly enhanced its scientific value. Perhaps an appendix containing a list of publications emanating from the I.M.R. during the last 25 years might help. Nevertheless, the I.M.R. is to be congratulated for issuing a publication of great historical interest and importance which should find its way into all medical libraries and the shelves of all doctors interested in Tropical Medicine.

TRANSACTIONS OF THE THIRD INTERNATIONAL ORTHODONTIC CONGRESS. Edited by J.T. Cook. *Crosby Lockwood Staples, London.* **1975 pp. 594. $16.00 net.**

THIS BOOK records the proceedings of the third international orthodontic congress held in London in 1973 with more than 1600 delegates from 50 countries. That this represents a ten-fold increase in the number of delegates and twice the number of participating countries over those at the second congress held in 1931 gives some idea of the growth of this speciality over the years. This book condenses in 56 well-illustrated chapters the material presented in more than a hundred papers and makes stimulating reading. This is an authorative account of the development of new techniques, the rapid advances in functional prosthesis and the fascinating variety of materials from which these can now be made and should find a place on the shelves of every orthodontist in the world.

HEALTH AND INDUSTRIAL GROWTH. *Associated Scientific Publishers,* **P.O. Box 211, Amsterdam. 1975. pp. 267.**

THE PUBLICATION of this book is opportune and is of special interest to development planners, health care workers, industrial sociologists and psychologists and all those concerned with the problems of industrialisation in developing countries. The majority of developing countries are determined to industrialise and upgrade their overall economy as rapidly as possible with a view to securing a higher standard of living, and Malaysia is no exception. The expanding industrialisation inevitably brings on the migration of people from the country to the urban areas resulting in problems of overcrowding, pollution, etc.

The book records the papers and the discussions at the Ciba Foundation Symposium on Health and Industrial Growth held in London in September 1974. It begins with problems of the directly harmful side-effects of industrial growth, the 'growing pains' of developing countries and how they might avoid repeating mistakes made in 19th century Europe and the impact of industrialisation on health of the working people and on society in developing countries.

HUMAN MALFORMATIONS. Edited by C.L. Berry. British Medical Bulletin Vol. 32 No. 1. Jan. 1976. *British Council* **65 Davies St., London W1Y 2AA pp. 98. $3.50.**

"IT IS a sobering thought," says Professor T. McKeown in his Introduction, "that, after several decades of research .... the problem of human malformations remain essentially unchanged ..... Yet the outlook is not so gloomy as this appraisal may suggest, and the papers assembled in this issue of the Bulletin show the range and prospects of current research." Four papers outline experimental work that is advancing understanding of malformations – infection, mechanical factors operating within the uterus and various environmental agents. Two papers are concerned broadly with epidemiological approach while the others deal with matters that have a direct bearing on clinical practice.