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The changing pattern of disease in Malaysia

by *V. Thuraisingam*

ANY DOCTOR who has been in medical practice for even 5 to 10 years in this country would have noticed the steady change in the disease pattern of their practice, whether they work in rural or urban areas or in clinics or wards. This change is not only in the types of diseases but also in the manifestations of familiar disorders. Younger members of the profession may not realise the extent of this changing pattern and others may even fail to recognize many a familiar disease in a new guise.

The decreasing incidence of infectious disease due to better public health control and the improving socio-economic environment is now leaving us with its legacy of degenerative and malignant diseases. These are visibly increasing in number and our practice will soon have to take on a geriatric bias with its own attendant medical, social and psychological problems. New disease syndromes are continually being described as increased specialization is aided by the modern medical application of scientific techniques and innovations. Infants who would previously perish soon after birth due to congenital disorders are now being given a new lease of life. What disease

patterns may yet unfold in these survivors?

Another factor which is already an important problem but which could pose a bigger menace is iatrogenic disease. Never in the history of medicine has the doctor been assailed as he is today even in Malaysia by the advertising power of the pharmaceutical industry. The temptation to change to new and potent drugs not only affects patients but doctors and this is already a significant problem, that now the chances of a person developing iatrogenic disease is fast approaching the declining incidence of infectious diseases.

The universal cry for industrialization, increased mechanization, use of pesticides and chemical fertilizers is already very much in our midst and we will be seeing many new diseases of industrial or occupational origin. Furthermore, the changing pattern of life in this country with a shift from rural to urban, improving education, influence of the mass media and many such factors is already evident in the increase of psychiatric and psychoneurotic disorders. The well-recognized geographical and racial incidence of disease may no longer be reliable with rapid free travel

and inter-racial marriages. Thus naso-pharyngeal carcinoma may affect the Indians and yellow fever may have to be considered in differential diagnoses.

The apparent change in pattern of disease, may, in many cases, be due entirely to a change in the manifestations of the disease from modifying factors in the host. The senile arteriosclerotic patient with an apparent stroke may have had a myocardial infarct which caused hypotension and transient cerebrovascular insufficiency. Immunization procedures may not entirely prevent some infectious disease but merely modify or attenuate the manifestations. Partial treatment may mask the signs and symptoms, the

emergence of resistant strains of organisms may also modify the clinical features and palliative surgery can change the classical clinical picture. These are but some of the many factors which contribute to the changing scene in disease pattern.

Change there will be and change there must be as long as man continues to dominate and control his environment. Medicine being the most human of all sciences is inevitably and inextricably involved in any change. In a developing country like Malaysia, the doctor cannot be content merely to know how to prevent, diagnose and treat his patient, but he should be alive and aware of the constant changes taking place in and around his patients.

Priorities in a modern tuberculosis program in developing countries

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(Paper presented at the XX International Tuberculosis Conference, New York, in September 1969)

A MODERN TUBERCULOSIS PROGRAMME in any country can be defined as a concerted official and community effort to reduce and eventually eliminate the needless human suffering caused by tuberculosis by utilising realistically and effectively all the knowledge which is available from the spectacular advances which have taken place in recent years in biomedical, technological and operational research in the fight against tuberculosis. This new knowledge must be applied in a manner which is practicable in and acceptable to the community for whom the program is intended. Above all, the program should ensure the utmost investment value for the effort and funds expended.

Particularly in developing countries which are plagued by many problems other than health and many health problems besides tuberculosis, the overriding need is to develop a Tuberculosis Program which makes minimal demands on the nation's limited resources and yet produces the maximal epidemiological impact on the tuberculosis problem without sacrificing any of the basic objectives of the program. In order to meet this pressing and inescapable

need, it is imperative to establish definite and precise priorities which must be strictly adhered to under all circumstances.

The basic objectives of a modern Tuberculosis Program require that at least three-quarters of the eligible population should be protected with BCG vaccination and at least two-thirds of the infectious cases in the country should be identified and, of these, at least 95% should be rendered permanently non-infectious by adequate treatment. Anything short of these minimum requirements renders the program ineffectual; the desired impact on the problem is not obtained and the effort expended in pursuing such a sub-minimal program is wasted.

The topmost priority in any developing country which is desirous of embarking on a modern Tuberculosis Program is to correct the grave disparity which exists in the provision of basic health services between the urban and rural population. The pattern of health service structure in almost all developing countries, certainly in Asia, is heavily biased in favour of the grossly over-pampered tiny minority which lives in the large towns. In the rural areas, where more

than three-quarters of the population live, where indisputably more than three-quarters of the tuberculosis problem can be found, basic health services are either non-existent or pitifully patchy and meagre. Obviously, this gross imbalance in the provision of basic health care for the community must be corrected before any public health program like the Tuberculosis Program can hope to succeed.

The Tuberculosis Program can succeed only if it is able to reach the entire population. In the affluent technologically advanced countries of the West, this does not pose a problem as the infrastructure of community medical and health care facilities are already in existence and well established. They are widely and adequately distributed to permeate all segments of the population in every section of the country so much so that good medical and health care is available to each and every member of the community no matter where he is living, whether it be in the city or in a remote rural area. In developing countries on the other hand, no such infrastructure exists except possibly in the capital cities and large towns.

All the developing countries in Asia are becoming increasingly alive to the urgent and pressing need for basic health services to cover the entire population and they are indeed striving hard to meet this need. The success they are achieving is generally poor because they are severely hampered by the tyranny of long-established tradition which discriminates heavily in favour of a vertically patterned urban-intensive medical and health policy. The rural areas, where the vast majority of the population lives and where the bulk of the nation's health problems can be found, receive but scant attention from the appointed guardians of public health who continue to pamper to the needs of the already over-medicalised urban minority.

It will need imagination and courage to break away from established practice and to withstand the pressures of urban-intensive forces. The solution is really simple. All that is necessary is to re-examine the national health budgetary provisions on a strict cost/benefit basis and to re-allocate the available financial and manpower resources to ensure the highest benefit for the greatest number of people.

If this is done, the development of a basic health service where none exists or the strengthening and extension of what little there is in order to cover the whole population can be undertaken with no appreciable increase in the health budget. Such a basic health service, which does no more than meet the felt

health needs of the rural folk and requires only trained technicians and para-medical personnel to man it on the ground with only periodic professional supervision by visiting teams, would amply provide the necessary infrastructure to mount and prosecute effectively and realistically most, if not all, the public health programs a developing country considers desirable.

Once the basic health service is established, the Tuberculosis Program is automatically provided with the ideal machinery for its operation. BCG coverage of at least three-quarters of the eligible population can be achieved by direct indiscriminate vaccination of all persons under the age of 20 years. The network of primary multipurpose health centres, providing a basic health service almost at the doorstep of every member of the community, cannot but ensure the desired coverage. Initially it may be necessary to mount a campaign, possibly with additional personnel, to hasten the coverage of the eligible population. After this has been achieved, all the primary health centre is required to do in the continuing phase of the BCG program is to cover only the yearly crop of newborn babies in the area.

Identifying at least two-thirds of the sources of infection in the area served by the primary health centre and ensuring that 95% of them are rendered permanently non-infectious by adequate treatment is well within the competence of the health centre. Nor does it throw an inordinately heavy load on the primary health centre if the real and basic objectives of the Tuberculosis Program are strictly kept in mind and full use is made of the new knowledge now available to perform these tasks efficiently and reliably.

We now know that an infectious case is one who has a cough and is excreting tubercle bacilli in his sputum demonstrable on direct smear microscopy. Cases whose sputum is positive on culture only are not infectious and, therefore, do not pose a danger to the community. Cases diagnosed on radiography alone with negative bacteriology are certainly non-infectious and in all probability not suffering from tuberculosis.

The conventional method of case-finding by periodic systematic screening of the healthy population is quite ineffectual as the yield is painfully small, the effort expended prohibitively excessive and new cases keep cropping up during the intervening period between the screening rounds.

We also know that radiography as a case-finding tool is quite unreliable and cannot be recommended.

It has no place in the Tuberculosis Program in a developing country.

Direct smear microscopy of sputum produced by symptom-motivated persons suffering from a cough of more than two weeks duration is the only reliable way of identifying sources of infection. Studies have shown that more than 90% of all the infectious cases in a community have symptoms and would voluntarily seek relief of their symptoms in a health centre if they had confidence in it and the service provided was readily available, convenient, courteous and free. A consumer-oriented basic health service offered by a primary health centre constitutes the key to a successful case-finding program.

Sputum collection and examination techniques have been so simplified and standardised for mass application that junior technicians can be trained in a few months to perform these tasks efficiently and reliably under periodic professional supervision.

While sputum collection can, and should, be undertaken by trained staff at all primary health centres, it is desirable that the actual examination of sputum is conducted in a larger or secondary health centre where adequate and reliable facilities are available for direct smear microscopy.

Case-finding, or rather the identification of sources of infection, can and should be developed, not as a specialized program but as an integral part of the basic health service.

The third objective of the Tuberculosis Program which is to render permanently non-infectious with effective treatment all the infectious sources identified can also be efficiently handled at the primary health centre level. There is now no justification whatsoever in a Tuberculosis Program to maintain expensive specialist institutions for the treatment of infectious cases. Simple standardised drug regimens have been evolved which can be applied on a mass scale with more than 90% effectiveness by trained nurses and technicians working in a multipurpose primary health centre. All they require is regular periodic professional and technical supervision.

Experience has shown, however, that self-administration of medicaments by the patient is quite undependable, particularly after distressing symptoms have been controlled. Entirely supervised chemotherapy is the only way to ensure that the drugs are definitely administered in the correct dosage. In offering treatment facilities close to the patient's home suiting his every convenience, the primary health centre makes entirely supervised chemotherapy possible and operationally feasible.

Isoniazid and Streptomycin are the two most potent specific drugs available to-day and the best chemotherapeutic regimen is one which employs both these drugs in combination. The best and most effective drug regimen which can be applied on a mass scale by trained para-medical personnel in a Tuberculosis Program at the primary health centre level is initial intensive chemotherapy with daily Isoniazid and Streptomycin for four to six weeks, followed by intermittent twice weekly Isoniazid and Streptomycin for one year. Evidence is accumulating which strongly suggests that Isoniazid alone for one year may prove adequate after initial intensive chemotherapy with daily Isoniazid and Streptomycin.

It is, of course, quite evident that in all community health programs embarked upon by the government of a developing country whose responsibility it undoubtedly is to undertake them, the general public for whom these programs are meant must respond by coming forward to take full advantage of them. This desirable participation of the public cannot be taken for granted. Experience has clearly exposed the folly of such a premise. Many community programs in developing countries have failed dismally because this very important requirement has been ignored. In a Tuberculosis Program, however, such a pitfall can be avoided if National Tuberculosis Associations play the role expected of them, which is essentially to rally public support for the program by instituting realistic measures to ensure active community participation in it. Being voluntary bodies organised by the community, they are best equipped to undertake this task and indeed, if they did nothing else, their contribution in this respect alone would easily match that of the official bodies in terms of effort and achievement.

In order to do this effectively, voluntary bodies need to extend their activities beyond the ivory towers of urban-based committee rooms. They must seek direct involvement and identification with the community at the ground level, much in the same way as the basic health service pervades every section of the country and permeates all strata of society. Their responsibility is to support and supplement official effort in all spheres and at all levels of activity by motivating the community to take the correct action to safeguard its health. If they are to play this vital role effectively, they must adhere strictly to this basic objective and desist from engaging in any activity which has even the remotest possibility of duplicating official effort.

It is abundantly clear that a modern Tuberculosis

Program in a developing country needs to be firmly structured on and fully integrated with the basic health service if it is to be effective. The operational expertise of a realistic program has been perfected to the last detail. If it is applied correctly with the basic objectives kept clearly in mind and the priorities firmly established, it is manifestly possible for any developing country, however thread-bare its economy, to embark on a modern Tuberculosis Program which will ensure the maximal epidemiological impact on the problem.

It is, therefore, rather depressing to report that, by and large, in the developing countries of Asia a wide and yawning gap still continues to separate the new knowledge available to fight tuberculosis effectively from its actual application on the ground. There is much bold talk and most impressive plans on drawing boards to bridge this gap but the actual attempts made are feeble and fall hopelessly short of target.

The Tuberculosis Program remains firmly fettered to the existing health service structure and operates essentially as a specialised service covering mainly the capital cities and large towns and catering consequently to the needs of only a small privileged segment of the population. Whatever the claims made for it, the program can only be as good as the health service on which it is structured. It is painfully evident that it certainly does not reach the entire population. The basic health services, if they exist at all, are at best patchy and meagre, ill-equipped and understaffed with poor logistics support and inadequate professional supervision, except for the bustling pilot projects which never seem to grow out of the pilot stage but continue to function almost indefinitely as permanent show-pieces to advertise the aspirations displayed on the drawing boards of national health planning.

It does seem, therefore, that it will be a long time before these glaring anomalies are corrected adequately enough to enable developing countries in Asia to set up the proper infrastructure of basic health services for mounting a modern Tuberculosis Program. The gallant attempts they are making to overthrow the tyranny of traditional health service policy do not match the strength of their convictions that such a deliverance is a compelling necessity. The only heartening note is that a move in the right direction is clearly discernible and that the pressures which are building up from enlightened opinion within the more progressive of these countries and from world opinion, exerted by international agencies like the World Health Organisation and the Inter-

national Union Against Tuberculosis, will tip the scales and force the desired break from the shackles of outmoded and discriminatory conventional practice. There is every hope, therefore, that a modern Tuberculosis Program may materialise in some of the developing countries of Asia much sooner than seems possible at the present time.

SUMMARY

A modern Tuberculosis Program in a developing country is a concerted official and community effort to control tuberculosis by applying the available operational expertise in a manner which makes minimal demands on the nation's limited resources and yet produces the maximal epidemiological impact on the tuberculosis problem.

The basic objectives of the program must be clearly defined and kept constantly in mind. Definite and precise priorities must be established and strictly adhered to.

The minimum requirements of the program are: firstly, that three-quarters of the eligible population should be protected with BCG; secondly, that two-thirds of the infectious cases in the country should be identified; and thirdly, that at least 95% of these infectious sources should be rendered permanently non-infectious with adequate treatment.

The program can achieve these basic objectives only if it is able to reach the entire population through an efficient network of primary health centres adequately distributed to serve all segments of the population in every section of the country.

All the developing countries in Asia are striving hard to provide such a basic health service but they are severely hampered by the dictates of traditional practice, which is biased heavily in favour of pampering to the needs of the already over-medicalised urban minority, leaving the vast majority of the population, which lives in the rural areas where the bulk of the nation's health problems can be found, virtually devoid of health care. The correction of this grave disparity must command the highest priority in the development and operation of a modern Tuberculosis Program. This can be accomplished if developing countries are prepared to overcome the pressures of urban-intensive forces and re-allocate their available financial and manpower resources on a strict cost/benefit basis which ensures the highest benefit for the greatest number of people.

The three basic objectives of the program can be achieved with complete success by the application at the primary health centre level of simplified, stan-

standardised highly effective procedures and techniques which can be undertaken with extreme competence by trained technicians and para-medical personnel working under periodic professional supervision.

The desired BCG coverage of the eligible population can be obtained by conducting direct indiscriminate vaccination of all persons under 20 years of age.

The conventional method of case-finding by systematic periodic screening of the healthy population is quite ineffectual and should be abandoned.

Cases whose sputum is positive on culture only are not infectious. Cases diagnosed on radiography alone with negative bacteriology are certainly non-infectious and in all probability not suffering from tuberculosis.

Radiography as a case-finding tool is unreliable and has no place in the Tuberculosis Program in a developing country.

Direct smear microscopy of sputum produced by symptom-motivated persons suffering from a cough of more than two weeks' duration is the only reliable way of identifying sources of infection. More than 90% of all the infectious cases in a community have symptoms.

If the basic health service is consumer-oriented, the infectious cases can be identified at the primary health centres from the symptom-motivated patients who come forward to seek relief of their symptoms.

Infectious cases can be rendered rapidly non-infectious by using standard drug regimens which are 95% effective and can be applied on a mass scale by trained nurses and technicians at the primary health

centre level.

Self-administration of medicaments by patients cannot be relied upon as defaulting is a common occurrence once symptoms are relieved. Entirely supervised chemotherapy, which is operationally feasible at the primary health centre level, is the only sure way of ensuring correct drug administration.

Active community participation is vital to the success of the official program mounted by government. Tuberculosis associations, being voluntary community organisations, should make it their primary concern to rally public support and foster community involvement in the program at all levels of its operation. To do this effectively, they need to extend their activities far beyond the urban areas to cover the whole community.

The Tuberculosis Programs in the developing countries of Asia are only as good as the health services on which they are structured. By and large, they operate as specialised services catering essentially to the needs of the small urban minority. The basic health services for the large rural majority, if they exist at all, are mostly inadequate on all counts. The infrastructure for a modern Tuberculosis Program is, therefore, lacking and will not become available until the glaring inequalities in the provision of basic health services between the urban and rural communities are corrected. A move in the right direction is, however, clearly discernible particularly in the more progressive countries. There is hope, therefore, that a modern Tuberculosis Program may materialise in some of the developing countries of Asia sooner than expected.

Ascariasis: Beliefs and practices of a rural Malay community

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INTRODUCTION

IN RURAL West Malaysia, the problem of intestinal helminthiasis is very considerable. Heyneman et al. (1967) observed that 94% of the residents of an island off the east coast of West Malaysia, Pulau Tioman, were positive for one or more helminth species. They noted that the percentage of *Ascaris lumbricoides* infections was the highest, being 89% compared with *Trichuris* (57%) and hookworm (31%) infections. In an effort to determine how rural Malays are attempting to control and to prevent the commonest intestinal helminthiasis, ascariasis, and in an effort to understand their reasons for these measures, the beliefs and practices of a rural Malay community were studied. The purpose of this paper is to present these beliefs and practices and to discuss their implications for public health programmes aimed at rural Malays of similar communities.

PROCEDURE

STUDY AREA AND POPULATION

A rural Malay community situated in the northern part of Kedah State, West Malaysia, was selected. It consisted of 54 households spread out on both sides of an earth track that passed through the valley. The

community was about five miles from the nearest metalled highway – the Asian Highway linking Malaysia with Southern Thailand – and was linked to it by a narrow single-laned earth track. The nearest government health centre, which had two resident doctors, was seven miles away in a small town which had one private practitioner and three Chinese drug stores. No scientifically trained medical and health personnel had been into the study area to carry out any public health activities. None of the households had any latrines, all residents resorting to the bushes for the act of defaecation. There were 283 persons, all of the Islamic faith, distributed among the 54 households. The two chief occupational activities were padi farming and rubber tapping. The modal range of income a month was Malaysian \$60.00 to \$79.00, 65% of households earning an income of less than Malaysian \$80.00 a month. Half (50.0%) of the heads of households and 59.3% of the housewives had never had any formal education and were illiterate. The community selected was thus a relatively remote one, still following traditional beliefs and practices.

DATA COLLECTION

The data were collected by the writer assisted by a trained interviewer. Three methods were utilised in

TABLE I
DISTRIBUTION OF BELIEFS ABOUT THE CAUSATION OF ASCARIASIS

Belief about the causation of ascariasis	Number and % of respondents mentioning belief	
1. Consumption of fish	36	(66.7%)
2. Consumption of mature coconuts	10	(18.5%)
3. Consumption of eggs	10	(18.5%)
4. Consumption of peanuts	8	(14.8%)
5. Weakness of the body	7	(13.3%)
6. Consumption of large quantities of sugar and sweets	5	(9.3%)
7. Consumption of unripe fruits	1	(1.9%)
8. Irregular meals	1	(1.9%)
9. Consumption of "dirty" food*	1	(1.9%)
10. Micro-organisms (kuman2)*	1	(1.9%)
TOTAL	80	(148.4%)

*Both beliefs were mentioned by one respondent, the average number of items mentioned being 1.48 per respondent.

the data collection, and this served as a cross-check in respect of several of the items.

- (i) Interview with key personnel — Key personnel in the community such as the local leaders (**penghulu**, **ketua kampung**, members of the **Jawatan-kuasa Gerakan Maju**) and traditional medicine-men (**bomoh**) were interviewed. These interviews did not follow any set pattern.
- (ii) Interview with housewives — Each housewife was interviewed in her own house. The interviews were conducted in Malay and were standardised by using a previously prepared list of questions. During the course of the interview, each housewife was shown a specimen bottle in which were mounted three *Ascaris lumbricoides* worms. She was asked if she had had personal experience with such worms — whether any members of her family had been known to expel similar worms. In addition, she was asked questions in relation to her beliefs about the causation of ascariasis and her practices in regard to treatment and prevention.
- (iii) Direct observations — Inspections *in loco* were made of sources of therapy to check the availability of the treatments mentioned by key

personnel and housewives. In the process, samples of materials used, therapeutically and/or prophylactically, were obtained from the three sources available to the villagers — drugs from the government health centre, drugs from the Chinese drug stores, herbal remedies and talismans from the traditional medicine-men (**bomoh**)

OBSERVATIONS

BELIEFS ABOUT CAUSATION

Table I shows the frequency distribution of beliefs about the causation of ascariasis. A total of 80 items was mentioned by the 54 respondents. The average number of items mentioned was 1.48 per respondent. The most common belief (mentioned by 66.7% of the respondents) was that ascariasis is the result of the consumption of fish. Some implicated only freshwater fish, **ikan darat**, while others believed that sea fish, **ikan laut**, as well as freshwater fish were the cause of ascariasis. Salted as well as freshly caught fish was included in both the above categories. Ten of the respondents (18.5%) believed that the consumption of mature coconuts was a factor. A similar number (18.5%) implicated eggs, while eight (14.8%) believed that the consumption of peanuts was

TABLE II
DISTRIBUTION OF TREATMENTS SOUGHT BY 52 HOUSEHOLDS

Type of treatment sought	Number of households	% of households
1. "Modern" drugs alone:	(30)*	(57.7)*
(i) Government health centre	10	19.2
(ii) Chinese drug stores	18	34.6
(iii) Both of the above	2	3.9
2. Both "modern" and traditional treatments:	(20)*	(38.5)*
(a) with "modern" as first choice:		
(i) Govt. health centre	2	3.9
(ii) Chinese drug stores	4	7.7
(b) with traditional as first choice:		
(i) Village herbs	4	7.7
(ii) Talismans	10	19.2
3. Traditional treatments alone:	(2)*	(3.9)*
(i) Village herbs	1	1.9
(ii) Talismans	1	1.9
(iii) Both of the above	0	0.0

Two households were excluded since their members had had no experience of ascariasis.

*Sub-totals are given in parenthesis.

another factor. All four of these food items are utilised in the cooking of a side dish known locally as *lauk*. Fish and the milk of mature coconuts are the basic ingredients of such side dishes. Crushed peanuts and eggs may occasionally be added. The local Malays have an expression which they direct at children who ask for a helping from such side dishes, "*makan lauk nanti chaching!*"

("If you take these side dishes, surely you will have worms!").

Seven (13.0%) of the respondents mentioned weakness of the body, *tidak sehat*, as another cause of ascariasis. The local Malays have noted that ascariasis is most commonly a disease of children who may expel as many as 50 worms on treatment. They have also noted that it is the weak and sickly child who tends to expel numerous worms – even occasionally expelling one or two via the naso-oral passages. They note that adults, who are naturally stronger than children, do not exhibit such phenomena presumably since they are strong. On the other hand, since children are generally weaker, it is not surprising to note that ascariasis is a paediatric

disease and hence weakness itself is an important causative factor.

Only two (3.8%) of the items mentioned – the consumption of "dirty" food and micro-organisms, *kuman-kuman* – can be included as causative factors in the light of modern parasitological knowledge about ascariasis. Both these items were mentioned by the same respondent, a 30-year-old woman. Her husband was a 35-year-old rubber tapper. Neither she nor her husband had had any formal education. However, they had four school-going children, the eldest of whom was a 15-year-old boy attending a secondary school in town. Obviously, some of the concepts he had acquired had been passed on to his parents.

TREATMENT SOUGHT

Fifty-two (96.3%) of the households acknowledged that they were familiar with *Ascaris* worms, some member having expelled worms similar to those exhibited in the specimen bottle. As shown in Table II, a total of 30 (57.7%) of the 52 households used only "modern" drugs to treat their members, two (3.9%) used only traditional treatments and 30 (38.5%) used both "modern" drugs as well as traditional treatments.

PIPERAZINE
from
GOVT. CLINIC:

PATENT MEDICINES
from
CHINESE DRUG STORES:



Fig. 1: Samples of "modern" anthelmintics obtained from the local government health centre and local Chinese drug stores. The three on the left (Nos. 1, 2 and 3) are piperazine preparations while the last (No. 4) contains santonin.

(a) "Modern" drugs.

As shown in Table II, a total of 50 (96.2%) of the households used "modern" drugs either alone (57.7%) or in combination with traditional treatments (38.5%). These are obtained either from the government health centre or bought from urban Chinese drug stores. Table III details their local source, their commercial names (by which they are known in the village), their chemical composition, and the approximate cost of a dose of each drug for a child of four years of age. The first three drugs listed all contain piperazine salts, while the last contains santonin, a relatively dangerous drug. Figure 1 shows samples of these "modern" drugs obtained from the local government health centre and from local Chinese drug stores.

The "modern" drugs are used when parents perceive that their children have signs and symptoms believed to be due to worms — poor appetite, distended abdomen, diarrhoea or paleness. Anything from one to 50 worms may be expelled.

(b) Combination of "modern" and traditional treatments.

As shown in Table II, six (11.6%) households used "modern" drugs as the first line of treatment, backing this up with traditional treatments — two households using village herbs and four relying on talismans as secondary boosters to the "modern" drugs. The talismans used in these instances were used in the belief that their magical properties would prevent *Ascaris* worms — stimulated by anthelmintics — from rising and appearing via the naso-oral passages.

A total of 14 (26.9%) households elected to use traditional treatments as the main therapeutic measure, conceding that "modern" drugs were to be used as supports only after the traditional treatments had been tried.

(c) Traditional treatments.

As shown in Table II, only two (3.9%) households used traditional treatments alone. One housewife treated her children with an indigenous herbal remedy while the other used talismans known locally as *tali chaching*.

TABLE III
THE "MODERN" DRUGS USED

Source	Commercial name	Chemical composition	Approximate cost of a recommended dose*
1. Government health centre	—	Piperazine citrate (equivalent to 750 mgm piperazine hydrate per 5 ml.)	Free
	(a) "Antepar"	Piperazine citrate (equivalent to 750 mgm piperazine hydrate per 5 ml.)	\$0.60
2. Chinese drug stores	(b) "Ridto"	Piperazine 550 mgm per fluid drachm.	\$0.50
	(c) "Flower cakes"	Santonin 0.33% Phenolphthalein 0.33% Colour Q.S. Saccharum ad.	\$0.20

*The approximate cost is the retail price, in Malaysian dollars, of the dose recommended by the manufacturers for a four-year-old child, where one Malaysian dollar is equivalent to US 33 cents.

The same herbal remedy was used by a total of seven households. It is obtained from the roots and leaves of the sweet sop, *Anona squamosa*, locally known as *nona sri kaya*. Corner (1952) notes that the *Anona squamosa* is common in Malaya. The fruit (Figure 2), which is edible, is set with knobby, separable bulges and is light green in colour. The tree is between ten and 20 feet high. An alkaloid, anonaine, has been found in this plant, and the leaves are used in South America and Gambia as an insecticide and to prevent bed-bugs (Irvine, 1961). Neal (1965) records that in the Philippines, the plant is believed to be efficacious against witchcraft. The root and bark of a related species, *Anona senegalensis*, is used as a vermifuge in Northern Nigeria, for dysentery and diarrhoea in Senegal, and as an antidote for snake-bite in Central Africa (Irvine, 1961).

A prescription for the herbal remedy *nona sri kaya*, as used for the treatment of intestinal worms by the Malays in the community studied, is given below: "Take the bark of the roots and the leaves of the *nona sri kaya* and boil them. When sufficiently

cool, bathe the sick child with it, and let the worms be expelled."

Burkill and Mohamed Haniff (1930), Gimlette and Burkill (1930) as well as Gimlette and Thomson (1939) have mentioned several Malay medicines for intestinal worms. Some of these, like the herbal remedy described above, are used externally, while others are taken internally. Burkill and Mohamed Haniff (1930) describe one vermifuge taken internally, it being made from garlic, the root of *Tinospora crispa* and coarse salt. The three ingredients are ground to a fine pulp, strained after steeping in water, and the fluid is given to the child to drink on three successive days. However, none of the several medicines described by the above authorities were in use within the community studied.

PREVENTION PRACTISED

Based upon their beliefs about the causation of ascariasis, as shown in Table I, the primary preventive measure practised was dietary taboos against the foods listed. Thus foremost amongst these foods were

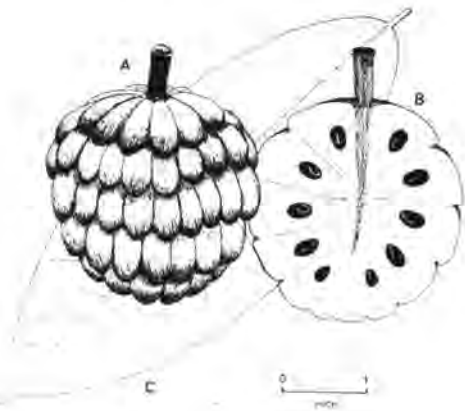


Fig. 2: *Anona squamosa*: A, the fruit. B, longitudinal section of the fruit. C, a leaf.

side dishes, known locally as *lauk*, containing fish, milk of mature coconuts, peanuts and eggs. The consumption of large quantities of sugar and sweets were also considered taboo for children although small quantities were permitted.

Other than such taboos, 24 (44.4%) of the 54 households used talismans as a preventive measure against ascariasis. These talismans were obtained from the traditional medicine-man, the *bomoh*. Figure 3 shows a pre-school child with a talisman round his neck. In the little black cloth bundle is a piece of paper inscribed with magical signs or some koranic text over which magical incantations have been pronounced. These talismans purport to protect toddlers from the unwelcome attention of *Ascaris* worms and are also reputed to prevent worms that develop in the bodies of weak children from rising and leaving via the naso-oral passages. Talismans for other diseases and other purposes were also found, but these will not be included in this paper.

With the exception of the household that mentioned the consumption of "dirty" food and micro-organisms as causative factors, none of the households mentioned any measures even remotely related to the sanitary disposal of infected human faeces or the encouragement of satisfactory hygienic habits on the part of children such as the washing of hands before the handling of food. On the other hand, all the 54 households admitted that human faeces were indiscriminately disposed of behind any bush, scrub or other vegetation that provide sufficient privacy for the act of defaecation. In the case of children, the act was performed in the immediate vicinity of the

dwellings, and it is here that soil contamination is most dangerous since the yard or garden is where they play and thus acquire *Ascaris* ova.

DISCUSSION

The most common belief among the community studied was that ascariasis is caused by children eating a side dish *lauk*, containing fish, the milk of mature coconuts, peanuts and eggs. In spite of their unscientific beliefs regarding causation and their consequently futile attempts at prevention, 50 (96.2%) of the households used piperazine or santonin preparations for treatment. Piperazine salts are relatively safe since piperazine narcotises *Ascaris* worms without causing stimulation and therefore the danger of obstruction or perforation is minimal. Santonin, once widely used as an anthelmintic in ascariasis, may produce violent gastro-intestinal irritation and severe disturbances involving the central nervous system in therapeutically effective doses. DiPalma (1965) notes that the use of santonin is no longer justified.

The adoption, by rural Malays, of "modern" drugs in the treatment of ascariasis makes the task of health education much easier. The evidence indicates that village herbs are being replaced by the truly effective "modern" drugs. The rural Malay undoubtedly recognises their frequently dramatic efficacy, reporting that as many as 50 worms may be expelled upon their use. However, from the preventive point of view, anthelmintic treatment alone, unless carried out on the whole population simultaneously and repeatedly, will be ineffective since repeated infections will occur from contaminated soils. The infective ova of *Ascaris lumbricoides* are chiefly transmitted from hand-to-mouth by children whose hands have come in contact with contaminated soil or by eating dirt. *Ascaris* ova are most abundant near dwellings where soil is contaminated through the lack of sanitary faecal disposal (Belding, 1965). The traditional method of faecal disposal among adults in rural Malay communities, as exemplified by the community studied, has been behind bushes close to human dwellings. In the case of children, defaecation is in the yard or garden. Undoubtedly, this accounts for the high prevalence of ascariasis noted at the beginning of this paper.

The dramatic success of "modern" anthelmintics has made a lasting impression and this augurs well for modern scientific medicine as successes of this nature will in turn open doors for other health services (Read, 1966). Their desire to prevent ascariasis is



Fig 3: A pre-school child wearing a talisman as a preventive measure against ascariasis.

evidenced by the food taboos rural Malays advocate and the talismans their children use. The challenge to modern medical services is to channel this desire towards effective prevention – sanitary faecal disposition. The acceptance of “modern” anthelmintics is evidence of faith in scientific medicine, and all health personnel concerned in rural health programmes should exploit this by persuading the people to place the same faith in and act upon the advice given to them regarding the prevention of a widespread and distressing condition as they do in the advice given to them by the same personnel regarding its cure. It must be recognised that one cannot expect the same immediate and dramatic results from preventive measures as from therapeutic, and the first step in health education is to acquire full understanding of relevant indigenous, traditional concepts

before attempting to replace them. Towards such understanding this paper is presented as a small contribution.

SUMMARY

The beliefs about causation and the practices, with regard to treatment and prevention of ascariasis, of a rural Malay community are reported. The most common belief was that ascariasis is caused by children eating a side dish, *lauk*, containing fish, the milk of mature coconuts, peanuts and eggs. The vast majority (96.2%) of households used piperazine or santonin preparations for treatment, some (38.5%) combining this with traditional treatments – village herbs and talismans. The use of talismans and food taboos against children constituted the main attempts at prevention. The whole community indiscriminately disposed of human excreta behind bushes close to human dwellings. None of the households encouraged hygienic habits on the part of their children, such as the washing of hands before the handling of food. The implications of the above observations are also discussed.

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Serum proteins, haematocrits, heights and weights of Aborigine subjects in West Malaysia

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Introduction

THE PRESENT paper is a record of the results of a study of the serum proteins, the haematocrits, the heights and weights of apparently healthy aborigines in West Malaysia. Differences have previously been observed in ethnically and geographically diverse groups, presumably related to genetic factors, diet and exposure to certain diseases. It is important that the normal variations in these values for any single population should be understood before any interpretation of a particular pathological condition is made. These results are presented because no previous determinations of these quantities for aborigines in West Malaysia have been published. The results are compared with those from other ethnic groups both in West Malaysia¹ and elsewhere^{2, 3}.

Materials and Methods

A total of 109 aborigine subjects, aged 4-45 years took part in the study (48 males and 61 females). The aborigines are composed of a number of ethnic groups whose common factor is that they are descendants of the original inhabitants of Malaya⁴. Most live on the jungle slopes of the central mountain range of northern Malaya and the remainder are scattered over the rest of the peninsula. Twenty-one of the subjects were classified as "deep jungle" aborigines - i.e. those who live in small units at a relatively high altitude and have little contact with other races. The other 88 subjects were considered as

"fringe jungle" aborigines - i.e. those who live in closer contact with other ethnic groups in the ecologically more disturbed outskirts of the forest. Each class comprises more than one ethnic group but differences in diet, and exposure to diseases, especially parasitic, could cause a divergence in biochemical values. All the subjects entered Gombak Hospital near Kuala Lumpur between April and August 1968. They were accompanying members of their family who were sick, but the subjects themselves were apparently healthy persons. All were bled within two days of their arrival at Gombak when their haematocrits, heights and weights were also measured.

Total proteins were determined at Gombak Hospital by the Biuret method of Wootton⁵. All determinations were done in duplicate and at the same time a Verstol or Hyland Biochemical control sera was assayed to within acceptable limits. The serum protein fractions were determined at the Institute of Medical Research, Kuala Lumpur, by paper electrophoresis on 2.5 x 12.0 cm. strips, using barbitone buffer, pH 8.6, ionic strength 0.05-0.07M, in a Shandon horizontal electrophoresis tank. 3 μ t. were applied to each strip and adequate separation was obtained after two hours at 25° C. Fixing was done in 5% trichloroacetic acid for at least 5 minutes. The strips were stained for 10 minutes in 0.2% solution of Ponceau S in 3% trichloroacetic acid, removed and washed in 5% trichloroacetic acid and dried between blotting paper. The individual bands were cut out and

Table I. Total serum proteins by age in Aborigine subjects, West Malaysia.

Age (years)	4-9	10-14	15-45
No. subjects (male & female)	18 (11 + 7)	12 (3 + 9)	68 (32 + 36)
Mean (\pm S.D.)* (gms./100ml.)	7.8 (\pm 0.7)	8.4 (\pm 0.6)	8.0 (\pm 0.6)
	Percent Distribution		
7.0 (gms/100 ml.)	5.6	0.0	7.4
7.0 - 7.9	66.6	25.0	44.1
8.0	27.8	75.0	48.5

* S.D., standard deviation.

Table II. Serum albumin, total globulin and gamma globulin levels by age in Aborigine subjects, West Malaysia.

Age (years)	4-9	10-14	15-45
No subjects (M + F)	17 (10 + 7)	12 (3 + 9)	44 (20 + 24)
Mean + albumin (\pm S.D.)	4.4 (\pm 0.5)	4.8 (\pm 0.7)	4.5 (\pm 0.2)
Mean + total globulin (\pm S.D.)	3.3 (\pm 0.5)	3.5 (\pm 0.5)	3.4 (\pm 0.5)
Mean + γ -globulin (\pm S.D.)	1.5 (\pm 0.5)	1.6 (\pm 0.3)	1.6 (\pm 0.4)
	Percent Distribution		
Albumin: 3.5 (gms/100 ml)	0.0	8.3	45.
3.5 - 4.4	47.0	16.7	36.5
4.5 - 4.9	41.2	33.3	45.5
5.0	11.8	41.7	13.6
Total globulin:			
2.0 - 2.9	29.4	8.3	22.7
3.0 - 3.5	41.2	41.7	40.9
3.6 - 4.0	23.5	33.3	20.5
4.0	5.1	16.7	15.9
γ -globulin:			
0.5 - 0.9	17.6	0.0	4.6
1.0 - 1.4	41.2	50.0	40.9
1.5 - 1.9	23.6	41.7	31.8
2.0	17.6	8.3	22.7

† Mean values in gms. per 100 ml.

Table III. Haematocrit levels by age in Aborigines and civilian and military dependants, West Malaysia.

Age (years)	Aborigines		Civilian and Military dependants	
	No. subjects (M+F)	Mean ⁺ (\pm S.D.)	No. subjects (M+F)	Mean ⁺ (\pm S.D.)
4-9	24 (12 + 12)	35 (\pm 4.5)	114 (55 + 59)	38.6
10-14	14 (3 + 11)	39 (\pm 5.0)	144 (80 + 71)	39.7
15-45	32 M	45 (\pm 4.0)	80 M	44.8 (\pm 3.6)
15-45	35 F	39.5 (\pm 4.5)	108 F	39.0 (\pm 4.3)

+ Haematocrit expressed as mean percent.

Table IV. Height and weight by sex in Aborigines, aged 20 years and above, in West Malaysia.

Sex	Height (inches)		Weight (pounds)	
	Male	Female	Male	Female
No. subjects	29	31	28	29
Mean (\pm S.D.)	62.0 (\pm 2)	57.5 (\pm 3)	110 (\pm 9)	96 (\pm 17)

Table V. Height, weight and age of Federation of Malaya Armed Forces¹

	Mean Height (inches)	Mean weight (pounds)	Mean age (years)
Malays	65.2	127.7	25.1
Chinese	64.0	125.5	23.6
Indians	65.7	131.0	23.0
Average all races	64.1	127.7	25.8

Table VI. Comparison of "normal values" for adults. (All values in gm. per 100 ml. + S.D.)

	Total protein	Albumin	Total globulin	Globulin
Malayan aborigines	8.0 (\pm 0.6)	4.5 (\pm 0.2)	3.4 (\pm 0.2)	1.6 (\pm 0.4)
Malays & Malayan Chinese and Indians ¹	7.5 (\pm 0.6)	3.9 (\pm 0.5)	3.5 (\pm 0.8)	
148 New York Caucasians ²	7.08 (\pm 0.56)	4.47 (\pm 0.53)	2.60 (\pm 0.44)	1.07 (\pm 0.28)
93 New York Puerto Ricans ²	7.41 (\pm 0.55)	4.66 (\pm 0.49)	2.74 (\pm 0.40)	1.26 (\pm 0.26)
72 New York Negroes ²	7.17 (\pm 0.46)	4.20 (\pm 0.47)	2.96 (\pm 0.37)	1.43 (\pm 0.32)
50 Ibadan Nigerians ³	6.8 (\pm 0.4)	3.35		3.45 2.10
25 Ibadan Europeans ³	6.9 (\pm 0.6)	4.05		2.85 1.20

Table VII. Comparison of "normal values" for children (All values in gm. per 100 ml. + S.D.)

	Total protein	Albumin	Globulin
Age 4-9 years:			
Aborigines	7.8 (\pm 0.7)	4.4 (\pm 0.5)	3.3 (\pm 0.5)
Malays & Malayan Chinese and Indians	7.2 (\pm 0.6)	3.7	3.4 (\pm 0.8)
Age 10-14 years:			
Aborigines	8.4 (\pm 0.6)	4.8 (\pm 0.7)	3.5 (\pm 0.5)
Malays & Malayan Chinese and Indians	7.4 (\pm 0.5)	3.8	3.6

the strained protein eluted in 0.2 N sodium hydroxide. The colour intensity was measured at 570 m μ . Micro-haematocrits were measured from venous blood and were taken to the nearest 0.5 percent. Heights were taken to the nearest 0.5 inch and weights to the nearest pound. Age estimation is based on the patient's or parents' statement and is at best approximate.

Results

Complete serum protein data was available on 73 subjects. The mean results and standard deviations for the various age groups are summarized in Tables I and II. The mean results and standard deviations for haematocrits in Aborigines are summarized in III. All the females taking part in these studies were non-pregnant and non-lactating. Table IV summarized the mean heights and weights of adult Aborigine subjects.

There was no significant difference in means for albumin or globulin between fringe jungle and deep jungle groups (albumin, respectively, 4.6 ± 0.6 gm. per 100 ml. and 4.4 ± 0.6 gm. per 100 ml.; globulin 1.5 ± 0.4 and 1.7 ± 0.4). There was, however, a tendency for a higher proportion of the deep jungle subjects to have a higher globulin (over 1.5 gm. per 100 ml.), shown by a X^2 of 3.878 (0.02 P 0.05).

Comments

The values for total serum protein, albumin, total globulin and globulin in the present study are compared in Table VI with those found by the 1962 ICNND (Interdepartmental Committee on Nutrition for National Defence) Survey for Malay and Malayan Chinese and Indian military personnel and departments, and also with those ethnic groups studied in New York by Seigal et al.² and with two ethnic groups studied in Nigeria by Edozien³. The values for children are compounded in Table VII with those of the ICNND study. The Aborigines in each age group have higher total protein levels than the other populations. At least for the adult aborigines and the Malayan ethnic groups, the differences are considered statistically highly significant ($p < 0.001$). These higher protein levels are due to higher levels of both γ -globulins in comparison with the New York groups, but due to higher albumins in comparison with the Malayan groups. In comparison with the Ibadan Europeans, they are due to both higher globulin and albumin levels. Various physicians of the Aborigine Medical Service have observed that the more varied diet of the Aborigines may lead to their having a better nutritional state (and thus higher albumins)

than rural Malays. However, both groups would appear to be exposed to similar disease problems since their globulins are comparable. The amount of serum gamma globulin reflects in part the activity of the immune mechanism, the effects of past exposures to antigenic stimulation, and the rate of metabolism of gamma globulin. No correlation were found between γ -globulins and albumins, between γ -globulins and haematocrits, or between albumins and heights in Aborigine subjects.

The values for haematocrits in the present study are compared in Table III with those found by the ICNND survey. In the higher two age groups, the haematocrit levels are comparable but in the 4-9 years age group, the Aborigines have lower haematocrits. In both populations, the haematocrits levels tend to decrease with age.

Table V summarizes the mean heights and weights of military personnel¹. The male Aborigine subjects have lower heights and weights than those of the Armed Forces.

The number of children and of deep jungle subjects used in the study is small and more work remains to be done in order to be able to compare the protein levels of deep and fringe jungle subjects.

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Pyloric obstruction due to formic acid ingestion

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Introduction

MODERN TECHNOLOGY requires extensive use of corrosives, thereby increasing the likelihood for medical accidents with these substances. Knowledge of the nature of injury caused by the different corrosives is obviously important. Thus forearmed, the physician or surgeon can determine the proper treatment without delay.

A recent instance of accidental ingestion of formic acid allowed us to document the development of pyloric obstruction from an unusually early stage. Formic acid is commonly employed to convert tree latex into a coagulum for processing into sheets. Planned surgical therapy permitted return of the patient to useful employment without excessive morbidity.

Case Report

A 21-year-old male rubber tapper accidentally drank a cup of formic acid on 7/1/69. Immediate oral, retrosternal, and epigastric burning occurred, but abated over the next two days with antacid

therapy. Examination one day post-ingestion revealed only injection of the pharynx.

Seven days after ingestion of the corrosive substance, a barium meal examination demonstrated marked mucosal irregularity and moderate narrowing of the gastric antrum (Figure 1). At this time, the patient denied symptoms and ate solids without difficulty. A second barium meal performed 28 days after ingestion showed severe narrowing of the antrum, complete absence of mucosal folds in the antrum, and sharp demarcation of the narrowed antrum from the body of the stomach (Figure 2). The oesophagus appeared normal at both examinations. About this time, the patient began vomiting all solids. Eight days later, he underwent a Bilroth I partial gastrectomy. After an uneventful recovery, the patient was discharged on the eighth post-operative day.

Examination of the resected specimen (Figure 3) revealed circumferential superficial ulceration of the entire antrum. Inflammatory cells infiltrated the muscular wall, but significant fibrosis had not occurred.

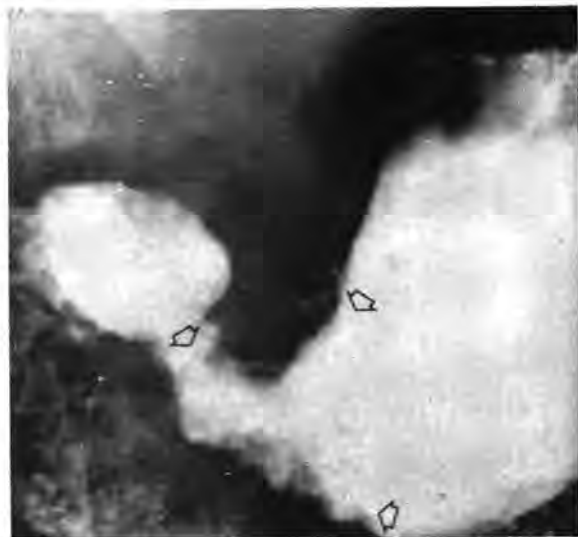


Fig 1: Barium meal 7 days after ingestion of acid corrosive shows (arrows) mucosal irregularity and diffuse narrowing of the gastric antrum.

Discussion

Acid corrosives preferentially affect the distal stomach and produce a progressive stenosis. Pyloric obstruction has been reported after swallowing hydrochloric acid, sulfuric acid, nitric acid, acetic acid, trichloroacetic acid, carbolic acid, oxalic acid, lye and lysol, ferrous sulfate, copper sulfate, bichloride of mercury, formaldehyde, clorox, zinc chloride, ammonium hydroxide, tincture of iodine, and chlorine (Poteshman, 1967). Hydrochloric acid is the agent most frequently incriminated in cases of stenosis while sulfuric acid is most likely to cause early death due to perforation and gangrene.

Only one-fifth of patients with pyloric stenosis due to acid ingestion develop an associated oesophageal stricture (Gray and Holmes, 1948). Alkaline corrosives have a more marked effect on the oesophagus, but occasionally also cause pyloric obstruction. These substances are usually more concentrated and corrosive than acids and therefore are more injurious to the resistant oesophageal squamous epithelium. The normal gastric acidity partially neutralizes the base with relative sparing of the gastric mucosa.

The selective damage by acid on the distal stomach is related to its rapid passage down the oesophagus and along the lesser curvature. The normal alkalinity of the pharyngeal and oesophageal mucosa tends to neutralize weak acids. However, when the corrosive reaches the antrum and pylorus, tetanic contractions



Fig. 2: Barium meal 28 days after acute injury shows the stenosis and complete absence of mucosal folds in the antrum (arrows).

are set up as experimentally demonstrated by Testa (Schulenberg, 1941). Contact is thus prolonged, resulting in severe injury to the sensitive gastric columnar epithelium. Poteshman (1967) and Nevin, Turner, and Gardener (1959) were able to show radiologic changes in the gastric mucosa as early as nine days after insult. The initial effect on the stomach is swelling of the mucosal folds. Then, depending upon the nature and strength of the caustic agent, inflammatory reaction sets in, followed by necrosis of the affected mucosal or submucosal layers. At this stage, large irregular gastric ulcerations may be present. Subsequent action of the gastric acid upon the denuded surface gradually leads to a chronic inflammatory process, ending in a severe scarring or stenosis. Our case illustrates this predictable course.

Initial treatment obviously consists of intensive antacid therapy. In spite of this, inflammatory thickening of the pyloric and antral wall occurs quite soon after initial injury and surgery for relief of obstruction is eventually required in almost all cases (Marks and colleagues, 1963). Non-operative measures for the treatment of obstruction in the hope of avoiding surgery have not often been successful and may increase the morbidity.

Early surgery, within the first two weeks after corrosive injury, may be hazardous because of friability and edema of the gastric wall. Marks and colleagues (1963) have found that a feeding jejunos-

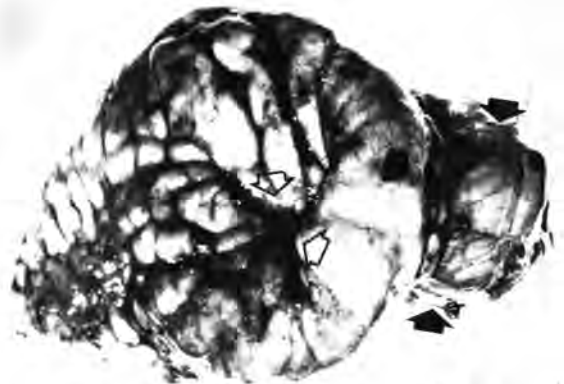


Fig. 3 and 4: The resected distal stomach is viewed from the greater curvature side (Fig. 3) and the lesser curvature side (Fig. 4). Arrows outline the stenotic segment.

greater curvature side (Fig. 3) and the lesser curvature side

tomy is often helpful in this acute phase. Subsequent operative relief of obstruction may either be by gastroenterostomy or limited gastrectomy. Cohen (1967) has advocated a posterior gastroenterostomy because of the danger of leaks at anastomotic sites after gastrectomy. A limited gastrectomy was done in the case presented without aid of a previous jejunostomy and no difficulties were encountered.

Summary

A case presentation illustrates the occurrence of severe gastritis and rapid development of antral obstruction following ingestion of acid corrosive. Radiographs show early mucosal inflammatory changes which progress to stenosis. Emphasis is placed upon the frequent necessity for eventual operative relief of the stenosis.

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The use of Clomiphene Citrate in the treatment of infertility

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IT USED to be only of academic interest to find out if the woman is ovulating in the investigation of infertility. As ovulation can now be successfully induced, it is important to determine the presence or absence of ovulation, and the frequency and regularity of ovulation if it is present.

Ovulation was successfully induced in the human by Gemzell, Diczfalusy and Tillinger with human pituitary gonadotrophin in 1958, by Kistner and Smith with MER 25 in 1960, by Lunenfeldt, Menzi and Blaise with gonadotrophin extracted from the urine of postmenopausal women in 1960 and by Greenblatt, Barfield, Jungok and Roy with clomiphene citrate in 1961.

Clomiphene citrate is an analogue of the non-steroid oestrogen, chlorotrianisene. Its precise method of action in the human female is still unknown. There may be two separate and independent actions. Firstly, it may stimulate the pituitary and probably the hypothalamus by displacing oestrogen, and hence removing the inhibitory effect of oestrogen, in these areas. Secondly, it may act directly on the enzyme systems involved in steroidogenesis in the ovary, reducing cytochrome-C reductase and making TPNH more available for the aromatisation reaction, thus increasing secretion of oestradiol and oestrone.

Kistner in 1965, from an analysis of 1,731 individual case reports, showed that 1,211, or about 70 per cent, had one or more apparently ovulatory cycles and that 333 or about 19 per cent (or 28 per cent of those with ovulatory response) subsequently became pregnant. In summarising the results of various clinical trials on 2,616 cases, Johnson, Bundle and Hoekenga (1966) reported apparent ovulation in 1,809 cases or 69 per cent and subsequent pregnancy in 429 or 16 per cent.

A Report on 4 Patients treated with Clomiphene Citrate

During the period of one year, from August 1968 to July 1969, four patients had been treated with clomiphene citrate at the University Hospital, Kuala Lumpur. Some of their salient clinical features are summarised and presented in Table I.

The first patient, aged 31, presented with primary infertility for 3½ years and amenorrhoea for 2 years, during which she would have a menstrual flow only if she had been given some hormonal pills or injections. She had also put on 15 pounds. Physical examination and laboratory investigations confirmed the diagnosis of sclerocystic ovarian syndrome (Stein-Leventhal syndrome) and excluded the presence of other causes

Table I
A Summary of the Report on 4 Patients treated with Clomiphene

Patient	Age	Presenting Symptom	Menstrual Cycle	Dose and Number of Course	Response
1	31	Primary infertility for 3½ years	Amenorrhoea for 2 years	250 mg. x 2	Ovulation
2	32	Primary infertility for 6 years	4-5/2-8 months	500 mg. x 2 700 mg. x 1	Pregnancy
3	27	Primary infertility for 3½ years	5-7/4-9 weeks	250 mg. x 2 500 mg. x 1 500 mg. x 3	Pregnancy Pregnancy
4	32	Secondary infertility for 3 years	4-5/6-16 weeks	250 mg. x 2 500 mg. x 1	Pregnancy

of infertility and that of other endocrine pathology. She was first seen in May, 1968 and had two episodes of spontaneous menstrual flow in June and August, 1968 respectively. Basal body temperature record, however, did not show any biphasic pattern. She was given two courses of clomiphene citrate, each course consisting of 50 mg. daily for 5 days. Since then, she had been menstruating regularly at 28 days' interval and biphasic curves were consistently shown in the basal body temperature record. She was, however, still unable to have a pregnancy.

The second patient presented with primary infertility for 6 years. She had very irregular and infrequent periods, the intervals varying from 2 to 8 months. She and her husband were investigated for infertility in another hospital, and other than the anovulatory cycles, nothing abnormal had been found. She had already been given two courses of clomiphene citrate before she sought advice at the University Hospital. The first course of clomiphene citrate, 100 mg. daily for 5 days, was started on 27th August, 1968. The basal body temperature showed a biphasic pattern and she had a menstrual flow from 27th to 29th September, 1968. The second course of the same dosage was started on 1st October, 1968. The basal body temperature remained persistently low and she did not have a period in early November. The third course of 100 mg. daily for 7 days was commenced on 14th November, 1968. The basal body temperature record showed a dip and then a rise

of temperature on 30th November, 1968 and the temperature remained elevated. Pregnancy was confirmed and followed a normal course. She had a normal spontaneous fulltime delivery on 8th August, 1969. The normal female baby weighed 2890 grams at birth.

The third patient presented with primary infertility for 3½ years and irregular and infrequent menstrual periods, the intervals varying from 4 to 9 weeks. Basal body temperature record revealed the presence of occasional and infrequent ovulation. No other causes of infertility could be found. She was given 3 courses of clomiphene citrate, 50 mg. daily for 5 days in each course, and each was followed by a biphasic curve of the basal body temperature and also by a normal menstrual flow 4 weeks after the commencement of the course. In the third course, the dosage was increased to 100 mg. daily for 5 days and she became pregnant as evidenced by the following observations: persistently raised basal body temperature, positive pregnancy test, nausea and frequency of micturition and an enlarged and soft uterus. Unfortunately, she had a complete abortion 10 weeks after her last normal menstrual period. Starting from 6 weeks after the abortion, 3 more courses of clomiphene citrate were administered (100 mg. daily for 5 days). She became pregnant again after the third (or the sixth for this particular patient) and she was given intramuscular injection of progesterone (100 mg. daily) till the 10th week and proluton (500 mg.

weekly) till the 20th week. At the time of report, she was 25 weeks pregnant and satisfactory progress was being made.

The fourth patient presented with infertility following an abortion which took place 3 years previously. She also had very irregular and infrequent menstrual periods, the intervals varying from 6 to 16 weeks. The basal body temperature record, however, showed the presence of a rise in temperature for 12 to 14 days before each menstrual flow. As no other abnormalities could be found, she was given 3 courses of clomiphene citrate (2 courses of 50 mg. daily for 5 days and the third of 100 mg. daily for 5 days). She was pregnant after the third course but unfortunately, the pregnancy terminated in abortion 14 weeks after the last normal menstrual period. As the patient had to leave the country, no further course was given.

Discussion

Correct selection of the patient is important as clomiphene citrate should be given only when it is indicated. As infertility is very often the chief complaint, various investigations, including seminal analysis and tests for tubal patency, should be carried out. Clomiphene citrate should be seriously considered for patients having oligomenorrhoea (or even amenorrhoea after ruling out an organic lesion in the hypothalamus or pituitary and ovarian dysgenesis) or anovulatory (or largely anovulatory) menstrual cycles (as in Cases 1, 2 and 3). Clomiphene citrate should also be considered for patients having ovulatory menstrual cycles which are very irregular and infrequent. Increasing the frequency of ovulation and correct timing of intercourse should increase the chance of pregnancy (as in Case 4). Most investigators are of the opinion that patients with sclerocystic ovarian syndrome (Stein-Leventhal syndrome) usually exhibit an ovulatory response to clomiphene (as in Case 1).

No side effects have been noted in these four patients following the administration of clomiphene citrate. Ovarian enlargement has been found in 2.7 per cent to 7.8 per cent of patients taking clomiphene citrate, depending on the duration of therapy. It is, therefore, recommended that careful pelvic examination be performed before each course of clomiphene therapy, with particular attention being given to the size of the ovaries. As the ovaries of some patients with sclerocystic ovarian syndrome are more sensitive to the stimulatory effect of clomiphene, greater precautions need to be taken. A higher dosage of clomiphene might succeed to lead to a pregnancy as

in Case 1. This had not been given because her ovaries were slightly enlarged even before the therapy and also because she was living and working in another town, and thus it was difficult to keep her under close and constant supervision.

Two courses of 250 mg. for each course (50 mg. daily for 5 days) have led to regular ovulatory menstrual cycles in Case 1. Whilst the first course of 500 mg. (100 mg. daily for 5 days) in Case 2 led to ovulation, the second course of the same dosage failed to do so. But when the third course of 700 mg. (100 mg. daily for 7 days) was given, the patient succeeded to have a pregnancy which ended in a normal spontaneous delivery. Whilst it is important in principle to use the minimal effective dose (so as to reduce the incidence of side effects, such as ovarian enlargement and multiple pregnancy), it is interesting to note that in both Cases 3 and 4, when a course of 250 mg. invariably produced ovulation, pregnancy only occurred when a course of 500 mg. was given.

Of the 12 patients treated with clomiphene citrate by Townsend et al (1966), ovulation was successfully induced in 9, and 3 became pregnant. Of 191 patients treated with clomiphene citrate by Osmond-Clarke et al (1968), 134 (70 per cent) had a clinical response (menstruation with evidence of ovulation); and of the 104 patients who responded to treatment and who also complained of infertility, 39 (37.5 per cent) became pregnant. Van Hall and Mastboom (1969) treated 27 women, of whom 18 also complained of infertility, with clomiphene citrate without a single pregnancy. Whilst ovulation was successfully induced in all the four patients in the present report, there were 4 pregnancies among 3 of the patients.

Even though it was an accepted fact that the incidence of abortion was higher among patients who gave a history of infertility, it was most disappointing to observe that 2 of the 4 pregnancies had ended in abortion. Supportive hormonal therapy probably should have been instituted as soon as pregnancy was confirmed. Goldfarb and Crawford (1969) gave their patients medroxyprogesterone and ethinyl oestradiol (20 mg. of the former and 100 ug. of the latter daily by mouth from the diagnosis of pregnancy till the 10th week and then 30 mg. and 150 ug. respectively daily till the 20th week). Of the 160 patients treated with clomiphene citrate by them, there were 37 pregnancies all of which were given supportive hormonal therapy. There were only 4 premature labours and 3 abortions.

The importance of carefully and accurately recording the basal body temperature cannot be over-

emphasised. It is the most practical method which can be used in any centre. It does not only show the presence of ovulation but also its time. And if a definite relationship between the first day of the last menstrual period and the time of ovulation can be shown by a recording of temperature over a few cycles (spontaneous or induced by clomiphene citrate), advice can then be given to the couple as regards the most appropriate time for intercourse to take place. The basal body temperature chart will also show the duration of the luteal phase. Although there is no evidence to suggest that clomiphene either increases the rate of abortion or the incidence of congenital malformations, the administration of this compound during early pregnancy should be avoided by recording the basal body temperature, looking for symptoms and signs of pregnancy and asking for pregnancy tests. On the other hand, absence of menstrual flow does not necessarily imply pregnancy, and, without a carefully kept basal body temperature record, the administration of yet another course of clomiphene citrate in higher dosage may be unduly delayed. The usefulness of the basal body temperature record in this respect has been well illustrated by Case 2.

SUMMARY

After a brief review of the literature, four patients treated with clomiphene citrate for infertility at the University Hospital, Kuala Lumpur, were reported.

The use of clomiphene citrate in the treatment of infertility is then discussed under the following headings: selection of patients, side effects, dosage, pregnancy, abortion and basal body temperature record.

Addendum:

After the submission of the article, the first patient (case No. 1) presented herself at the out-patient clinic and was then found to be 16 weeks' pregnant.

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The place of vaginal hysterectomy in the management of genital prolapse

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INTRODUCTION

IN SPITE of great advances in anatomical knowledge and technical procedures in gynaecologic surgery, there is still a great diversity of opinion as to the principles involved and the best operative technique for the cure of prolapse. The advent of vaginal hysterectomy combined with repair is a comparatively new approach and, I believe, it is an outstanding contribution to gynaecology. The popularity of this procedure is increasing, but there is still considerable disagreement as to its place in the cure of prolapse. A review of the current position is therefore made.

GENERAL CONSIDERATIONS

The repair of genital prolapse has remained a problem, as no single operation has been entirely satisfactory. The age and parity of the patient, the symptoms and the degree of prolapse, the desire for children and the presence or absence of concomitant uterine disease affect the choice and extent of the operation.

Generally, the Manchester operation has been the most successful. Many advocates of this procedure hold that a retention of the cervix is essential for a successful repair, since they believe it forms the "keystone of an arch."

However, this traditional view has been shown to be outmoded. If the cervix were so important, total abdominal hysterectomy would be followed by prolapse. That this was not so was shown long ago by the figures of Read and Bell (1933). In their series of 605 total hysterectomies, there were no cases of prolapse, while 4 occurred after 173 subtotal operations. The cervix, therefore, is only the meeting place of the supports of the uterus and its retention is not essential for the cure of prolapse. Thus vaginal hysterectomy in the course of a repair in no way prevents one from performing an effective repair.

INDICATION

Vaginal hysterectomy, combined with repair, is indicated under the following circumstances:

- (1) The prolapse is associated with uterine disease or the symptoms of it.

These include menorrhagia and menstrual irregularities. The best that the Manchester repair can do is to repair the prolapse and leave a uterus which has to be dealt with subsequently. In many cases after a vaginal repair, menorrhagia or postmenopausal bleeding necessitates further surgical treatment. This could have been avoided if the uterus had been

removed at the time of repair. Further, if hysterectomy has to be performed after a Manchester repair, there is a chance of damage to the supports of the vault.

(2) The prolapse occurs beyond childbearing years. The removal of the uterus in this age group is an excellent prophylaxis against cervical and uterine cancer.

(3) The prolapse occurs in a group of women who are thought to have an unusual liability to carcinoma body of uterus. This group includes diabetic women and those who have a late menopause.

(4) Third degree prolapse is perhaps the most widely accepted indication for a combined procedure. The Manchester operation on its own is unsatisfactory. In third degree prolapse, it is very difficult to secure a high elevation of the vault by the Manchester technique. The uterine ligaments are grossly elongated and attenuated and it is difficult to replace an atrophic uterus usually with a long hypertrophied cervix lying outside the vagina, inside the pelvis.

On the other hand if a vaginal hysterectomy is performed, the round, cardinal, and utero-sacral ligaments can all be shortened to whatever extent is desired, so that when they are sutured together in re-forming the vault, a high elevation is obtained. Thus vaginal hysterectomy is the only procedure which gives good results in third degree prolapse.

Those who believe in preserving a part of the cervix in repair advise that even in major prolapse, there are positive advantages in preserving some part of the cervix. Morris (1965) believes that the addition of vaginal hysterectomy adds nothing to the security of a repair. However, it must be stressed that the repair after vaginal hysterectomy is in no way inferior to that obtained by the Manchester technique. The enthusiasts of the combined procedure feel, as does Williams (1962), who stated that there is nothing that can be achieved by a Manchester repair that cannot be equalled by that repair performed immediately after vaginal hysterectomy, which uses precisely the same tissue to achieve its results. Indeed I would say, in many cases the wider approach and exposure of vaginal hysterectomy offers the opportunity for a superior repair.

CONTRAINDICATIONS:

Vaginal hysterectomy in the course of a repair is

contraindicated under the following circumstances:

- (1) The young patient desires more children.
- (2) Gross pelvic pathology with fixity and distortion of the uterus.
- (3) Endometriosis.
- (4) Absence of uterine mobility with a high fixed cervix which cannot be drawn down towards the introitus.

One of the criticisms levelled against vaginal hysterectomy is said to be the development of an enterocele. However, Read (1933) had correctly pointed out that in the vast majority of cases, the so-called post operative recurrent enterocele is not recurrent, but in fact a neglected enterocele. It can be prevented by diligently searching for any actual or potential enterocele and excising it.

RESULTS

Very satisfactory results have been reported from many centres. To quote one, Watson (1963) reviewed 145 patients several years after vaginal hysterectomy and repair and found that in over 90% of cases, there was satisfactory anatomical and functional result.

CONCLUSION

The combined operation of vaginal hysterectomy and repair should have an important place in the management of utero-vaginal prolapse. It is likely to supercede the Manchester operation when the prolapse is associated with uterine disease and when the prolapse occurs in the perimenopausal or postmenopausal woman.

SUMMARY

There is controversy as to the best technique for the repair of genital prolapse. The combined operation of vaginal hysterectomy and repair is a new approach, superior in many cases to the standard Manchester repair. The combined procedure is especially indicated where the prolapse is associated with uterine disease, in peri and postmenopausal women, and in third degree prolapse.

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Selection of *Culex Pipiens Fatigans* for vector ability to the rural strain of *Wuchereria Bancrofti* - a preliminary report

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INTRODUCTION

CULEX PIPIENS FATIGANS is the most important vector for *Wuchereria bancrofti* in many parts of the world. In West Malaysia, two biological variants of *W. bancrofti*, namely a rural and an urban strain, have been recognized (Wharton, 1960). The rural strain of *W. bancrofti* is mainly found among Orang Asli (aborigines) and rural Malays in West Malaysia, living away from the urban and semi-urban areas. This strain develops poorly in *Culex pipiens fatigans* and appears to be transmitted by anophelines in the few areas investigated so far (Wharton, 1960; Wharton et al., 1963). The urban strain of *W. bancrofti*, which is found mainly in cities like Penang, Kuala Lumpur and Singapore, had been introduced since the turn of the century by immigrant Chinese and Indians (Poynton and Hodgkin, 1938; Wilson and Reid, 1951). This strain develops very well in *Culex pipiens fatigans*

(Wharton, 1960) which has been shown to be the natural vector of the parasite in the city of Singapore (Danaraj et al, 1958).

Ramachandran et al (1964), in a filariasis survey among Orang Aslis living close to Kuala Lumpur, showed that 9 out of 43 people examined were positive for microfilariae and 6 among them were infected with the rural strain of *W. bancrofti*. They also confirmed Wharton's (1960) observation that although *Culex pipiens fatigans* was capable of supporting development of the microfilariae up to the infective third stage, it was however a poor host. The infectivity rates among five different lots of *Culex pipiens fatigans* obtained from different localities in West Malaysia and fed on a *W. bancrofti* - infected donor on the same occasion varied from 4 to 30 percent. In the present study, similar results were obtained (Table I) with five colonies of *Culex pipiens*

TABLE I

Infectivity rates of *Culex pipiens fatigans* obtained from various localities in West Malaysia to the rural strain of *Wuchereria bancrofti*.

Colony	Collected from	Generation No. of mosquitoes fed on the donor	Number of microfilariae per cmm of donor's blood at the time of mosquito feeding	Number of mosquitoes dissected	Number of mosquitoes with infective larvae	Percentage infective
'A'	Kuala Lumpur	P	3.0	75	5	6.6
'B'	Kuala Lumpur	P	2.7	40	8	20
'C'	Cameron Highlands	F ₁₁	2.8	117	21	17.9
'D'	Port Dickson	F ₁	3.1	48	8	16.6
'E'	Colony selected for dieldrin resistance	F ₁₇	2.8	96	27	28.1

fatigans collected from different parts of the country. It was considered that these variations in vectorial capacity in the same species of mosquito collected from different parts of the country may be due to different gene frequencies.

Huff (1927) was the first to show that the susceptibility of a vector to a parasite could have a genetic basis. He also showed that the number of *Culex pipiens fatigans* susceptible to infection with *Plasmodium cathemerium* could be increased or decreased by selection (Huff, 1929). Huff (1931) suggested that the factor controlling susceptibility of *Culex pipiens fatigans* to infection with *P. cathemerium* was a simple Mendelian recessive. Macdonald (1962a) selected out a strain of *Aedes aegypti* highly susceptible to infection (mean susceptibility rate 84.8 percent) with the sub-periodic form of *Brugia malayi* from a colony which showed only 12 to 31 percent infectivity rate (Ramachandran et al., 1960). Macdonald (1962b) also showed that the vectorial susceptibility to the parasite was controlled by a sex-linked recessive gene which he labelled f^m .

The present work was undertaken to study the possibility of selecting out strains of *Culex pipiens fatigans* which are highly susceptible to the Malayan rural strain of *W. bancrofti*. Such a study could indicate if there was a possibility of populations of *Culex pipiens fatigans* in West Malaysia developing

susceptibility to *W. bancrofti* as a result of changes in the gene frequency of the field population due to some natural or artificial selection pressure. If by laboratory selection studies, pure homozygous resistant and susceptible strains could be obtained, it may then be possible to work out the mode of inheritance of vector susceptibility of this species to the rural strain of *W. bancrofti*. Besides, it will provide the opportunity to study the possibility of replacing the indigenous parasite-susceptible strains with a parasite-resistant strain, involving a possible biological method of control for filariasis transmitted by *Culex pipiens fatigans*.

MATERIALS & METHODS

The colonies ('A' and 'B') of *Culex pipiens fatigans* reared from egg rafts collected in Kuala Lumpur were used. These field populations were used in order to get a high degree of genetic variability.

The larvae were reared under laboratory conditions at temperatures between 72° and 80° F. Adult mosquitoes were maintained at the same temperature and at a relative humidity of 70 to 80 per cent.

Female mosquitoes, 5 to 10 days old, were fed on *W. bancrofti*-infected donor between 2030 and 2230 hours. Estimates of microfilariae counts were made from the donor before and after a batch of mosqui-

TABLE II

Results of feeding six successive generations of two selected susceptible (+) strains ('A' and 'B') of *Culex pipiens fatigans* on a donor infected with the rural strain of *Wuchereria bancrofti*.

Strain	Gene-	Number of micro-filariae per cmm of donor's blood at the time of mosquito feeding	Number of mosquitoes fed	Number of mosquitoes that died before egg laying	Number of mosquitoes that died after egg laying	Percentage of mosquitoes that died	Number of mosquitoes dissected	Number of mosquitoes (+) with infective larvae	Percentage of infective (+) mosquitoes	Average number of mature larvae per infective mosquito
'A' (+)	P	3	92	4	13	18.4	75	5	6.6	3.4
	F ₁	2.2	1	—	1	100	—	—	unknown	—
	F ₂	2.2	17	3	2	29.4	12	5	41.6	1.6
	F ₃	2.7	21	4	3	33.3	14	9	64.3	4.4
	F ₄	2.8	60	14	7	35	39	13	33.3	2.4
	F ₅	2.7	24	8	2	41.7	14	10	71.4	2.7
	F ₆	2.8	20	3	4	35	13	7	53.8	2.8
'B' (+)	P	2.7	92	26	26	56.5	40	8	20	2.4
	F ₁	2.6	19	4	4	42.1	11	2	18.1	2.5
	F ₂	2.8	14	4	1	35.9	9	2	22.2	1.5
	F ₃	2.8	16	3	1	25	12	4	33.3	2.0
	F ₄	1.7	6	2	1	50	3	2	66.6	1.5
	F ₅	2.8	4	2	2	100	—	—	unknown	—
	F ₆	2.3	4	—	—	50	2	2	100	1.0

toes had fed. The average microfilariae count was between 1.7 and 3 per c.mm of peripheral blood (Table II). Wharton (1960) has estimated that a female *Culex pipiens fatigans* would take in about 4 c.mm of blood during a single feed.

The blood-fed mosquitoes were kept individually in 9 cm x 4.5 cm tubes which were closed with a pad of wet cotton wool. This kept the humidity in the tube high. No sugar solution was given until eggs were laid. On the 4th day after the initial blood meal, water was given to each mosquito for egg laying. As soon as a mosquito laid eggs, it was given a serial number and was then removed into a numbered tube and maintained on sugar solution until dissected. The egg raft laid was also given the same serial number. Many of the females laid eggs on the 4th or 5th day after the blood meal; some delayed egg laying for varying periods while a few never laid eggs at all. Irrespective of whether they laid eggs or not, all mosquitoes were dissected 14 to 16 days after the

infective blood meal.

Each numbered egg raft was placed in water, in individual rearing bowls and the larvae which hatched from the raft were reared together. The mosquito larvae obtained were separated into two groups, depending upon the results of the dissections. The larvae derived from mosquitoes which had supported the development of the parasite to the infective third stage were pooled together as the susceptible (+) group or strain. Those derived from mosquitoes which had not supported the development of the parasite were pooled together as the resistant (-) group or strain. The adult mosquitoes which emerged from each of the strains were fed separately on the donor. In subsequent breeding operations, susceptible strains were maintained by using the progeny of susceptible parents only. Whenever sufficient number of males and females were available from a single susceptible parent, strict brother-sister matings were carried out. However, it was extremely difficult to

maintain a strictly inbred line for more than two generations. In-breeding depressions, resulting in heavy mortality of larvae as well as of adults, was observed. Out-breeding was done only with virgin mosquitoes taken from closely related lines.

RESULTS

Results of feeding five different colonies of *Culex pipiens fatigans* on a donor harbouring the rural strain of *W. bancrofti*, showed that their infectivity rates varied from 6.6 to 28.1 percent (Table I). The highest degree of infectivity rate was noticed among mosquitoes from a colony 'E' which has been previously selected out for dieldrin resistance for seven generations. It is difficult to say whether selection for dieldrin-resistance has had any concurrent effect on the selection of individual mosquitoes susceptible to *W. bancrofti*, as well.

In the two strains ('A' (+) and 'B' (+)) which have been selected for susceptibility to infection with *W. bancrofti*, it was found difficult to get sufficiently large numbers of female mosquitoes to feed on the donor. This was perhaps due to the selection and inbreeding pressure in successive generations. The number of female mosquitoes which fed on the donor in successive generations varied from 1 to 92 (Table II). Among those that fed, there was a high mortality rate varying from 18.4 per cent to 100 per cent before dissection. As a result, the number of mosquitoes which were dissected were small and varied from 12 to 75 in 'A' (+) strain and 2 to 40 in 'B' (+) strain in the various generations.

In spite of the small number of mosquitoes available for study, it was possible to select out from both strains of *Culex pipiens fatigans* a high degree of susceptibility to infections with the rural strain of *W. bancrofti*. The original susceptibility levels of 'A' and 'B' colonies were 6.6 percent and 20 percent respectively. In strain 'A' (+), the susceptibility rates had increased to 64 percent in the 3rd generation and, except in the 4th generation, this high level of susceptibility was maintained.

Similarly in strain 'B' (+), the susceptibility rates had increased to 66.6 per cent by the 4th generation. The degree of susceptibility was not measured in the 5th generation as all the 4 fed mosquitoes died before dissection. The susceptibility rate was 100 per cent in the 6th generation when only 2 mosquitoes were available for dissection. As the number of mosquitoes was only two, this 100 per cent susceptibility rate may not be as significant as it might have been if a larger number of mosquitoes had been dissected.

CONCLUSIONS

This preliminary work, in general, has shown that there is a low gene frequency in Malaysian *Culex pipiens fatigans* for susceptibility to infection with the rural strain of *W. bancrofti*. By careful isolation and selection, the susceptibility rates could be increased to a high degree over a few generations. If the gene frequency of the field population of mosquitoes changes due to some selection pressure in nature, the possibility exists that *Culex pipiens fatigans* may become good vectors for the rural strain of *W. bancrofti*.

It is hoped that further experiments will lead to isolation of pure homozygous lines which are susceptible and resistant to infection with the rural strain of *W. bancrofti* and that this would lead to the study of inheritance of vector ability of *Culex pipiens fatigans*.

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INFANTILE SCURVY IN MALAYSIA

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INFANTILE SCURVY in the tropics has been reported to be a rare disease. (12) (6) In Malaysia and Singapore, only three cases of scurvy have been described, all in Singapore, and all in older persons, aged 4, 17 and 50. (17) (18) (7) Only one was an infantile scurvy. At the time that these reports were made, the authors and others (12) (9) felt the disease to be a rarity.

There have been no comprehensive surveys of Vitamin C nutrition in Malaysia or Singapore. However, a survey of 2,000 consecutive admissions (13) in the Pediatric Department of the General Hospital, Singapore, in 1939 showed 118 clinically diagnosed cases of rickets, 8% with X-ray diagnoses as well. Congenital syphilis was ruled out but scurvy was not. Many were diagnosed on the enlargement of the costochondral junction alone, which may have been rachetic or scorbutic. The author has subsequently stated in retrospect that scurvy may have been present in a percentage of these cases. (15)

Four cases of scurvy were diagnosed at Gombak Aborigine Hospital and the University Hospital, Kuala Lumpur in a 5-month period, April-August, 1969. This paper includes the case reports of these four cases and a brief review of some of the

radiological signs and diagnostic laboratory tests in scurvy.

CASE 1

This patient was a 9-month old female Aborigine Senoi child with a history of drinking unsupplemented sweetened condensed milk since birth because the mother was not able to breast-feed her. Two other siblings, who had received the same diet, were well. Three months prior to admission, she developed an intermittent cough, fever and diarrhoea and failed to thrive.

Three weeks prior to admission, she became irritable, crying when moved or picked up and was unable to sit up or move her left arm or legs well. She developed a continuous fever one week prior to admission, became anorexic and began to show bilateral knee swelling.

On examination, she was irritable, emaciated, dry and pale, lying on her back in a "frog leg" position, an expression of pain on her face and appearing to cry but producing no sound. Weight was 7 lbs. 12 ozs. There were no petechiae or purpuric spots. Her skin appeared rough and red with a light fine maculopapular rash over her scalp and forehead. There was



Fig 1
Case 1, showing enlarged costochondral junctions, the "scurvitic rosary".

no neck stiffness and the fontanelle was moderately depressed. Her eyes rolled vertically and to the left and there was frequent blinking. Gums were normal around 4 erupted teeth. Respiratory, cardiovascular and lymphatic systems were normal. The abdomen was protuberant and the colon appeared to be filled with faeces. Liver and spleen were not palpable.

There was marked enlargement of the costochondral junctions ("rosary"), which were round to the touch and painful when pressure was applied. (Fig. 1)

There was no voluntary movement of her left shoulder or either leg and passive movement of these joints gave pain. Both knees and dorsums of the feet were oedematous. On admission, laboratory data



Fig. 3
Case 2, hypertrophic, bleeding, bluish coloured gums, characteristic of scurvy.



Fig. 2
Case 2, child in "pithed frog" position. Also seen are scurvitic rosary and leg swelling bilaterally.

were an hematocrit of 30; WBC of 9,800 with normal differential; CSF colorless, clear and non-cellular under low pressure. A tournique test was negative. CSF culture was negative and stool culture grew salmonella ϕ_2 . Radiological examination of her chest revealed normal lung and heart shadows but prominent large costochondral rib junctions. (Fig. 4) X-rays of the extremities showed decreased density and loss of trabecular pattern in the diaphyses. There was cupping, spreading and spurring of the metaphyses and ring epiphyses in the ankle joints, knees, hips and wrists. (Fig. 5) There was a fracture dislocation through the left proximal humeral ephiphyseal plate. These findings were consistent with scurvy.



Fig 4
Case 1, chest X-ray showing enlarged costochondral junctions and a dislocation-fracture of epiphysis of humerus.

The child was treated with ascorbic acid 50 mgm IM q6h., tube feeding, multivitamins and antibiotics for the Salmonella. Within one week, abnormal eye movements and blinking had ceased and the child could again cry. In 10 days, the frog leg position was lost, leg and arm tenderness gone and knee swelling down. On X-ray, calcification of subperiosteal hematomas about the distal ends of the femurs appeared. (Fig. 7) At one month, she completely desquamated an outer layer of skin but recovered well and was discharged after three months. Her weight on discharge was 10 lbs. 4 ozs. (4.66 kg.)

CASE 2

This 12-month-old Aborigine female presented with a history that she had been breast-fed until the age of six months. At this time, the supply of breast milk failed and she was fed on sweetened condensed milk supplemented occasionally with rice. She had had fever and cough for 3 weeks and swollen bleeding



Fig. 5
Case 1, X-ray of right knee at admission, showing thickening and spurring of provisional line of calcification, a radiolucent wedge-shaped "corner sign of scurvy" and a dense outlining of the epiphysis, the "ring sign of scurvy".

gums, swelling and tenderness of the legs for two weeks prior to admission.

She presented as a very irritable, pale, crying child with a grimacing expression, unable to close her painful mouth. She lay in a "frog leg" position, showing little voluntary leg movement and would not sit up. (Fig. 2) Her gums were blue, bruised, hypertrophic and bleeding around the few erupted teeth. (Fig. 3) There was a fine rash of small hyperkeratotic nodules over the forehead and back through the hairline. Other than a few rales in the base of the left lung, respiratory and cardiovascular systems were normal. Lymph nodes were palpable



Fig. 6
Case 2, X-ray of right knee at admission, showing a thickening and spurred provisional line of calcification and an adjacent radiolucent "scurvy line".

bilaterally in the neck and in the left axilla. The spleen was palpable 2 cm. below the costal margin. A well demarcated rosary was present, each costochondral junction feeling quite round to the touch. There were no petechiae or purpuric spots and the tourniquet test was negative.

Admission laboratory data included an hematocrit of 22.5%, a WBC of 9,300, polys 36%, lymphs 62%. The blood film showed microcytic hypochromic changes. Serum Vit. C was 0.2 mgm%. Urine vitamin C values were, for the 2nd 24 hours after admission, 0.4 mgm/150 cc, for the 3rd 24 hours 2.4 mgm/150 cc, and the 4th 24 hours 149 mgm/150 cc. Radiological examinations of the chest showed prominent rib costochondral junctions bilaterally. X-rays of the extremities showed changes in the elbows, knees and ankles. There was thickening and spurring of the provisional line of calcification with adjacent radio-



Fig. 7
Case 1, follow-up X-ray of right knee two weeks after admission showing periosteal calcification.

lucent bands. The epiphyses were outlined with a radio-dense line. The X-rays were considered diagnostic of scurvy. (Fig. 5) The child was given 50 mgm Vitamin C P.O. with 500 mgm IM on the 2nd day. In three days after beginning treatment, the gum hypertrophy had diminished markedly, there was no further bleeding and the forehead rash had almost disappeared. One week after admission, the fever and leg tenderness were gone and the child was sitting by the 12th day. Follow up X-rays at 10 days showed periosteal calcification around the lower ends of the femur. The child continued to improve uneventfully.

CASE 3

This 15-month-old Chinese female child was well until 4 days before admission when she stopped walking and protested when her right leg was moved passively. She was the fourth child of a shop assistant

TABLE 1⁽¹⁹⁾

Frequency of symptoms in scurvy patients

Tenderness of legs	77%
Irritability	70%
Pseudoparesis of legs	64%
Anorexia	31%
Fever	19%
Swelling over long bones	14%

TABLE 2⁽¹⁹⁾

Frequency of signs in scurvy patients

Rosary	80%
Leg tenderness	67%
Pithed frog position	52%
Haemorrhagic gums	44%
Fever	44%
Palpable subperiosteal haemorrhages	48%

Frequency of symptoms and signs in infantile scurvy in a North American population.

who earned M\$160 per month. She had been fed entirely on sweetened condensed milk until the age of 9 months. Subsequently, she was offered rice and fish in addition, but she seldom ate these.

Physical examination revealed an irritable child who cried whenever her lower extremities were handled. She held her hips abducted and externally rotated and her knees flexed. There were purpuric spots on her face, neck, hands, and feet. Her gums were spongy and bled easily. A tournique test was positive. She weighed 6.65 kg. and measured 73 cm. The rest of the physical examination was unremarkable.

Laboratory data included: Hgb. 9 gm%; PCV 31%; MCHC 29%; platelets 194,000/cmm; WBC 4100/cmm; neutrophils 51%; lymphocytes 40%; eosinophils 1% and monocytes 3%. A chest X-ray showed expansion and concavity of the anterior ends of the ribs bilaterally with normal lung shadows. X-rays of the long bones revealed generalised loss of bone density and a line of increased density across the distal ends of the femur and tibia bilaterally. The X-rays were considered compatible with but not diagnostic of scurvy.

The child was offered a full cream full strength milk and multiple vitamins. In addition, she was given Vitamin C 125 mgs. q6h by mouth. Four days after admission, there was no more bleeding from the gums, the purpuric spots were fading and movements of the legs were painless. When followed up in the clinic one month later, she weighed 7.7 kgm. and was walking again.

CASE 4

A 10-month-old female Indian child presented with a history that she had fallen down from a height of about 3 feet a week prior to admission. On the day

of her fall, she developed a low grade fever and productive cough. Two days later, she stopped walking and began protesting when she was handled. At the same time, a lump was noticed on her forehead. The lump increased in size until the day of her admission.

She came from a poor family and was the last of five children. Her father earned M\$3 per day as a gardener. She was the product of a full-term normal delivery, weighing 5 lbs. at birth and was considered normal until the present illness. She had been fed entirely on sweetened condensed milk since birth.

Physical examination revealed an irritable pale child weighing 5.48 kgm. A soft, almost cystic swelling 7.5 by 7.5 cm., was seen on the right side of the forehead. The lower extremities were held flexed and showed very little spontaneous movement. However, she cried and moved them when touched. The costochondral junctions were prominent and the spleen and liver were enlarged. There were no haemorrhages in the skin, gums or optic fundi.

Laboratory data included a Hgb. of 7.0 gms.%; PCV of 25%; MCHC of 28.8%; a WBC of 4,600 with 66% neutrophils and 34% lymphocytes. A chest X-ray showed expansion of the anterior ends of the ribs. X-rays of the long bones showed diffuse osteoporosis. In the femurs and tibia, there were dense lines through the metaphyses with adjacent wedge shaped areas of reabsorption. The epiphyses were outlined by a ring-like dense line. X-rays of the skull were normal. The X-rays were considered to be diagnostic of scurvy. The child was treated with Vitamin C 100 mg. three times daily and was also given iron, folic acid and penicillin. She gradually lost her irritability and five days after her admission, she was moving her legs well and was free from pain and tenderness. However, she developed a bronchopneumonia one week after

admission and responded well to penicillin. Two weeks after admission, her haemoglobin was 10.1 gms.% and when discharged home a week later, she weighed 6.6 kgms.

CLINICAL PICTURE

Scurvy, as the full blown deficiency state, is easily recognized clinically in infants. It presents most frequently with the symptom triad of leg tenderness, irritability and pseudoparalysis.⁽¹⁹⁾ If severe, there may be fever and anorexia. The physical signs are the scorbutic rosary, leg tenderness and swelling, the "pithed frog" position of hip abduction, lateral rotation and knee flexion and haemorrhagic hypertrophic gums.

Hypertrophic, perifollicular changes, especially over the forehead, may occur and petechiae and purpura may appear. The tourniquet test is at this stage usually positive.

Scurvy in its earlier stages presents a less clear picture. The child may become irritable and move about less, eventually regressing from an ability to stand or sit to that of lying. There may be a failure to thrive and a tendency to increased chest infections. The earliest physical signs include gum hypertrophy if teeth are present, characterized by a bluish purple discoloration of spongy swellings around the teeth which may at times conceal the teeth. As well the costochondral junctions become increasingly palpable although not yet visible and tenderness about the legs, especially the distal femur or any other epiphysis with fast growth, occurs.

The frequency of major signs and symptoms in scurvy patients will depend on the health facilities and medical standards in a given area as well as on the stage that the disease is allowed to reach before help is sought. The frequency of some of the presenting signs and symptoms in cases of scurvy in North America is shown in Tables 1 and 2.

Scurvy must be differentiated from osteomyelitis, traumatic fractures, poliomyelitis, bone tumours, cellulitis, syphilitic periostitis, and from rickets. The gums and haemorrhagic changes must be differentiated from leukaemia, teething problems and bleeding disorders.

RADIOLOGICAL DIAGNOSIS

The radiological skeletal changes in scurvy are in general due to a decrease in normal bone cellular activity, both productive and destructive, while non-cellular activities, such as deposition of lime in the provisional zone of calcification and internal resorp-

tion of bone salts, are not disturbed.⁽¹⁾ This generalized bone atrophy results in a "ground glass" appearance of the shaft. With decreased cellular resorption, the zone of provisional calcification becomes thickened and casts a heavy transverse line on the radiograph. These findings are found in many non-scorbutic types of bone atrophy. But the combination of diffuse bone atrophy and multiple spurs at the cartilage shaft junction occur only in scurvy. This spurring occurs with the extension of the provisional zone of calcification laterad beyond the usual limits of the shaft. Fractures and fissures appear in this brittle zone, particularly in its lateral aspects. Atrophy and demineralisation on the metaphyseal side of the provisional zone of calcification produce a transverse radiolucent band termed the "scurvy line". Radiolucent laterad metaphyseal clefts through this weakened scurvy line result in a cortical and spongiosal defect called the "corner sign of scurvy". Both the "scurvy line" and the "corner sign of scurvy", when found with generalised bone atrophy, are valuable diagnostic features of scurvy.

Transverse fractures at the cartilage shaft junction may occur either through the weakened "scurvy line" or through the brittle provisional zone of calcification. These fractures may give rise to epiphyseal displacement or separation.

Although the diagnostic signs of scurvy are seen in the cartilage-shaft junctions of long bones, changes occur in other bones also. In the secondary centers of ossification, the changes parallel those described above, the center becoming atrophic and "ground glass" like and being surrounded by a dense zone of provisional calcification, called the "ring sign of scurvy". In the ribs, the costochondral junctions become enlarged and subluxed to give the "scorbutic rosary". This is a useful radiological sign as these enlarged joints can be easily seen on routine chest films. Subperiosteal haemorrhages may appear most commonly in the larger bones such as the femur, tibia and humerus and are noted as areas of increased radiolucency in the soft tissue shadows, or most easily after treatment begins, when a shell of radio-opaque subperiosteal bone is laid down around the hematoma.

LABORATORY DIAGNOSIS

Although it is considered that positive clinical and radiological features are sufficient to make a diagnosis of scurvy, laboratory analyses of Vitamin C nutrition are available as additional diagnostic aids.

After beginning a completely Vitamin C deficient

diet, the plasma Vitamin C level reaches zero in approximately 40 days;⁽²⁾ in the whole blood the level reaches zero in 80-90 days,⁽¹⁶⁾ and in the white cell-platelet layer it reaches zero in approximately 120 days.⁽¹¹⁾ The signs of scurvy appear in approximately 130 days.⁽²⁾

Whereas the white cell-platelet layer Vitamin C level gives the best index of scurvy and a reading of zero equates well with clinical scurvy, this is a difficult study and not readily available. Serum Vitamin C levels are of little value other than for large nutritional surveys, except that a fasting Vitamin C level of over 0.6 mgm/100ml aids in the exclusion of scurvy as a diagnosis.

Many Vitamin C loading tests are available, a common one being the intramuscular administration of 200 mgm. of Vitamin C to a fasting infant, with collection of urine and blood after at 4 hours.⁽¹²⁾ A low urine excretion of 15% of load or less and a low serum Vit. C level, is compatible with but not diagnostic of scurvy.

A more quantitative measure of Vitamin C level is a saturation test⁽¹¹⁾ based on the number of days required to produce a urinary excretion of 50 mgm. of ascorbic acid during the 4th-7th hour after a daily dose of 5 mgm/1b.

This test correlates well with the actual white blood cell-platelet layer Vitamin C level but as with most loading tests, is cumbersome and time consuming.

DISCUSSION

Four cases of scurvy have been found in two Malaysian hospitals over a five-month period, a large number for a disease which is considered rare. Several reasons are postulated for this number of cases. Both

lack of recognition on the part of doctors unfamiliar with infantile scurvy and lack of medical services to the rural and poor urban populations who appear to be the ones most likely to suffer from the disease, partially explain the rarity in the past of this disease. All four children reported in this paper developed scurvy on diets of sweetened condensed milk. In the past, when a mother could not breast feed an infant, a wet nurse was found. Now bottle feeding is more common. Sweetened condensed milk, which contains no Vitamin C, is the cheapest milk product available and many manufacturers advertise it as a baby food. Unless the mothers' standards of health education and knowledge of infant nutrition are greatly improved, or manufacturers are required by law, or themselves show enough public spirit, to indicate on the cans, the dangers of sweetened condensed milk if Vitamin C is not taken as a supplement, it would appear that infantile scurvy may be on the rise in Malaysia.

SUMMARY

Infantile scurvy has been reported to be a rare tropical disease. We report four cases diagnosed during a 6-month period in two hospitals in Kuala Lumpur. The diagnostic value of some of the radiological signs and laboratory tests have been received. The reasons for the rarity of reports in the past and for possible increasing incidence in the future have been discussed.

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Acetate and glucose utilisation and lipid synthesis by cold-acclimated and hypothermic rat-brain homogenates

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THE PHYSIOLOGY of cold exposure has been a favourite topic in the fields of comparative physiology and biochemistry (1). The effects of cold on the central nervous system has been under study for the past few decades. Growing interest in the application of acute hypothermia in surgery (2) has resulted in the study of thermogenesis of organ systems. Attempts at integration of the physiological response pattern to cold acclimation with tissues at cellular levels have found great difficulties. Though hypothermia has become a useful and extremely vital adjunct to cardio-vascular surgery and therapy of various diseased conditions (3), much of the biochemical changes occurring to the brain during hypothermia are still unclear.

In the *in vitro* studies reported in this paper, an attempt was made to reveal the incorporation of labelled glucose and acetate into lipids by cold acclimated and hypothermic rat-brain homogenates. When the rats were exposed continuously to cold for a period of two weeks, the term 'cold-acclimated rats' is used to denote such animals.

Materials and methods

Adult male albino rats, 14-16 weeks in age, reared in our own animal house and kept on normal rat pellets, were used for experimental studies. For cold acclimation, the rats were placed in straw-based cages

and exposed to cold at 0-2° C. for 14 days. For control experiments, rats of the same age group and sex were kept at room temperature (29° C.). Both the control and experimental groups were fed *ad libitum* with normal rat pellets.

The reagents and solvents used in the experiments were all of analytical grade. Sodium acetate [$1\text{-}^{14}\text{C}$] and D-glucose [$\text{U-}^{14}\text{C}$] were both purchased from the Radiochemical Centre, Amersham, England.

Following the desired period of exposure in the cold room, the rats were immediately sacrificed by decapitation, the whole brain was carefully removed, completely blotted of blood and kept in chilled aluminium foils at 0° C. Using chilled vortex homogenization flask and ice-cold Krebs-Ringer phosphate buffer, pH 7.4, which was saturated with a mixture of $\text{O}_2 + \text{CO}_2$ (19 : 1) at 0° C., a 10% whole-brain homogenate (w/v) was prepared by homogenizing for 2 minutes at a speed of 14,000 r.p.m. Rat-brain homogenate from control, normothermic rats was prepared in the same way and both the homogenates were kept at 0° C. until used.

For incubation, bottle of 150 ml. capacity was used. The bottle was fitted with a rubber-based screw cap. A circular puncture was made at the centre of the cap material but not on the rubber, to facilitate injection of fluids into the flask without opening the cap and thus maintaining a closed system throughout.

Table 1

THE CONVERSION OF ^{14}C FROM (U- ^{14}C) GLUCOSE AND (1- ^{14}C) ACETATE INTO ^{14}CO BY CONTROL, COLD-ACCLIMATED AND HYPOTHERMIC RAT-BRAIN HOMOGENATES

Substrates No. of observations	$\mu\mu$ moles substrate converted/mg. N	
	(U- ^{14}C) Glucose 6	(1- ^{14}C) Acetate 6
Normothermic	11360 \pm 108	786 \pm 18
Cold-Acclimated	12572 \pm 93	604 \pm 15
Hypothermic	5562 \pm 41	423 \pm 11

5 ml. portions of the whole-brain homogenate from test and control rat-brain tissues were taken in separate flasks. 0.1 ml. of (1- ^{14}C) acetate (5 μc) containing 125 millimicromoles of ^{14}C -acetate or 0.1 ml. of (U- ^{14}C) glucose (5 μc) containing 173 millimicromoles of ^{14}C -glucose were added to each flask followed by 2.4 ml. of Krebs-Ringer phosphate buffer to give a total volume of 7.5 ml. of the incubation material. A small test-tube (1 x 7 cm.) containing 1 ml. of 10% KOH (w/v) was lowered into each flask with a pair of forceps. The gaseous atmosphere of the bottle was replaced with a mixture of $\text{O}_2 + \text{CO}_2$ (19 : 1) and the cap air-tightly fastened. The incubation was carried out in an Aminco Shaker for 3 hours at $37.5 \pm 0.5^\circ\text{C}$. Similar incubations were carried out at $27.5 \pm 0.5^\circ\text{C}$. Two ml. portions of the homogenates from control and experimental groups were taken for nitrogen determination according to the methods of Markham (4) and Felick and Munro (5).

The reaction was stopped at the end of the three-hour incubation period by injecting 0.5 ml. of 10N H_2SO_4 through the rubber cap. The bottle was shaken at 0°C : for a further 30-minute period to enable complete absorption of the $^{14}\text{CO}_2$ formed, by the KOH placed in the small tube. The tube containing KOH was removed, the bottom of the tube was rinsed with 3 ml. distilled water into the incubation bottle, the KOH containing $^{14}\text{CO}_2$ was diluted 100 times with distilled water and the radioactivity of $^{14}\text{CO}_2$ determined by using a Philips Liquid Scintillation Counter (6).

The contents of the incubation bottle was saponified by adding 3 g. solid KOH and 10 ml. absolute methanol and autoclaving for 2 hours by the method of Burchfield and Stores (7). The non-saponifiable portion was extracted five times with 25

Table 2

THE INCORPORATION OF (U- ^{14}C) GLUCOSE AND (1- ^{14}C) ACETATE INTO FATTY ACIDS BY NORMOTHERMIC, COLD-ACCLIMATED AND HYPOTHERMIC RAT-BRAIN HOMOGENATES

Substrates Number of observations	$\mu\mu$ moles substrate converted into fatty acids/mg. N ₂ of tissues	
	(1- ^{14}C) glucose 6	(1- ^{14}C) Acetate 6
Normothermic	3.4 \pm 0.6	76.7 \pm 3.1
Cold-Acclimated	3.5 \pm 0.3	88.5 \pm 2.8
Hypothermic	2.6 \pm 0.2	34.8 \pm 1.2

ml. portions of petroleum ether (boiling point $40-60^\circ\text{C}$). The pooled extract was washed free of alkali with distilled water, dried with anhydrous Na_2SO_4 and the quantity of the substances extracted determined by completely evaporating the solvent and weighing the contents after keeping it overnight in vacuum desiccator. The dry residue was dissolved in 10 ml. of petroleum ether, 1 ml. taken for radioactivity determination. Another 2 ml. of the petroleum ether solution of the lipids were used for the precipitation of cholesterol as digitonide (8), a part of the cholesterol digitonide was used for radioactivity determination and the other part for chemical estimation of cholesterol by making use of the Libermann-Burchard reagent.

The contents remaining after the extraction of the non-saponifiable matter were freed completely of methanol by evaporating it on a water bath by passing a stream of air through the solution. Then it was cooled, acidified with 10N H_2SO_4 and the free fatty acids liberated were extracted with petroleum ether, and the weight determined exactly as in the case of non-saponifiable matter. The dry residue was dissolved in 10 ml. of petroleum ether, 2 ml. portions in duplicate were used for chemical estimation of free fatty acids by titrating against 0.01N NaOH and 1 ml. portion taken for radioactivity determination.

Results and discussion

The results are expressed as $\mu\mu\text{moles}$ of substrate (1- ^{14}C) acetate are shown in table 1.

The results are expressed as moles of substrate converted into $^{14}\text{CO}_2$ by normothermic, cold acclimated and hypothermic rat-brain homogenates. It could be noted that glucose was utilized much better than acetate for conversion to $^{14}\text{CO}_2$ by a

Table 3

THE EFFECT OF COLD-ACCLIMATION AND HYPOTHERMIA ON THE INCORPORATION OF (1-¹⁴C) ACETATE AND (U-¹⁴C) GLUCOSE INTO THE UNSAPONIFIABLE AND DIGITONIN PRECIPITABLE FRACTIONS

Substrate	μμ moles of substrate converted per mg/Nitrogen			
	Unsaponifiable fraction		Digitonin precipitable fraction	
	(1- ¹⁴ C) Acetate	(U- ¹⁴ C) Glucose	(1- ¹⁴ C) Acetate	(U- ¹⁴ C) Glucose
Number of observations	6	6	6	6
Normothermic	48.1	2.3	7.6	1.3
Cold-Acclimated	56.1	2.2	8.8	1.3
Hypothermic	25.4	1.4	4.1	0.8

factor 14, 21, 11 times respectively by normothermic, cold acclimated and hypothermic rat-brain homogenates and that cold acclimated rat-brain homogenates utilized the maximum and the homogenates incubated at 27.5° C. the minimum quantity of glucose. Under hypothermic conditions, the rate of conversion of (1-¹⁴C) acetate and (U-¹⁴C) glucose to carbon dioxide was only about 50% when compared with that of the normothermic rat-brain homogenate at 37.5. At the same time, cold-acclimated rat-brain homogenate showed a greater ability to convert glucose to ¹⁴CO₂ as shown by the elevation of respiration by about 11%, but acetate utilisation for ¹⁴CO₂ production was down by about 23% in the same homogenate. These observations are in conformity with the manometric studies conducted earlier (9).

The extent of incorporation of ¹⁴C from (U-¹⁴C) glucose and (1-¹⁴C) acetate into fatty acids is shown in table 2.

There was no appreciable difference in the incorporation of ¹⁴C from (U-¹⁴C) glucose into fatty acids in all the three types of homogenates. But radioactivity from ¹⁴C-acetate was incorporated into fatty acids to a much higher extent by all the three categories of brain-homogenates when compared with the radioactivity from (U-¹⁴C) glucose. The disparities in the incorporation of ¹⁴C acetate into fatty acids by the three categories of rat-brain homogenates are rather conspicuous since cold-acclimated rat-brain homogenates incorporated 115% and that incubated at 27.5° only 45% of that of normothermic controls.

The incorporation of radioactivity into non-saponifiable fraction of the total lipids is shown in table 3.

The results showed that more than half the amount of glucose converted into non-saponifiable fractions was found to be the digitonin-precipitable (cholesterol) portion, but from acetate the digitonin-precipitable fraction was about 14% only in all the three cases. At the same time, it was observed that ¹⁴C-acetate was utilised 20 times better for the formation of non-saponifiable portion of the lipids as compared with (U-¹⁴C) glucose. The nature of the unaccountable portion of the non-saponifiable lipids was unknown and further work is needed to elucidate the identity of this portion. There was an elevated lipogenesis from ¹⁴C-acetate and increased ¹⁴CO₂ production from (U-¹⁴C) glucose in the cold-acclimated rat-brain homogenate and it is possible that there may be some relationship between these two observed phenomena. With (U-¹⁴C) glucose, it was observed that very little ¹⁴C-activity was incorporated into the lipid fraction in all the three categories. This shows that cold acclimation or hypothermia have very little effect in *in vitro* lipogenesis from glucose by rat-brain homogenate.

A striking observation was that (1-¹⁴C) acetate utilisation was at a very much higher level for fatty acids and cholesterol synthesis as compared with (U-¹⁴C) glucose utilisation for the same purpose. Fatty acid synthesis, utilising acetate, is largely extra-mitochondrial (10, 11). This may account for the greater fatty acid synthesis when acetate was used as the substrate since the cells may have broken yet most of the mitochondria remaining intact.

Van Bruggen et al (12) and Srere et al (13) have observed that there was negligible incorporation of 1-¹⁴C acetate into the cholesterol of the brain and spinal cord of adult rats. In young rats, however, when the body fluids were enriched with D₂O, Deterium was rapidly incorporated into the unsaponifiable fraction of the brain lipids (13, 14). The reported experiment shows that very little, if at all, of the ¹⁴C-acetate was incorporated into the cholesterol molecule and thus confirms the earlier reports.

The findings that only a fraction of the total unsaponifiable portion from ¹⁴C-acetate and about 50% from (U-¹⁴C) glucose were digitonin-precipitable, imply that formation of other steroids or non-saponifiable materials from these substrates in the rat-brain is a possibility.

The greater conversion of ¹⁴C-acetate into fatty

acids by cold-acclimated rat-brain homogenates as compared with normothermic controls may possibly be due to the enhanced activity of hexose monophosphate pathway in the brain homogenates (15) with resultant accelerated generation of NADPH_2 , which is most essential for the synthesis of fatty acids.

Abstract

Some aspects of the incorporation of (1- ^{14}C) acetate and (U- ^{14}C) glucose by cold-acclimated and hypothermic rat-brain homogenates were studied and compared with those of normothermic control. There was found to be a greater incorporation of (1- ^{14}C) acetate into lipid fraction compared with (U- ^{14}C) glucose. But for $^{14}\text{CO}_2$ production (U- ^{14}C) glucose was found to be a better substrate.

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AORTIC SADDLE EMBOLECTOMY via femoral arteries

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(This case was presented at one of the scientific meetings of the Singapore Surgical Society)

SADDLE EMBOLISM of the aorta constitute about 9 – 12% of all peripheral embolism (Haimovic 1950) and is the most serious of all types of embolism. Without treatment, over 75% of cases die within a few days and the rest require major amputations (Griffiths 1938). It is generally believed that embolectomy is unsuccessful beyond 12 – 14 hours after onset due to the high incidence of thrombosis that occurs and spreads proximal and distal to the obstructing embolus within a few hours. (Poole & Farrar 1952).

The following case is reported because the circulation into the lower limbs has been successfully re-established by saddle embolectomy, 14 hours after onset of embolism by using the retrograde femoral route.

Case Report:

K.C.M., male Chinese taxi-driver, aged 23 years, woke up on 30 July, 1966, at 4 a.m. and felt numbness in his legs. After he had been to the toilet, when he got up from a squatting position, he felt pins and needles and loss of power in the lower limbs. He also had excruciating pain in the legs which radiated

upwards to the thighs and abdomen. He was seen in the local tuberculosis hospital and was transferred to the Orthopaedic Unit with a diagnosis of tuberculosis paraplegia. He was transferred to our unit at 4.30 p.m.

Previous History:

He gave no history of claudication, coronary or other heart diseases. He had treatment for pulmonary tuberculosis since 1956 and had had a right upper and middle lobectomy in December 1964 and a right thoracoplasty in June 1965 for resistant tuberculosis. In December 1965, he had exploratory burr-holes made for suspected extradural haematoma when he was admitted in deep coma and was only later discovered as having had an overdose of barbiturates.

On examination, he was a small man of thin build. His blood pressure was 150/100 and pulse 80 min. He had no motor power or sensations below the trunk. The legs were pale, cold and toes mottled. The superficial veins were not visible. There was no arterial pulsation in the femoral, popliteal or at the ankles on both sides. The pulsations in the carotids and upper limbs were normal. His heart was normal

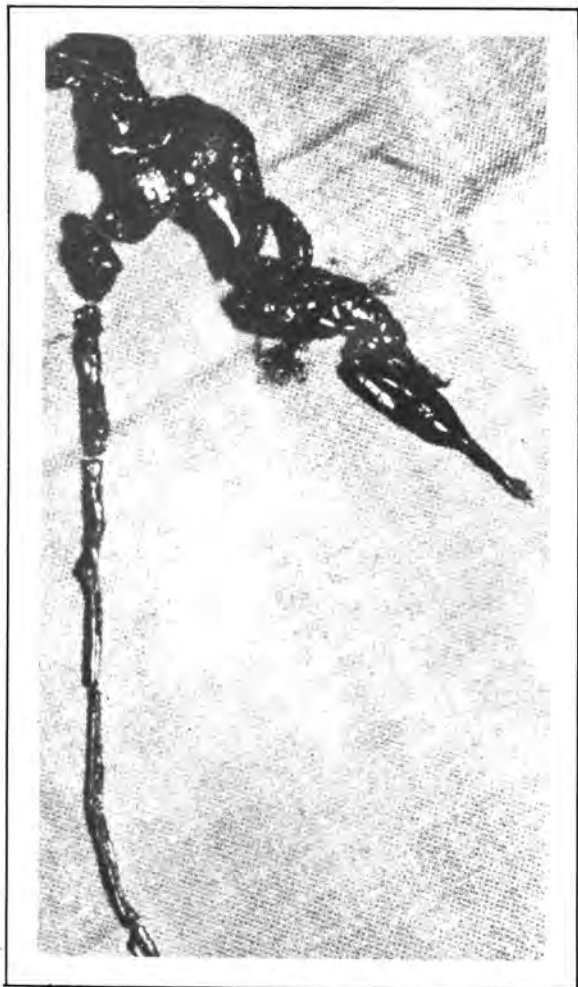


Fig. 1: The saddle embolus that was removed.



Fig. 2: The post-operative aortogram showing completeness of removal.

clinically, radiologically and on E.C.G. examination. There was no lesion detected in X-ray of the lumbar spines.

A diagnosis of saddle embolus of the aortic bifurcation was made and he was operated upon immediately (14 hours after onset). Under general anaesthesia (Dr. M.G. John), the patient was first catheterised and bladder emptied. Vertical incisions were made from the mid-inguinal point downwards below the inguinal ligament. The common femoral and its bifurcation were exposed within the femoral sheath and umbilical tapes placed around each of these vessels. There was very little bleeding during exposure of the vessels. The arteries were felt empty and had no pulsation. A transverse arteriotomy was

made at the broadest point in the common femoral artery. Heparin solution was injected distally and vascular clamps applied. A well lubricated Jacques catheter was passed through the arteriotomy upwards to the aortic bifurcation till the catheter could not advance further. Suction was applied to the catheter and as much clot as possible was removed by withdrawing the catheter out and repeating this on either side. An endarterectomy wire loop stripper (Connell's) was gently passed upwards to loosen any clots stuck to the side of the vessel. The catheter was reintroduced and suction applied as described above, withdrawing the catheter each time to remove the clots till the entire clots were removed. (See fig. 1). This was confirmed by the gushing out of pulsatile blood flow.

There was some resistance felt at the origin of the left common iliac artery although free pulsatile flow was obtained on both sides. The arterial clamps were tightened and the arteriotomy was closed with a continuous everting suture with 5.0 atraumatic silk. Before the final stitch was tied, the lumen of the

vessels was flushed with heparinised solution.

At the end of the operation, there was excellent femoral pulsation on both sides. The veins were filled and the posterior tibial pulses could be felt. Post-operatively, the patient was put on antibiotics and Chymar 5,000 units daily for 3 days. Intravenous fluid therapy was continued to keep the blood pressure over 110.

Six hours after the operation, the patient could move the limbs and the cramp-like pain disappeared. Both pulses in the ankles were felt. He developed subcutaneous haematoma in the groins which had to be evacuated. After 24 hours, he was started on Dindevan (Phenindione) 150 mg., and continued on maintenance dose to keep the thrombotest level at about 20%. This was continued for about eight weeks.

He was discharged well on 19 August, 1966, and has remained well since, without pain or claudication in the legs. He has had numbness over the outer sides of both ankles since the operation. An aortogram (translumbar) done (see fig. 2) six months after the operation shows completeness of removal of emboli.

Discussion:

The success in the treatment of arterial embolism depends on early diagnosis and prompt surgical treatment. The classical features as exemplified in this case are sudden pain and numbness and cold, pulseless extremities on examination.

The surgical approach may be made either by trans-abdominal route or retrograde femoral route. The trans-abdominal route has the advantage that the lesion can be directly attacked, the completeness of removal can be ascertained and any associated athero-

matous lesions can be discovered and dealt with at the same time. Most of the authorities accustomed to this approach disapprove the femoral route as opening the smaller femoral vessel and passing catheters may produce more trauma, spasm and secondary thrombosis. It is also claimed that the completeness of removal cannot be determined and any associated proximal lesion may remain undiscovered (Linton 1945). However, most of these patients with embolism are seriously ill with auricular fibrillation or coronary insufficiency and are unlikely to stand the stress of a laparotomy. On the other hand, femoral approach, being a much simpler procedure, can be done even under local anaesthesia. Since Rividin (1941) reported the first successful case by this method there has been sporadic reports of such successful cases. Willmann and Rollins (1959) reported four consecutive successful cases and Colt (1965) has presented three consecutive cases. Recently, May et al (1967) have described further successes using Fogarty's catheter for clot extraction. The experience in this case shows that even in a late case, the femoral route is a highly satisfactory and adequate method.

Summary

The successful treatment of Saddle embolism of aorta by retrograde femoral route 14 hours after onset is described with relevant literature on the operative methods.

Acknowledgement:

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Recurrent respiratory tract infection due to isolated absence of IgA:

Report of a case

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RECURRENT RESPIRATORY tract infection is often found in bronchiectasis, generalised malignancy, fibrocystic disease or when the patient is receiving prolonged immunosuppressive therapy. An unusual but important cause which has always to be considered is the absence of the globulin, as in agammaglobulinaemia which can either be congenital or acquired. Very rarely, however, the total amount of globulin in the blood may be normal, but there is a selective absence of only the IgA group of the immunoglobulins.

We report here a patient who has a complete absence of the IgA in the serum, saliva and nasal washings presenting as recurrent respiratory tract infection in different parts of his lungs during a follow-up period of almost four years. The aetiology of the recurrent infection posed initially as a diagnostic problem as all the commonly known causes were excluded, and the solution was obtained only

after sending his serum for quantitative immunoglobulin estimation. As far as we are aware, no such case has been reported in the literature from either Singapore or Malaysia.

CASE REPORT

L.C.H., a 14-year-old Chinese male, was first admitted to Tan Tock Seng Hospital, Singapore, on 24th November, 1965, with a four-day history of fever, cough and breathlessness. He also had a chronic left ear discharge which was purulent on and off ever since he was a child. There was no history of chronic diarrhoea or arthritis. Clinical examination revealed that he was rather small for his age (4 ft. 9½ ins.), but no other obvious abnormalities were found. Examination of the chest revealed a left pleural effusion. This was confirmed by a chest X-ray which in addition showed streaky opacities in the right first intercostal space, presumably of tuberculous origin.

Investigations.

Total White 13,300. Differential count: Polys. 77%, Lymphocytes 18%, Monocytes 3%, Eosinophils 2%, Haemoglobin Estimation 11.2 gms.%. Sputum for pyogenic culture grew no organisms. A tuberculin test of 1 T.U. was strongly positive (18 mm.). Repeated sputum examination for acid fast bacilli was negative both on direct microscopy and culture.

Progress.

In view of the presence of pleural effusion, a radiological shadow suggestive of Tuberculosis and a strongly positive tuberculin test, he was started on injection Streptomycin $\frac{1}{2}$ gm. daily together with tabs. Para-aminosalicylic Acid 7 gms. and tabs. Isoniazid 210 mgms. daily. On his discharge from the hospital on 19th March, 1966, injection Streptomycin was stopped, but both Para-aminosalicylic Acid and Isoniazid were continued for a total period of two years. He was followed-up regularly as an out-patient in the hospital. At the time of his discharge, his chest X-ray was completely normal except for minimal residual opacities in the right first intercostal space.

He was re-admitted on 20th March, 1967, for fever, and a chest X-ray showed consolidation of the apicoposterior segment of the upper lobe of the left lung. Again there was a leucocytosis and he responded completely to penicillin. Sputum for culture grew no pyogenic organisms. In view of his chronic discharging left ear, he was seen at the Ear Nose & Throat Department at the Outram Road General Hospital where a diagnosis of chronic otitis media was made and Chloromycetin ear drops were prescribed.

His third admission to the hospital was on 10th April, 1967, for similar complaints of fever and cough. This time the chest X-ray showed a complete right upper lobe consolidation. On this admission, a protein electrophoresis was done and this showed: albumin 2.3 gms.%, α_1 globulin 0.4 gms.%, α_2 globulin 0.8 gms.%, β globulin 0.4 gms.%, γ globulin 2.7 gms.%. As fibrocystic disease was considered, the patient's sweat was estimated for total sodium and chloride, both of which were within the normal limit. Again he was treated with injection penicillin and he responded very well.

On 3rd April, 1968, he was admitted to the hospital for the fourth time for a pneumonic consolidation of the posterior segment of the upper lobe of the right lung. Once again he improved with chemotherapy. Since no cause of his recurrent respiratory infection could be found so far, a quantitative

estimation of his serum immunoglobulin was carried out, employing a modification of the technique described by Sharpless and LoGrippe, using the micro-double diffusion agar plate (Sharpless and LoGrippe 1965). The results were as follows: IgG 1,460 mgms.%, IgA not detectable quantitatively, IgM 78.0 mgm.%.

Vitamin A absorption test and liver function tests done were all normal. Blood for LE cells was negative, but the R.A. factor was positive.

Bilateral bronchogram done on 6th June, 1968, showed a normal bronchial tree. On 19th June, 1969, immunoglobulin estimation in the serum was repeated: IgG 1272 mgms.%, IgA absent, IgM 92.5 mgm.%. The saliva of the patient, together with his nasal washings, were both sent for quantitative estimation of IgA, and this could not be detected in any of the specimens sent.

Since the last admission, the patient has been followed up regularly and has remained well.

Discussion.

The huge numbers of the anti-bodies found in the serum can be conveniently divided, basing on chemical, physical and immunological characteristics into 5 major immunoglobulin groups – IgG, IgA, IgM, IgD, IgE. Each of these five groups of immunoglobulins have different biological properties and disease states occur where there is either an excess or deficiency in one or more of these immunoglobulin groups. The IgA molecule, like the other immunoglobulins, is composed of two heavy and two light chains and has a molecular weight of 180,000 with a sedimentation coefficient of 7S. Unlike in the serum where nearly all the immunoglobulin groups are represented, IgA is the predominant immunoglobulin in the external secretions of the body such as the saliva, tears, colostrum, nasal and bronchial fluids, gastrointestinal fluids and urine. The IgA found in secretions differs from that found in the serum in that it is 11S instead of 7S due to the presence of a low molecular weight protein, "the transfer piece", attached to the usual IgA molecule. It has been suggested that this "transfer piece" enables the IgA molecule to be secreted by some of the organs in the body (Terry, 1967).

Secretory IgA has been shown to possess anti-bacterial and anti-viral properties, and is thought to provide an immune protection for the mucous membranes of the body.

Deficiency of IgA can be divided into two groups:—

(a) Deficiency of IgA combined with other

immunoglobulin deficits as in agammaglobulinaemia and Type I and Type II dysgammaglobulinaemias.

(b) Isolated deficiency of IgA (Tomasi, 1968).

Recurrent respiratory tract infection is common to both, but a variety of conditions have been described, associated with the isolated IgA deficiency group. These are hereditary telangiectasia (4 out of 5 patients have deficiency of IgA), cirrhosis of liver, Still's disease, systemic lupus erythematosus and recurrent malabsorption. The last is particularly interesting because the majority of patients with idiopathic steatorrhoea have normal immunoglobulins, although a few have shown isolated absence of IgA.

The exact relationship between IgA deficiency and most of the syndromes it is associated with, such as systemic lupus erythematosus and hereditary telangiectasia, is unknown, although the presence of recurrent respiratory tract infection can be readily explained by a lack of protective IgA anti-bodies bathing the mucous membrane of the bronchial tree. Furthermore, isolated absence of serum IgA in apparently healthy and asymptomatic individuals have been described in 1 out of 700 of the normal population.

The patient we have described is particularly interesting because he presented with the diagnostic problem of recurrent respiratory tract infection of unknown aetiology following treatment for a pleural effusion which was thought to be tuberculous in origin. Bronchiectasis, fibrocystic disease and a few other conditions were all excluded in our investigations. Because it was felt that some lowering of his immune mechanism was responsible, quantitative estimation of his immunoglobulins in the serum and later the IgA in his saliva and nasal washings were done. Chew and his colleagues found that in a survey of the levels of IgG, IgA, IgM in the serum of the normal population in Singapore, employing a modification of the technique described by Sharpless and LoGrippe using the micro double diffusion agar plate, the average levels for Chinese males were as follows:—

IgG 774 mgms.%, IgA 206 mgms.%, IgM 73 mgm.% (Chew et al 1969). Using the same method, no IgA could be detected in the patient's serum, saliva and nasal washing.

It must be realised, however, that deficiency of IgA in the serum need not necessarily be accompanied by deficiency of IgA in the secretions, but the converse has not yet been described. The patient described above has a deficiency of IgA in both his serum and his secretions. Rockey and his co-workers described two cases of isolated IgA deficiency in the serum, whose serum IgG were found to be high for some unknown reason, although the IgM was normal (Rockey et al, 1964). It is interesting to note that in our patient, the serum IgG estimated on the two occasions were 1,460 mgms.% and 1,272 mgms.% respectively both of which were much higher than the average IgG level of 774 mgms.% in the normal Singapore Chinese male population as found by Chew et al.

In addition to the recurrent respiratory tract infection, our patient also has chronic otitis media which has been described with IgA deficiency. However, he has no clinical evidence of the other associated syndromes as listed above, and this was confirmed by all the negative investigations, such as the LE cell test and tests for liver function and malabsorption, except for a positive R.A. factor.

Summary.

A 14-year-old Chinese male, presenting with recurrent respiratory tract infection and chronic otitis media due to an isolated absence of IgA in the serum, nasal washings and saliva, is described. The literature regarding the role of IgA and the various syndromes associated with its absence is reviewed.

Acknowledgement.

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Evaluation of a broad spectrum anthelmintic tetramisole on threadworms

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INTRODUCTION

MANY ANTHELMINTHIC drugs are in the market, some simple and safe and some very toxic but specific. Hence any anthelmintic with a broad spectrum activity, which could eliminate most of the parasitosis and yet have negligible side effects besides being cheap, could be extremely advantageous. Since 1965, Tetramisole has undergone various clinical trials. In one of these (Tolat R.S. 1968) Ascariasis clearance was found to be 98% in one week and complete within two weeks. 85% Ancylostomiasis cleared in one week and 95% in two weeks; complete in three weeks; of *Trichuris Tricuris* 70% cleared in the first week.

In another trial (Jose' Waks 1968) the following results were excellent against Ascariasis, good against Ancylostomiasis and Oxyuriasis, satisfactory against Strongyloidiasis, fair against *Trichuris* and none against Plathyhelminthiasis and Trematodiasis.

As most results have been excellent with *Ascaris Lumbricoides*, a simple clinical trial was set out with the aim of judging whether Tetramisole is effective against *Enterobius Vermicularis* i.e. threadworm in general practice. This simple procedure could also be repeated with other worms in mind.

PHARMACOLOGY

Tetrahydrophenylimidazotiazol, commonly known as Tetramisole, is a soluble white crystalline substance. It hydrolyses down to its major metabolite 2-Ox0-3-(2-mercaptreoly)-5-phenylimidazoidrine which is insoluble in water and rapidly excreted.

Tetramisole has a quick but short action. Ingested, it disappears from the blood stream in a few hours. It is highly active against all Nematodes but inactive against Trematodes and Cestodes tested. It claims no activity against bacteria, fungi or protozoa. Animal experiments showed that a low concentration of Tetramisole (2-40mg/Kg. depending on the species) is hypothesised to exert a rapid paralysing effect by inhibiting succinate dehydrogenase activity in the worm's muscle. Most nematode worms are expelled within one day after its administration; those expelled later became discoloured, swollen and partially decomposed (Tolat R.S. 1968)

METHOD AND MATERIAL

One hundred patients, aged one to twelve years, were selected over a period of three months regardless of sex, ethnic groups. Indications of patients' choice arose from symptoms and signs of threadworms infestation as volunteered by the parent or from the

patient if old enough; ranging from the presence of thread-like worms, pruritus perianal and perineal, vague abdominal pains, chronic eczema around perineum, loss of appetite, pot belly, pica nocturnal enuresis and general signs of vitamin deficiencies or of multiple worm infestations.

Single dose used in other trials was recommended at 25–100mg, depending on body weight. In this trial, dosage used depended on age and subsequently on weight.

Babies age 1 – 4 = 1 tablet (40mg)

Children age 5 – 15 = 2 tablets (80mg)

Each parent was given a clean slide to collect Enterobias eggs. On first waking in the morning, from the perianal region of the patient by sticking a piece of cellophane tape one inch long. This was done just before Tetramisole administration. Another piece of cellophane tape was used to collect eggs in a similar fashion seven days after the drug had been administered.

RESULT OF THERAPY

Count of Enterobias eggs (size 50 – 25 μ) was scanned by low and then under a single medium field. All other eggs were ignored. Heavy infestations ranged between 30–50+eggs, moderate from 10–30 and light 1–10 per medium power field (x 40 objective).

Heavy 30–50 eggs		
Patients	Before	After
A	30	10
B	35	0
C	40	8

Moderate 10–30 eggs		
Patients	Before	After
D	12	2
E	15	0–4
F	20	0
G	30	1–2

Light 1–10 eggs		
Patients	Before	After
H	1	0
I	2	0
J	5	0

A sample of the results is shown as tabulated above. Breakdown results showed that of a hundred patients so chosen, about 25% were heavily infected, 40% moderately so and 35% were classified as light shedders.

Worms continued to be shed up to 72 hours or more as seen when some collections were returned by 48 hours with a moderate egg count. However, by end of one week most egg counts were negligible.

Breakdown results also showed that in heavy infestations, Tetramisole eliminates worms down to a moderate light infestation and complete in a third of them by end of one week. In moderate infestation, 90% worms were eliminated in one week. But with light infestation, Tetramisole cleared worms completely by end of one week.

TOLERABILITY

Side effects were few. In some 4%, patients' complaints ranged from anorexia, vomiting, mild abdominal pain and occasional giddiness. All started an hour after ingestion and disappeared within a few hours.

CONCLUSION

A total of one hundred children between one and twelve were treated with Tetramisole, with the aim of judging its effect on Threadworms. Results showed that single doses between 40 – 80mg carried good worm clearance with little or no side effects in light and moderate cases. In heavier infestations, a second dose is recommended one week later to eliminate all threadworms.

In previous trials where this drug has proved effective against roundworms, side effects monitored by S.G.O.T., S.G.P.T., blood picture and urinalysis were devoid of any real toxicity on liver, blood or kidneys.

Tetramisole could offer good prospects of being an effective, single dose, broad spectrum anthelmintic, of low cost and easy tolerability in practical use or for mass treatment for most nematodes.

ACKNOWLEDGEMENTS

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MALARIA IN RURAL MALAYA

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(Paper read at a seminar on "Rural Health in Malaya" organised by the Malaysian Society of Parasitology and Tropical Medicine, Kuala Lumpur, Jan. 20, 1970)

IT HAS long been known that malaria is prevalent in many parts of rural Malaya. It does not, however, make the same impact on the public as does malaria in urban areas or agricultural holdings. In these latter places, the population is more concentrated and the cost per head of protecting them is relatively low while at the same time the economic effects of malaria are so evident that anti-malaria measures are instituted early. Until recently, these measures consisted of drainage, oiling and drug prophylaxis, all of which are costly and involve recurrent expenditure and cannot be applied to vast areas with a scattered and impoverished population. Hence, malaria in rural areas has been for the most part neglected. Naturalistic measures limiting the multiplication of vectors have been tried without obtaining consistent results. Residual insecticides have been introduced since World War II and this offers a possible line of attack for the rural areas because of its relative cheapness.

MALARIA IN MALAYA IN RELATION TO TOPOGRAPHY

Malaya lies in the equatorial zone with a constantly high temperature and humidity suited for the perennial transmission of malaria. The intensity of transmission, however, varies from place to place; in general, it may be said that malaria exists in most parts of Malaya in endemic, and in some places, hyperendemic form.

Brackish Water Zone: The prevalence of malaria in any locality is largely determined by whether or not conditions exist there for the breeding of vector species of *Anopheles*. The untouched mangrove swamps along the coast are relatively free from malaria because of the absence of vectors. When the mangrove is cleared and the tidal waters are allowed to come in contact with collections of fresh water exposed to sunlight, *A. sudaicus*, Rodenwaldt, 1925 breeds prolifically and transmits malaria.

Coastal Plains: This zone which extends from the sea to the hills, if they remained as untouched jungle swamps, would be sparsely populated. If houses are built in cleared areas inside or close to the edge of such swamp forests (that is within half a mile, the distance which is the average flight range of mosquitoes) or if workers take shelter in the jungle during the day, they may be bitten by *A. umbrosus* Theobald, 1903. In north-east Malaya, where climatic conditions approach those of the monsoon countries to the north of Malaya, *A. balabacensis balabacensis* Baisas, 1936, is found in the swamp and hill forest and transmits malaria.

The cleared areas of the coastal plain may remain as open swamps or be under rice cultivation; in such areas the most important vector is *A. campestris*, Reid, 1962, and to a less extent *A. nigerrimus*, Giles, 1900. If the cleared area is a kampong or is under coconut or rubber cultivation, *A. letifer*, Sandosham,

1944, plays a part in transmission. If the cleared coastal plains are close to cleared hill forests, then *A. maculatus*, Theobald, 1901, the most important malaria vector of Malaya, takes a share in the transmission.

The Hills and Mountains: If this remained as virgin jungle, it would be sparsely populated. The Orang Asli (Aborigines) and jungle tribes living in such areas have malaria which may have been transmitted to them by members of the leucosphyrus group or other jungle species, but more often infection is due to *A. maculatus* which establishes itself in streams and seepages in hill-slope 'ladangs' or clearings prepared for their shifting cultivation. The Orang Asli also move around the country and may encamp close to malarious areas in the hills or in the coastal plains and become infected there, and take malaria from place to place.

Whenever the cover of jungle is cleared from hilly areas *A. maculatus* breeds prolifically in seepages and streams and is mainly responsible for the high malaria endemicity in the rubber and oil palm estates on the hill slopes. The rice fields in the valleys and ravines between the hills are also malarious because of *A. maculatus* breeding in the exposed seepages along the hill slopes or streams. The rubber-cultivated and partially cleared valleys may also breed *A. letifer* which may transmit malaria.

PREVALENCE OF MALARIA IN THE COUNTRY

Throughout the history of tropical enterprises, the opening up of land, especially with non-immune imported labour, has produced violent outbreaks of malaria and Malaya is a typical example of this. In assessing the economic losses caused by malaria, one should take into account not only the value of the lives lost but also the cost of medical care, loss of working time, lessened efficiency of labour, property losses by depreciation, loss of crop, etc. Government, estate managers and health officers recognised the extent of the economic losses and instituted anti-malaria measures early in Malaya. There has been an exacerbation of malaria in the country every few years which has often been associated with the periodic influx of foreign labour in connection with new planting and replanting of rubber. After a period of high incidence of malaria, the community develops a relatively high degree of immunity and therefore enjoys a period of decreasing endemicity. The natural removal of older immune members of the community

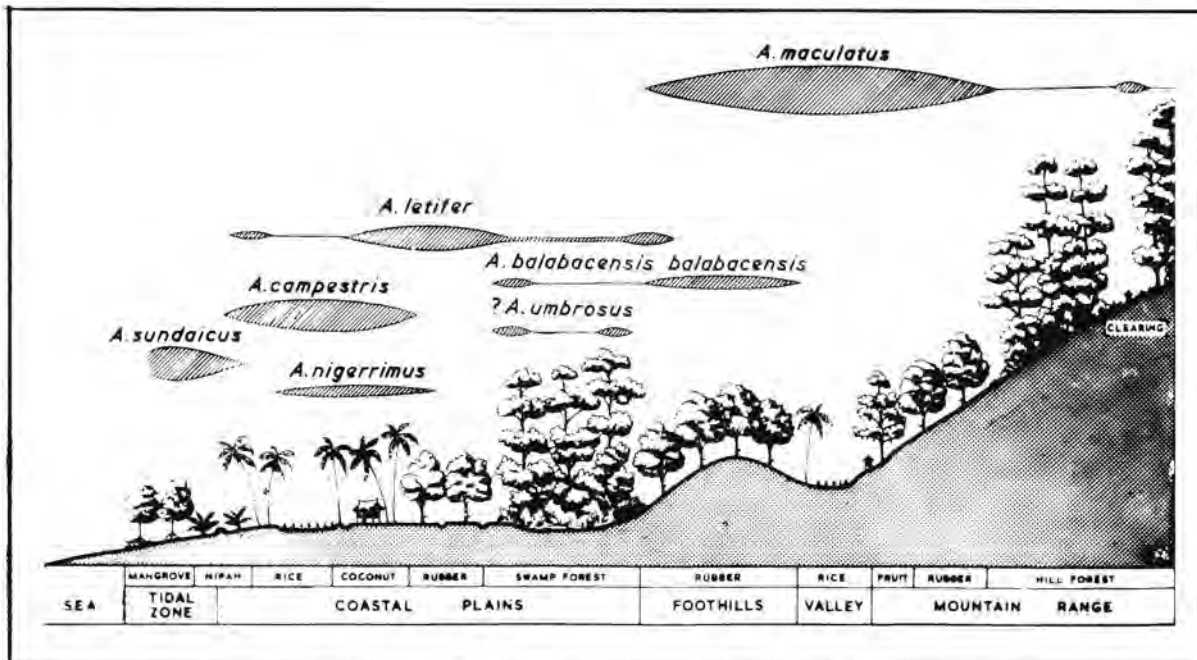
by death and the introduction of non-immunes by birth and immigration produce conditions particularly suited for increased prevalence of malaria. If this coincides with an increase in the population of vectors, as it happens during the opening up of new land and replanting of rubber, then conditions are suited for malaria to attain epidemic proportions.

PREVALENCE OF MALARIA IN RURAL AREAS

The malaria situation in rural areas of Malaya will depend largely on where the kampong is situated. It may be in an area of the country where malaria vectors are absent or rare, in which case there will be no malaria. Clearings and land development may make an area, previously free of vectors, suitable for the breeding of vectors. Thus fisherfolk living along the coast and riverine estuaries create conditions for *A. undaicus* to breed by clearing the mangroves in the brackish water area. The flat coastal plains may be cleared for coconut, rubber or rice cultivation and *A. letifer* and *A. campestris* appear. If the kampongs adjoin swamp or hill forest in N.E. Malaya and if there is logging or other activities in these forests, then *A. balabacensis balabacensis* may transmit malaria. If the kampong is on a hill slope or adjoins a hill which is cleared for development, the dangerous *A. maculatus* will start to breed and transmit malaria.

In many of these kampongs, no anti-malaria work has been done and malaria is prevalent in holo and hyperendemic forms, but clinical manifestations of the disease are often not so evident among these people. Malaria surveys carried out in many rural areas and offshore islands in Malaya have shown high parasite rates among the population which manages to carry out its normal daily chores. They are people who have developed immunity to child morbidity and mortality.

A malaria survey in four rural valleys in the Kuala Pilah District of Negri Sembilan, where control measures had not been carried out, done by the staff of the Institute for Medical Research (Edeson et al 1957) in 1948 and 1949 showed that among a population of 4,000 examined, the spleen and parasite rates of children varied from 54 to 60% and 26 to 37% respectively. In a similar kampong some miles away, where there were no medical facilities, spleen and parasitic rates in 1948 were 79% and 18% respectively among 130 children examined and were still about the same in 1952, i.e. 74 and 35% respectively in 95 children examined.



The distribution and abundance of vectors of malaria in different ecological zones in Malaya.

NEED FOR ANTI-MALARIA MEASURES IN RURAL AREAS

The rural community constitutes about 60% of the total population of Malaya and little has been possible for them in the past because of the prohibitive cost and impracticability of chemoprophylaxis and anti-larval measures over a large expanse of the country. With the advent of the cheaper residual insecticides, there is a no justification for postponing the attempt to control the infection among our rural folks.

It may be argued that if the folks have malaria parasites in their circulation and yet can carry on their normal activities, why interfere? This, to my mind, is a defeatist attitude. I have already mentioned that the immunity the people have gained is at the expense of a high child morbidity and mortality. Those children must be saved from dying and from suffering from the harmful effects of malaria. They deserve to have the benefits of modern science so that they can develop to the fullest their potentialities to enjoy life, be educated and become normal healthy citizens of this country. It has been said that the rural folks of Malaya have a 'tida-apa' or apathetic attitude towards life. If that is true, it may well be due to the continuous destruction of red blood cells from

malaria and the consequent anaemia leading to lethargy. If free of malaria, the rural folks may become more ambitious and work harder and improve their lot and nutrition and take their place side by side with the industrious urban folks. As equal citizens of the country, they have every right to expect Government to provide them that protection.

Another reason why we should attempt to control malaria in rural Malaya is that there is a constant danger of the infection being introduced to the urban and estate community which is relatively better protected. The urban areas carry out anti-malaria work and spend considerable sums of money keeping the vector population down. Even so, building operations, road construction, expansion of city into suburban areas, etc. that are continuously going on, keep producing conditions favourable for vector breeding. The urban population is relatively free of malaria and the small amount of breeding, limiting the numbers of vectors to a level below the critical density, will make little difference. But a continuous stream of gametocyte carriers from the rural areas visiting relatives, seeking treatment, etc., in cities, will constitute a serious menace. If this rural influx of malaria carriers can be stopped or if the rural areas can be freed of malaria, then the urban health

authorities can afford to relax and cut down on anti-malaria activities which are costing the City Councils so much in recurrent expenditure.

There is also an extensive programme of land development and resettlement of newly-opened up areas in the country at the present time. These are potential grounds for vector breeding and if malaria is introduced from various parts of rural Malaya, there is every likelihood of a flare-up. It will be much easier to keep malaria out of an area than to try and control or eradicate it after it has obtained a foot-hold.

MEP IN NEIGHBOURING COUNTRIES

Ideally, the disease should be eradicated from a country. The big question is whether eradication is technically and administratively attainable within a reasonable period of time. I raised this question back in 1962 after my experience with WHO. If achieving eradication is not time-limited, then is it economically justifiable? Would it not be more expedient to try and bring down the infection to a low level and maintain it at that level?

The doubt as to whether malaria eradication should be attempted in Malaya arises from the experience gained in some of the neighbouring countries like Thailand, Philippines, Ceylon and India. In Thailand, the total cost has far exceeded the original estimated figures and the target date for achieving eradication has long gone by and the prospects of attaining the goal early are not good. For instance, in 1968 the MEP officials report that in the areas they examined, there were about ninety thousand positive blood films. Among the problems there are: (1) a high turn-over rate of trained field personnel, (2) the migratory habits of the population, (3) the legal and illegal opening up of new areas at periphery of settlements, (4) the wide distribution of chloroquine-resistant falciparum malaria and (5) the exophagic and exophilic habits of *A. balabacensis*. About 25% of the total cost has so far been contributed by USAID, and with the cessation of that source of income this year, it has been suggested as a measure of economy that attempts should be made to maintain the gains achieved so far and modify the programme in the low receptive areas to a mere protective level.

In the Philippines, another of the early countries to start eradication, malaria endemicity in most areas is said to be low (below 2 percent prevalence rate in 334 indicator villages and between 2 and 12 percent in 336 others), but certain localities in Mindoro, northern Luzon, Palawan and Sulu Archipelago, are

still highly malarious. Here, too, the movement of people, including the nomadic tribes and the opening up of fringe areas for cultivation, constitute a big problem to the areas which have been cleared of malaria but where the vectors have been allowed to come back. It must be remembered that a malaria eradication programme does not envisage the eradication of vectors although the almost wholly house-resting mosquitoes like *A. minimus* and *A. campestris* may remain scarce after the campaign.

In Ceylon, after five years of comparative freedom from malaria and where malaria incidence had been reduced to about 10 indigenous cases in a whole year, nearly two million cases have been reported, and has necessitated a further eradication programme of at least 10 years' duration and at a cost of many millions of rupees.

In India, transmission has been re-established in areas in the maintenance phase and it has accordingly been necessary to reinstate spraying in many parts of the north and central regions of the country.

ERADICATION PROGRAMME IN MALAYA

The 85-million-dollar (originally estimated at 118 millions) malaria eradication programme was launched in Malaya on July 1st, 1967 according to information provided at the WHO 6th Asian Malaria Conference held in Kuala Lumpur last October. The plan entails the staggering of the Preparatory, Attack and Consolidation phases State-wise, starting at the north-west area of the Peninsula so that the whole country will be covered over a 11-year period. Houses are sprayed with DDT (75% WDP being used) at six-monthly intervals at the rate of 2 grams of technical DDT per square metre of sprayable surface. This is supplemented by radical chemotherapy of positive malaria cases and presumptive drug treatment of fever cases.

At the national level, the MEP is directed by the Head of the Malaria Division at the Ministry of Health. At the State level, the State Malariologist receives operational directions from the MEP Headquarters at the Ministry of Health, but is under the overall administrative supervision of the State Chief Medical and Health Officer.

Exophagic and Exophilic Vectors

The present malaria eradication programme in Malaya consists of DDT-spraying of the inside of houses and the exhibition of drugs. The 1962 survey in Perlis (Sandosham et al 1963) had shown that the vector was *A. balabacensis balabacensis* and that transmission was going on to the extent of more than

half the people being infected although the Government Health Department had been spraying the houses with dieldrin for about two years. Similarly, it was found that residual spraying in Negri Sembilan in an area where *A. maculatus* was the vector did not prevent the continued transmission of malaria though it was at a low level. In view of the difficulties of giving drugs to a scattered rural community, with an infection producing little obvious clinical manifestations, it is going to be difficult to achieve eradication by these means. When giving daily treatment in Perlis to those having parasitemia and suspected of having chloroquine-resistant falciparum malaria, it was often difficult to find the individuals at home because they had left for work. It was also difficult to persuade them to take the drugs even under direct supervision of the doctor and it is not likely that they can be expected to follow a treatment regimen if the drugs are distributed by lay personnel with the instructions they are to observe. This is understandable as the individuals are not suffering from obvious clinical symptoms of the disease like high fever, chills, sweating, etc. and cannot understand why they should be drugged.

Chloroquine-resistant falciparum malaria

It has been shown (Sandosham et al 1963, 1966) that a strain of chloroquine-resistant falciparum malaria was present in North Malaya and transmitted by *A. balabacensis balabacensis*. Cheong (1963) had shown that this strain could develop readily in *A. maculatus*, the important vector of malaria in Malaya. At that time, it was pointed out that this strain of malaria parasite appeared to be confined to north Malaya and that steps should be taken to prevent its spread in the rest of the country. There is growing evidence that troop movements, migration of people to land settlement areas and elsewhere have resulted in a wider distribution of the chloroquine-resistant strain of falciparum malaria in the country (McKelvey 1969 and Fredericks, personal communication) which is going to make the task of the eradication of the disease with the present armamentarium difficult.

ADMINISTRATIVE MACHINERY

It is questionable if the State Chief Medical and Health Officer is the best person to be placed in administrative charge of the State Malariologist. It has been said that to achieve success, an eradication programme has to be prosecuted with the vigour and thoroughness as in waging war. Can the necessary intimate knowledge and devotion be expected of an officer who has so many other responsibilities to

shoulder and who is so frequently changed from State to State because of the exigencies of service? In a health service, which is inadequately staffed, isn't there a danger that the State Malariologist will be expected to shoulder other health responsibilities as well? Isn't there a danger that the Chief Medical and Health Officer and the State Malariologist (who combine other administrative and health duties) are likely to be overwhelmed and tend to neglect the eradication campaign especially at a time when their attention is most needed, that is when the disease incidence has been brought to a low level? Could Professor Gabaldon's assertion, "Having personal knowledge of many tropical health administrators, I am convinced that the regular local health services are entirely incompetent to take care of the actions required during the maintenance phase" apply to Malaya also?

Use of Primaquine

A disturbing aspect of the MEP in Malaya is the use of Primaquine (an 8-amino-quinoline) in daily dosage of 15 mg. for 5 days in the treatment of the people. Lie-Injo Luan Eng et al (1966) have shown that Glucose-6-Phosphate Dehydrogenase deficiency has a frequency among the local population of Malaya of about 2 per-cent and that among them they reported 45 cases of haemolysis, most of them severe, in 2 years at the General Hospital, Kuala Lumpur. They stated that "this abnormality poses an important medical problem and is one of the major causes of acute haemolysis at least in Malaya." They also reported that the degree of G6PD deficiency was greater in Asia than in Africans and others so that the exhibition of primaquine in Asia becomes doubly serious. Lie-Injo et al (1964 & 1969) also reported that the frequency of G6PD deficiency was particularly high (9 to 23%) among the (Malayan Orang Asli (aborigines); in spite of this, it is proposed to use primaquine for mass treatment among them. (MEP Hqs K.L. M.C. 5.3.68). It is well recognised that erythrocyte G6PD deficiency is an inherited abnormality and results in acute haemolytic anaemia after ingestion of 8-amino-quinolines. The Orang Asli are a very shy and sensitive people and it has taken Government and Medical Officials years of patient work among them to gain their confidence to the present level as a result of which they are beginning to seek modern medical treatment. There is a danger that if the exhibition of primaquine on a mass scale handed out by non-medical personnel as part of the MEP should result in untoward accidents, then we

may lose the confidence of the Orang Asli and defeat our objective, namely the eradication of malaria in Malaya.

CONTROL VERSUS ERADICATION

As pointed out by Professor Gabaldon, the discredited concept of malaria control leading to a reduction of the disease incidence to a level at which it ceases to be a major public health problem, should be the immediate aim of many developing countries. The question is whether in Malaya we should not confine our activities to an attempt to reduce the prevalence of malaria to a low level by concentrating only on the heavily infected areas and ignoring those areas where the infection is low or practically absent. By doing this, it should be possible for spraying teams to cover a much wider area more quickly for the same amount of money and manpower. Once the prevalence is brought down, the prevention of an exacerbation of malaria will be relatively easier and cheaper by maintaining mobile teams to deal with emergencies than having to spray the inside of every house every six months for three years or more and continue with the expensive surveillance and maintenance programmes probably indefinitely.

CONCLUSION

In the short time allotted to me, I have tried to

outline the malaria situation in Malaya with special reference to the rural areas. I have also emphasised the importance of carrying out anti-malaria measures in the rural areas. As becomes a talk at a seminar, open for discussion, I have tried to be provocative and critical. I have outlined the results of MEP in neighbouring countries, problems of exophily of certain vectors, drug resistant malaria, etc. and have suggested that control leading to a reduction of the disease to a level at which it ceases to be public health problem may be a more readily achievable and a more economic target than complete eradication. I have also questioned the wisdom of exhibiting one of the 8 amino-quinolines among a population known to have a high degree of G6PD deficiency.

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PNEUMATOSIS INTESTINALIS:

A case report with a brief review of literature

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A 49-YEAR-OLD Kadazan male was seen at the Queen Elizabeth Hospital, Sabah, on July 18th 1969 with complaints of severe abdominal pain and vomiting of 24-hour duration. He also gave a history of recurrent attacks of epigastric pain after meals for the past 10 years, often associated with vomiting of food. A clinical diagnosis of acute intestinal obstruction was made supported by pre-operative portable X-rays of the abdomen which showed evidence of intestinal obstruction. At laparotomy, no abnormality except "a mass 12 inches long in the lower ileum" was found. A post-operative diagnosis of ? pneumatic cysts was made and the specimen was sent for histopathological examination. The affected segment was resected and an end-to-end anastomosis was performed. Post-operatively, the patient lapsed into irreversible shock and died the following day.

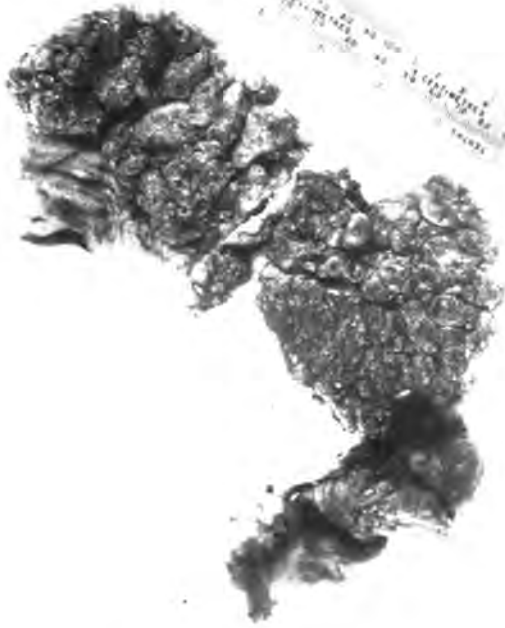
The specimen of lower ileum, measuring about 12 inches long, was covered by grape-like clusters of gas cysts of varying sizes with thin fairly transparent walls, and on cutting, they appeared smooth-walled and empty. (Photographs 1 & 2). Histologically, there were numerous subserosal cysts lined by flattened cells and some of the cysts were communicating with one another. The mucosa and submucosa of the ileum were normal. Thus histology confirmed the gross diagnosis of Pneumatosis Intestinalis.

DISCUSSION

Incidence

The occurrence of gas in linear or cyst-like forms within the subserosal, the submucosal or both layers of the intestinal wall, is termed Pneumatosis Intestinalis. Since Duverney's (1648) original description of this condition, many reports have appeared from time to time in the literature. Hunter (1728), Bang (1876), Lerner and Gazin (1946), Burt (1949), Marshak et al (1952), Greese (1954), Sedgwick and Ruddell (1954), Mathews (1955), Witowski et al (1955), Kutty & Unni (1965), Moore (1968), Dodd (1968). Though the exact incidence of this condition has not yet been ascertained, it appears that by 1965 more than 289 cases had been reported in the world literature. It is likely that in many patients with vague gastrointestinal symptoms, the diagnosis is often overlooked, and in the event of secondary obstructive complications, the condition is often missed. This condition being exceptionally rare, this case is deemed worthy of record. And this will stress that Pneumatosis Intestinalis should be entertained in the differential diagnosis of chronic gastro-intestinal diseases and acute abdominal conditions.

Majority of the reported cases have been in adults; however, the condition has also been described in infants, but this is to be considered acquired rather



Photograph 1



Photograph 2

than congenital. Paris (1955), in a review of a series of affected infants, noted that the gas cysts were invariably associated with acute gastro-enteritis.

Pathology and Aetiopathogenesis

It is known that there are two types of Pneumatosis Intestinalis. (1) Primary Pneumatosis Intestinalis which develops spontaneously, and (2) Secondary Pneumatosis Intestinalis related to pathologic processes, such as peptic ulceration, neoplasms and emphysema. The gross appearance is that of gas cysts in the submucous or subserous layers of the intestine and though the site of occurrence is commonly the colon and the small intestine, rectal involvement has been reported (Griffiths 1955). In the colon cysts are located predominantly in the serosa, but the two may be combined in the same patient. The cysts may occur singly or in clusters not communicating with the intestinal lumen.

Though no conclusive evidence has so far been adduced regarding the etiology and pathogenesis of this condition, many theories, some factual and some

conjectural, have been postulated, from which it appears that Pneumatosis Intestinalis is not *per se* a disease entity but the result of a variety of conditions. The mechanical theory postulates a breach such as in peptic ulceration, enteritis and neoplasm in the mucosal surface of the intestine, allowing for abnormal entrance of gases and air which permeate the nearby lymphatics. Increased intra-luminal pressure of doubtful origin augments the gaseous influx with resultant distension of the gas-filled lymphatics. Occurrence after such procedures like sigmoidoscopy and polypectomy, as suggested by Marshak et al (1956) should be reflected in a far greater incidence of the condition than that actually observed. This not being the case, such procedures cannot be incriminated so readily. The mechanical theory finds support in the frequent association of the condition with peptic ulcer. Nitch (1924), in a review of 85 cases, reported peptic ulceration in 50% of cases and of these, 80% had stenosis, while many of the remainder had mucosal lesions. Koss (1952) reported 58% associated with stenotic lesions of the pylorus.



Microphotograph 1

Ischemic necrosis of the mucosa as a consequence of chronic distention is thought to be another cause of intramural gas (Rigler & Pogue 1965). Altered permeability of the mucosa as a result of nutritional deficiency or nearby intestinal disease, is suggested as another mechanism in the occurrence of intramural gas. Pneumatosis Intestinalis of the swine has been produced experimentally by feeding them purely on polished rice. It appears more reasonable to combine the mechanical and altered mucosal permeability theories to explain the presence of abnormal intramural gas. Though Sauser-Hall (1940) suggested that gas cysts arose secondary to intestinal obstruction, the reverse is generally accepted. Masson (1920) regarded intra-mural gas a derivative of chemical interaction of chyle with the acid products of intestinal fermentation in the lymphatics. Alford (1956) attributed the symptoms of diarrhoea, flatulence and abdominal distention to excessive intestinal fermentation resulting in increased lactic acid and gas-forming bacteria. A defective absorption of these gases by the blood stream was thought to result in retention of gases within the intestinal wall, leading to the formation of giant cells and connective tissue which encapsulates the gas to form cysts. The neoplastic theory, like the infective theory, has been discarded for want of substantiative evidence.

It has recently been postulated that intra-mural gas cysts are produced as a result of rupture of emphysematous bullae and conditions of raised intra-thoracic pressure causing retrograde diffusion and distension of lymphatics of the gut-wall. The significant occurrence of allergic respiratory complaints in 15 out of 16 cases reported by Doub & Shea (1960) and others, lists chronic respiratory diseases as another possible etiological factor in the development of intestinal gas

cysts. It is of interest that Pneumatosis Intestinalis has been described in patients with intestinal scleroderma Seaman et al (1966), Meihoff et al (1968) and Atlas (1968), but whether this association is merely fortuitous or has a causal relationship is not known.

Pre-operative diagnosis

Since there are no symptoms peculiar to this condition and when present are referable to any number of intestinal conditions, the diagnosis is difficult. Somerville (1951), while noting aerophagy in cases of Pneumatosis Intestinalis, conceded that symptoms were often those of the underlying disease. Many cases, however, are asymptomatic if unassociated with complications. Some are discovered incidentally at laparotomy for some other condition, or at post mortem. While sometimes sigmoidoscopy is sufficient to diagnose cysts of the descending colon, radiographic studies are the best diagnostic aid available. Plain X-rays of the chest and abdomen reveal lesions of the hepatic and splenic flexure as small gas shadows adjacent to or superimposed on the air in the colon; sometimes in abdominal films in the erect position, the cysts appear as grape-like clusters of air shadows, the walls of the intestine being delineated by a double-contoured line. (Paris 1955). Evidence of pneumoperitoneum, in the absence of bowel perforation may be pathognomonic of gas cysts. In the absence of obstruction, films after a barium enema reveal gas cysts as discrete cystic translucent areas indenting the intestinal wall as a series of filling defects of varying sizes. Sometimes the barium obliterates the cysts and characteristic findings are seen in post-evacuation films as cysts or as linear radiolucent stripes along the intestinal margin.

Progress and Termination

From the case reports of Jones (1948), Griffiths (1955) and Moore (1968), there is some evidence to suggest that Pneumatosis Intestinalis is insidious in onset. Though spontaneous disappearance of the cysts is possible as suggested by some — Koss (1952), Doub & Shea (1960) however, reported one case where there was complete resolution within 5 years. Untreated, the cysts may increase in number, causing various types of intestinal obstruction and pneumoperitoneum. Griffiths (1955), reported a case with severe obstructive symptoms in whom resection of the affected bowel segment was followed by an asymptomatic and satisfactory follow-up period, indicating that Pneumatosis Intestinalis is probably self-limiting.

SUMMARY

Pneumatosis Intestinalis is a rare condition characterised by the presence of gas-filled cysts in the submucosal, the subserosal or both the layers of the intestine. The paucity of such reports in the literature prompted us to place this on record and it is felt that this should be considered in the differential diagnosis of chronic or acute gastro-intestinal diseases. A brief review of the literature, touching upon certain important aspects such as pathogenesis and pre-

-operative diagnosis, has been made.

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PRIMARY MUCOCUTANEOUS HISTOPLASMOSIS

by *A. K. Dutt*

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FEW CASES of primary mucocutaneous histoplasmosis were reported in the literature. Two such cases are illustrated here.

Case report

A Chinese male, aged 56 years, was seen on 28.4.66 with cough and hoarseness of voice of 10 days' duration. He was a hospital sweeper. Roentgenogram of chest revealed patchy wooly opacities in both upper, and left middle zones. The lesion was thought to be tuberculosis of lungs. Repeated sputum smear and culture for acid-fast bacillus were negative. He received a course of anti-tuberculosis therapy, followed by disappearance of shadows of both lungs. In June, he developed few nodules on the dorsal surface of the tongue. Subsequently, these nodules coalesced and formed a large painful ulcer with irregular raised margin (fig. 1). Cervical lymph nodes were not palpable. He received a course of penicillin therapy on the basis of positive Kahn test but there was no improvement of the ulcer. On 3.7.66., histological section of ulcer of tongue showed diffuse granulomatous inflammation with massive infiltration of histiocytes containing clusters of *Histoplasma capsulatum* in the submucosa (fig. 2 & 3). Sputum smear and culture for histoplasma were negative.

In August, he presented few umbilicated nodules on the skin of flexor surface of both elbows (fig. 4). After few days, they became ulcerated. Then few fresh nodules appeared inside the cheeks and around the ulcer of the tongue. Histological section of the forearm nodule showed granulomatous lesion caused by *H. capsulatum*.

On 5.10.66., amphotericin B was administered and continued till 16.10.66. when it was withdrawn due to the development of toxic symptoms. There was remarkable improvement of the oral and cutaneous lesions but he died on 23.10.66.

Discussion

Histoplasmosis caused by the fungus called *Histoplasma capsulatum* has world-wide distribution but is particularly endemic in certain zones of North America. Few cases of histoplasmosis have been reported from Southeast Asia. 15 cases of histoplasmosis from Thailand, 6 cases from Indonesia, 7 cases from Malaysia and one case from Singapore have been documented (Ponnampalam, 1968). Symmers (1966) found 7 cases of ulcerative histoplasma lesions of mouth, throat, anus or vulva occurring among South-east Asians.



Fig. 1: Mucosal histoplasmosis. Note ulcerative nodular lesion on dorsal surface of tongue.

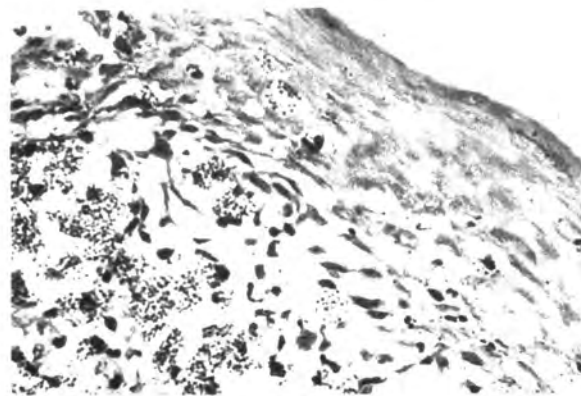


Fig. 2: Clusters of histoplasma capsulatum are seen in mucosa and submucosa of tongue (hematoxylin and eosin x 160).

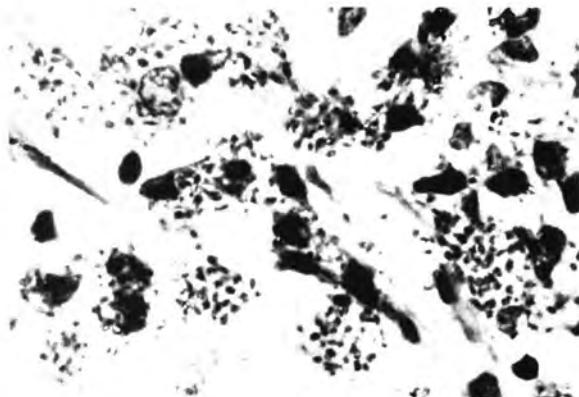


Fig. 3: Higher magnification of Fig. 2, showing histiocytes containing histoplasma capsulatum (hematoxylin and eosin x 1025).



Fig. 4: Cutaneous histoplasmosis. Note ulcerative nodular lesion on flexor surface of both elbows.

Histoplasma capsulatum has been isolated from the soil, dust, air and animal excreta particularly of chickens: it has been found in old silos and caves. There are a number of clinical types of histoplasmosis which are diverse in their manifestations. These are:

- (1) subclinical infection,
- (2) localised primary pulmonary,
- (3) diffuse primary pulmonary,
- (4) localised mucosal or intestinal infection,
- (5) disseminated infection,
- (6) subacute primary infection,
- (7) epidemic histoplasmosis, and
- (8) reinfection histoplasmosis.

The vast majority of histoplasma infection are subclinical or at least produce symptoms which could not be differentiated from mild intercurrent bacterial or viral infection (Smith, 1963).

Localised mucosal infection may result from local infection in the ear, nose, pharynx, larynx, lip, penis: the localised infection may at times be local manifestations of a systemic invasion (Smith, 1963). Ponnampalam (1968) in his series observed that, of 7 cases of histoplasmosis, 6 involved oral cavity, and one occurred in the socket after extraction of teeth. Sometimes histoplasmosis may complicate tuberculosis, sarcoidosis, Hodgkin's disease, leukaemia and immunosuppressive disorders. Diagnosis of histoplas-

mosis is established by skin test, precipitation and complement-fixation tests, culture of sputum, bronchial aspirate and gastric lavage, and histological examination of tissues stained by P.A.S. or Grocott's method. Amphotericin B is the treatment of choice for progressive pulmonary, disseminated or acute localised lesion. Most pulmonary lesions are benign. Disseminated disease, if left untreated, is usually fatal.

Summary

A rare case of primary mucocutaneous histoplasmosis is described here. We are not aware of such cases being reported from Malaysia.

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Sarcoidosis among Chinese in Malaysia:

with a report of 10 cases

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Introduction

IT SEEMS from the study of voluminous literature on sarcoidosis that the condition is less common in Asians than Europeans and white Americans. Ten cases of sarcoidosis are reported here. Most of them occurred in mediastinal and peripheral lymph nodes. One case was associated with leprosy, one with facial paralysis and one with arthritis. Sarcoidosis is extremely rare in the Chinese race as evidenced by the report of only 3 cases in the literature to date. We could not find a single case of sarcoidosis among Chinese in Malaysia and Singapore from the exhaustive search of literature. This paper draws attention to the fact that, of 10 cases of sarcoidosis, 3 occurred in Chinese.

Hutchison (1898), Besnier (1889) and Boeck (1899), as quoted by Mayock et al (1963), were credited with earlier descriptions of sarcoidosis. Sarcoidosis is a multisystem disease of world-wide distribution. The cause of the condition is obscure. Terris and Chaves (1966) failed to demonstrate association of sarcoidosis with tuberculosis and pine pollen after analysing 240 histologically — confirmed cases. James (1967) postulated that hyporeactivity of immunologically — competent lymphocytes to various antigens might produce sarcoid granuloma in the body. Ten histologically — confirmed cases of

sarcoidosis are reported here.

Brief report of cases

Case I: 59-year-old Chinese woman had cervical lymphadenopathy since birth. Biopsy of lymph node showed sarcoid granuloma. (Fig. 1, 2 & 3)

Case II: 21-year-Chinese male was seen with cervical lymphadenopathy of 3 years' duration. Biopsy of lymph node showed sarcoid granuloma. (Fig. 4 & 5)

Case III: 29-year-old Malay male was asymptomatic. On routine roentgenogram of chest, mediastinal lymphadenopathy was found. Biopsy of lymph node showed sarcoid granuloma.

Case IV: Routine X-ray of chest of an Indian woman, aged 16 years, revealed mediastinal lymphadenopathy. Biopsy of lymph node showed sarcoid granuloma.

Case V: A 28-year-old Malay woman presented recurrent polyarthritis of 2 years' duration. Subsequently, she developed nodular skin eruptions, mediastinal and cervical lymphadenopathy. Biopsy of skin nodule showed sarcoid granuloma.

Case VI: 33-year-old Indian woman developed cervical and axillary lymphadenopathy. Chest X-ray was normal. Biopsy of lymph node showed sarcoid granuloma.

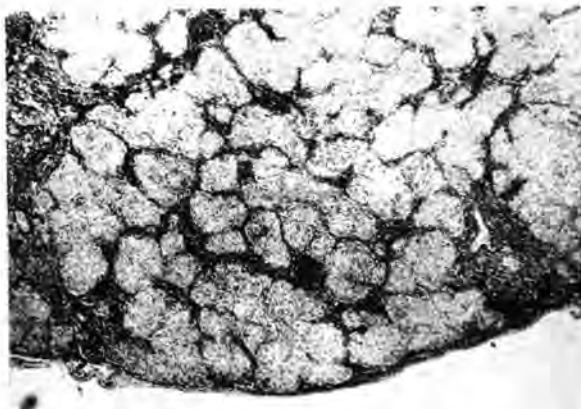


Fig. 1: Extensive uniform sarcoid granuloma of lymph node (hematoxylin and eosin x 65).

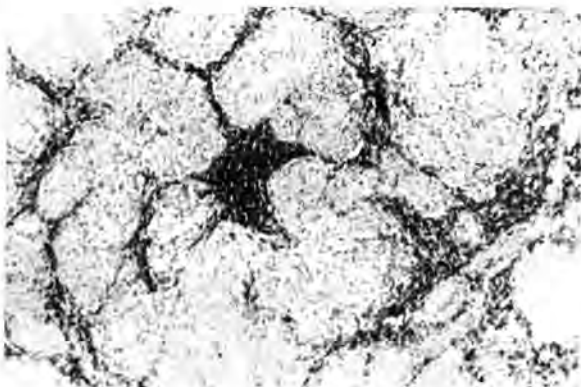


Fig. 2: A group of coalescent sarcoid granulomas of lymph node (hematoxylin and eosin x 160).

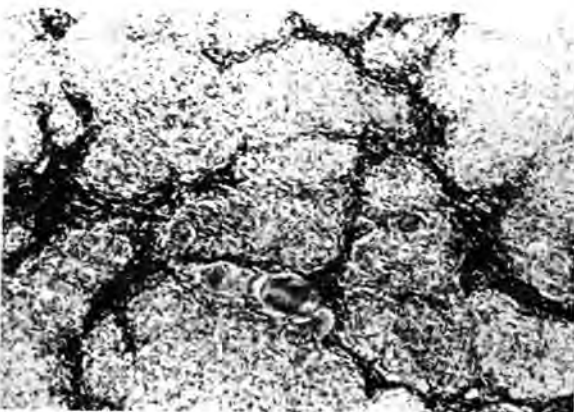


Fig. 3: Few foreign bodies and Langhan's type of giant cells in sarcoid granuloma of lymph node (hematoxylin and eosin x 160).

Case VII: Malay male, aged 17 years, had cervical lymphadenopathy and left facial nerve paralysis. Biopsy of lymph node showed sarcoid granuloma.

Case VIII: 13-year-old Indian girl was seen with cervical lymphadenopathy of 6 years' duration. Biopsy showed sarcoid granuloma.

Case IX: 15-year-old Indian male presented cervical lymphadenopathy of 2 months' duration. Biopsy of lymph node showed sarcoid granuloma.

Case X: 25-year-old Chinese woman, who had lepromatous leprosy, was on sulphone therapy for a long time. Recently she developed bilateral inguinal lymphadenopathy. Biopsy of lymph node showed sarcoid granuloma. Kveim test was positive. (Fig. 6)

Discussion

Siltzbach (1965) reported that the highest prevalence rate of sarcoidosis is among the Swedish and lowest among Indians and Eskimos of Canada, and Chinese with high incidence of tuberculosis among the latter three races. Sarcoidosis among the Chinese is extremely rare. Hsing et al (1964) had not found a single case of sarcoidosis among Chinese after reviewing M.M.R. survey of 3.5 million Chinese people in Taiwan during a period of 10 years. Present and Siltzbach (1967) recognized 3 cases of sarcoidosis among the Chinese after exhaustive search of literature. However, they were unable to record a single case of sarcoidosis from the study of M.M.R. survey of 0.6 million Chinese in Singapore. It is interesting to note that we recognized 3 cases of sarcoidosis among Chinese during 4-year survey of 25,000 biopsies at the Institute for Medical Research, Kuala Lumpur. The disease usually occurs in second and third decade of life, both sexes being equally affected. Clinically, sarcoidosis may be classified into 3 types: (I) mildest and most frequent which is characterized by mediastinal lymphadenopathy, erythema nodosum, lung mottlings with 2 years' course; (II) manifested with lung mottlings, extra-thoracic lesions with 2-7 years' course, often followed by healing with residual scarring; and (III) exhibited by generalized lesions with chronic intractable course followed by 10% mortality.

According to James and Sharma (1967), sites of lesion of sarcoidosis in order of frequency are as follows: intrathoracic 84%, eye 27%, erythema nodosum 31%, other skin lesions 25%, spleen 12%, nervous system 7%, parotid 6% and bone 6%. Mayock, in his series of 1,254 cases, found peripheral lymphadenopathy in 76% of cases which fairly correspond to our finding. Occasionally, cases may be associated with

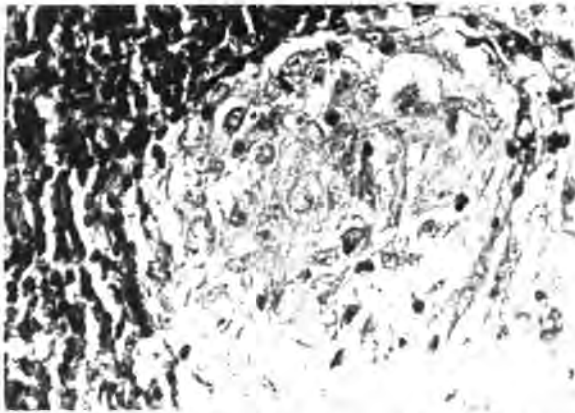


Fig. 4: An epithelioid cell granuloma of sarcoid of lymph node. Note absence of caseative necrosis (hematoxylin and eosin x 1025).



Fig. 5: Normal architecture of reticulin is maintained in sarcoid granulomas of lymph node (Gordon and Sweete x 160).

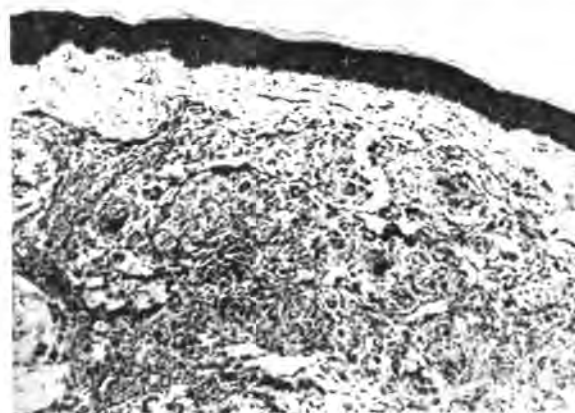


Fig. 6: Strongly positive Kveim test (hematoxylin and eosin x 160).

leprosy, arthritis and facial paralysis (Ramachandran, 1963; Maycock et al 1963). Israel (1964) observed that in most cases clinical and radiological features are not diagnostic; diagnosis is confirmed by Kveim test or biopsy.

According to International Conference of Sarcoidosis, as quoted by Kitamura et al (1967), criteria for diagnosis of sarcoidosis are classified into 4 groups; group I, both biopsy and Kveim test are positive; group II, biopsy negative or omitted but Kveim test positive; group III, biopsy positive but Kveim test negative or omitted; and group IV, both biopsy and Kveim test negative. Diagnosis of four cases was made on the basis of group III classification. Kveim test was performed in only one case. Incidence rate of tuberculin-negative cases is variable; as for instance 86% in the series of 419 cases of Maycock et al (1963) and 52% of 219 cases studied by Kitamura et al (1967).

Histologically, the lesion of lymph node, as observed by Williams (1967) is characterized by extensive uniform multiple granuloma replacing almost whole structure. There is focal infiltration of epithelioid cells without or with Langhan's or foreign body giant cells surrounded by scanty lymphocytes; central caseative necrosis is strikingly absent. Normal reticulin structure is maintained. 50–75% intrathoracic lesions, as quoted by Reisner (1967), regress spontaneously; 15–20% of cases is progressive causing irreversible organic changes with chronic disability.

Corticosteroid is the treatment of choice for the lesions of eye, disfiguring skin lesions, persistent hypercalcemia, progressive pulmonary lesion and myocardial sarcoidosis (Israel, 1964).

Summary

10 cases of sarcoidosis involving mediastinal and peripheral lymph nodes, of which 3 occurred in Chinese, are reported. Literature on sarcoidosis is reviewed with special reference to the incidence of the condition among Chinese.

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Reviews

HISTOPATHOLOGICAL DEFINITION OF BURKITT'S TUMOUR:

C. Berard and others.

**Offprint from the bulletin of the World Health
Organisation**

1969, 40, 601-607. Price 6 sh.

IN THE INTERESTS of accurate typing and diagnosis of cancers, the World Health Organization is sponsoring a series of International Classification of Tumours. The above memorandum is the most recent to be published in this series.

Since Burkitt's original description of this malignant tumour in African children, considerable confusion has arisen about its diagnosis because of semantic differences between pathologists and inaccurate interpretations of inexperienced investigators. In 1967, an international meeting was arranged by WHO in collaboration with the International Agency for Research on Cancer to draw up a definition of Burkitt's tumour, and an attempt was made to include participants representing a wide range of the differing opinions throughout the world.

Of the 18 consultants who participated in the meeting, 16 were convinced that Burkitt's tumour is indeed a pathological entity. A detailed memorandum was prepared, covering its clinical aspects and gross pathology, histo- and cytopathology, histo- and cytochemistry, and ultrastructure. A description of tumours resembling Burkitt's tumour and the differential diagnosis was added.

The memorandum was drafted by C. Berard, G.T. O'Connor, L.B. Thomas and H. Torloni on behalf of the consultants and it has been illustrated with 26 carefully chosen photomicrographs, most of which are in colour. The specimens illustrated have been fixed and stained by a variety of techniques to show the characteristic appearances and cell types of Burkitt's tumour. Two electronmicrographs are included.

Since Burkitt's tumour appears to be the commonest malignant oral tumour in children in West Malaysia and the actual incidence seems to be much more than the number of recorded cases, this

memorandum, with its detailed description of the tumour and the excellent photographs, should prove to be a valuable diagnostic tool for pathologists and a convenient handbook for paediatricians. This lowly-priced memorandum should find a ready place in the book-shelves of pathologists and paediatricians.

THE MEDICAL ANNUAL 1969

Edited by Sir Ronald Bodley Scott

K.C.V.D., M.A., F.R.C.P. and

R. Milnes Walker

C.B.E., M.S., F.R.C.S., F.A.C.S. (Hon.)

John Wright & Sons Ltd. Bristol.

644 pp. 143 illus. 63 s.

THE EIGHTY-SEVENTH ISSUE of this book of treatment has maintained its usual high standard and reviews of the year's work and brings to the medical public up-to-date information on a wide variety of diseases. There are special articles on 'The concept of alcoholism,' 'Some problems in medical care,' 'Uses of extra-corporeal circulation' and 'Indigestion'.

'Tropical Diseases' by Sir Robert Drew deals with 'Metronidazole treatment of amoebiasis', 'Malaria', 'Echinococcosis (hydatidosis)' and 'Surgical management of hydatid disease in Iraq'.

The Practitioner's Index gives short descriptions of Ethical Proprietaries and Medical and Surgical Instruments and Appliances which have been introduced during the past year. This is followed by a list of English and American medical works and new editions published during the preceding twelve months. There is a comprehensive general index, the more important articles being in heavy type.

Those who get the Medical Annual regularly need no recommendation but those who do not do so are strongly advised to get the 1969 volume; they will find it a sound investment.

VENEREAL DISEASES

by Ambrose King T.D., M.B.B.S., F.R.C.S.

and Claude Nicol T.D., M.D., F.R.C.P.

Bailliere Tindall and Cassell, Lond. 1969.

Second Edn. 340 pp. 175 illus. 75 s. nett.

IN SPITE of the availability of potent therapeutic drugs, venereal diseases continue to present serious problems of incidence, diagnosis and treatment as well as the important social problem inherent in the control of the disease. This is no doubt due to habitual promiscuity being more widespread than

formerly, especially among the younger people who lack the discipline and the care and affection of a satisfactory home life.

The book gives a comprehensive, well-written and up-to-date account of the epidemiology, pathology, diagnosis and treatment of venereal diseases which the medical student, general practitioner and venereologist will find profitable reading.

The authors include trichomoniasis, nongonococcal urethritis and Reiter's disease in this volume on the grounds that these conditions are related to sexual intercourse. The inclusion of other lesions of the genitalia should be of help in differential diagnosis. There is a chapter on the public health control of venereal disease and an appendix on routine investigation of new patients. The book is well illustrated, including 4 colour plates and 7 monochrome plates. References are included for each chapter which will give guidance for further reading. There is an adequate index.

GERIATRICS AND THE GENERAL PRACTITIONER TEAM

By M.K. Thompson

Bailliere, Tindall and Cassell, Lond. 1969.

128 pp. 4 plates. 20 s.

THE NEED for the general practitioner to be conversant with geriatric problems is becoming more obvious to-day with an ever-increasing number of people living on with age. This little book aims to awaken the interest of the reader and make him aware of the importance of subjects which he might previously have thought irrelevant.

The book had its origin in a series of tapes on geriatric care in the work of the family doctor prepared by Dr. Thompson for the Medical Recording Service of the Royal College of General Practitioners. It is a readable survey of some practical aspects, such as diagnosis and care of a subject of great importance to the practitioner. Dr. Trevor Howell has contributed a chapter for the consultants' point of view.

ELEMENTARY STATISTICS, A WORKBOOK

By K. Hope M.A., Ph.D.

Pergamon Press, Oxford. 1967.

101 pp. 25 s. net.

OUR VIEWS on this book stem from the remarks made in the Foreword that it is designed for people "who have to overcome a severe emotional block"

and that "learning to use statistics means learning to walk both ways" across the bridge between empirical science and mathematics.

The workbook does achieve its primary aim of overcoming the "emotional block" but it leaves a state of askance in the mind of the reader who is wholly unacquainted with the "numerosity" of the subject of numbers. In any case, the book can be profitably used by uninitiated students of mathematics with adequate guidance from a teacher.

However, the amount of space devoted to "Factor Analysis" exaggerates the importance given to the book title "Elementary Statistics." Those without any knowledge of mathematics are expected to be conversant after reading "Matrices", which precedes the chapter on "Factor Analysis". Though a fair amount of detail is included in "Factor Analysis", equal importance should have been given to basic sampling techniques and other methods of experimentation procedures that are conveniently used by students of the social and biological sciences.

A favourable comment may be made here of the "Bibliography" which lists the books and articles which are "clearest and easiest" for non-mathematicians. The comments accompanying the references are not only handy to non-statistical students but also to learned members of the statistical profession who are called upon to solve problems in fields beyond their competence.

DISEASES THAT PLAGUE MODERN MAN

by Richard Gallagher

Oceana Publications, Inc. New York 1969

288 pp. US \$6.00

THIS IS an interestingly written history of ten communicable diseases that still afflict man; they are: cholera, influenza, leprosy, malaria, bilharziasis, onchocerciasis, plague, smallpox, syphilis and tuberculosis. It retraces from the earliest times to the present, the history covering the misconceptions, epidemics, and the economic and social significance of each disease. It is essentially addressed to the layman but is nevertheless accurate and informative and should appeal to health officers also. It contains a number of unusual early illustrations which enhance its interest to the reader.

It is pointed out that an area's health involves food, clean water, education, disease prevention, therapy and control. The prosperous countries can usually provide these for themselves but the nations most in need are least able to help themselves, but to

be effective, what is done in one country must be done in neighbouring areas as well. Our hope lies in international health effort and an account is given of the scope of the work carried out by WHO — our only hope.

**THE MEDICAL JOURNAL OF MALAYA (add)
"AN INTRODUCTION TO HUMAN PHYSIOLOGY"**

by J. H. Green
2nd Edition

Oxford University Press, London
pp. 170, Illustrations 211, 28s. net.

THERE IS a considerable gap existing between the Matriculation Biology and the first year Medical Physiology courses in this country. The situation is further accentuated by the scarcity of a suitable introductory book on human physiology. With the new edition of this book, a long felt need for a succinct, up-to-date account of basic physiologic knowledge within a brief compass may perhaps be filled. Written in a simple, concise manner and unobscured by controversy, this book provides the fundamental concepts of human physiology to which additional knowledge or interests may be added by consulting the more detailed and elaborate texts or original papers. Despite its simplicity, a reasonable level between main facts and fine detail has, nevertheless, been maintained. The idea of inserting simplified accounts of many new laboratory techniques to integrate the practical experiments with the theory is excellent and stimulating.

Two new chapters "Respiration and hydrogen ion concentration" and "The control of respiration" have been added in this edition. Updated information on phonocardiography, auto-immunity, DNA, hepatic insufficiency, renal failure, thyrocalcitonin, brown adipose tissue, EEG, synapse, nerve cell potentials and the function of the hypothalamus, has been included. though this book is too concise to be acceptable as a major textbook for medical students, nevertheless, as an introductory, it is highly recommended.

"BASIC CLINICAL PHYSIOLOGY"

by J. H. Green

Oxford University Press, London
pp. 135 Illustrations 169 25s. net.

THIS BOOK is written by the same author of "An Introduction to Human Physiology" and bears many resemblances to its antecedent, both in its content

and in its style of writing, aided by profuse and comprehensive illustrations. As this book is meant for the student nurses in the study of human physiology, it is more simplified and the emphasis is basis upon the integration with the clinical medicine. For the requirements laid down in the statutory syllabus for general nursing in Malaysia, the material is more than adequate, while for those seeking more detail, it provides a sound and stimulating basis. With every confidence, this book can be certainly recommended.

T. T. Loh

BRITISH MEDICAL BULLETIN
Publ. by the British Council. Lond. 1969 £2.

NEW ASPECTS OF HUMAN GENETICS.

Vol. 25, No. 1, Jan. 1969.

Edited by C.E. Ford and H.Harris, 118 pp.

THE 16 PAPERS included are by 19 leading geneticists, who cover common malformations and common disorders as well as thalassaemia, haemocystinures and porphyria. They provide critical reviews of work accomplished and indicate fruitful lines of enquiry. The symposium was planned by a Committee headed by the late Professor W.M. Court-Brown and edited by Dr. C.E. Ford F.R.S. and Professor H. Harris F.R.S. Professor L.S. Penrose has written an illuminating introduction.

IMMUNIZATION AGAINST INFECTIOUS DISEASES

Edited by D.G. Evans. 100 pp.

Vol. 25, No. 2, May 1969.

PROFESSOR D.G. EVANS F.R.S. was chairman of the Committee which planned this comprehensive symposium and assembled a group of 17 eminent British scientists to elucidate the problems of immunization. They have tried to evaluate the results of current research and point out the perplexities and problems of interpretation and pinpointed the lives along which future research may most profitably proceed. The Scientific Editor was Professor Evans who summarises the achievements in a challenging introduction.

MECHANISMS OF TOXICITY

Edited by W.N. Aldridge

94 pp. Vol 25 No.3 Sept. 1969.

DR. J.R. BARNES who writes the introduction has brought together 23 specialists to discuss the various

aspects of the mechanisms of toxicity in this symposium. This is a valuable contribution, especially at the present time, when there is much concern about toxic hazards in the human environment. Of particular

interest to the medical man are the discussions on the metabolism of toxic substances, diet and toxicity, toxic activities of microbes and actions of some toxic substances on the CNS.

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