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Review

THE EPIDEMIOLOGY AND CHEMOTHERAPY OF SCHISTOSOMIASIS AND OTHER SNAIL-BORNE TREMATODE INFECTIONS

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Abstract: The different life cycles of the human digenetic parasitic trematodes *Schistosoma japonicum*, *S. mansoni*, *S. haematobium*, *Clonorchis sinensis*, various species of the genera *Opisthorchis* and *Paragonimus*, and those of lesser pathogenic importance, *Fasciolopsis buski*, *Heterophyes heterophyes* and *Metagonimus yokogawai*, illustrate the complexity of the clinico-epidemiological profiles of these syndromes.

The one factor common to all of infections is the necessity of a primary snail intermediate host to complete the biological life cycles: some additionally require a secondary intermediate host which may be several species of fresh-water fish, crustaceans or aquatic plants. Conversely, the mode of transmission to man varies from dermal penetration of infective cercariae in the schistosome infections, to the consumption of infective metacercariae in raw or undercooked cyprinoid fresh-water fish in clonorchiasis and opisthorchiasis and the eating of fresh-water crabs or crayfish in paragonimiasis or the ingestion of water caltrop, water chestnut and bamboo in fasciolopsiasis.

Yet, despite these variations, several general common features characterize the different epidemiological cycles:—

1. the prevalences of the infections are highest in rural populations, frequently higher in males, commonly occurring in the younger age-groups and the distributions all follow the inverted binomial pattern, itself characteristic of those infections in which there is no replication of a parasite population within the human host;
2. an important feature of their propagation is the indiscriminate disposal of human faeces in areas deficient in sanitary provisions or in the use of "night soil" where this practice remains part of the prevailing agricultural pattern;
3. transmission in all of these infections is via human behavioural variables— either obligatory water-contact in the case of the schistosomes, or age-old eating habits in the other trematodiasis— human attitudes and customs which are extremely difficult to alter and which are often resistant to conventional health education;
4. animal reservoirs of infection are, with the exception of *S. haematobium*, extremely common.

It thus appears inherently improbable that complete eradication of these infections by the permanent interruption of transmission will be achieved on a global scale— at least in the immediate future and certainly not before the year 2000.

Since schistosomiasis is the major globally-distributed example of the human trematode infections, it will be taken as an example of the linkage between epidemiological analysis and control strategy and will be dealt with in greater detail than the other trematode infections which, nowadays, are of greater regional than global

significance.

The control of schistosomiasis will be covered under the headings of objectives, minimal requirements for the planning of control, epidemiological, parasitological and biological techniques in current use, the concept of an "integrated" approach with emphasis on population-based chemotherapy to reduce human morbidity, the importance of the chemotherapeutic "delivery system", the principles of health care and participation in and by the community, the analytical framework necessary for decisions on follow-up action, the importance of primary health care in control and the constraints experienced in the management of operations.

A discussion on the drugs available for chemotherapy of trematode infections is incorporated into the epidemiological section of the control approach.

INTRODUCTION

It has been estimated that parasitic infections are the most widespread of all major diseases, currently affecting about 3×10^9 people in the world, innumerable domestic animals and a high proportion of plant growth.

The depressingly high prevalence rates of parasitic infections in man have several common, yet general determinants, including poverty, inadequate or absent sanitary facilities, absence of safe drinking water supplies, ignorance of health-promoting practices, high birth-rates and persistent deleterious human behavioural patterns such as indiscriminate defaecation or urination or unchanging age-old eating habits. Above all, the prevailing socioeconomic factors and the existing ecological conditions are favourable to the many vectors or intermediate hosts that transmit infection to man.

In epidemiological terms, many of the parasitic infections are advancing in the "Third World", not receding, and this is occurring despite the technological revolution of the 20th century. The problems lie less in the areas of diagnosis and treatment than in the low priority which the governments of endemic countries and governing bodies of international organizations accord to the control of parasitic diseases when faced with a multiplicity of often competing health problems, constrained— and finite— financial resources and an extreme shortage of skilled and knowledgeable personnel. There exists a great need to convince governments of the importance of the burdens, in both human and economic terms, resulting from the chronic sequelae of parasitic diseases.

THE EPIDEMIOLOGY OF THE SNAIL-BORNE TREMATODE INFECTIONS

The different life-cycles of the human digenetic parasitic trematodes *Schistosoma japonicum*, *S. mansoni*, *S. haematobium*, *Clonorchis sinensis*, various species of the genera *Opisthorchis* and *Paragonimus*, and those of lesser pathogenic importance, *Fasciolopsis buski*, *Heterophyes heterophyes* and *Metagonimus yokogawai*, illustrate the complexity of the clinico-epidemiological profiles of these syndromes.

The one factor common to all of these infections is the necessity of a primary snail intermediate host to complete the biological life-cycle; some additionally require a secondary intermediate host which may be several species of fresh-water fish, crustaceans or aquatic plants. Conversely, the mode of transmission to man varies from dermal penetration of

infective cercariae in the schistosome infections, to the consumption of infective metacercariae in raw or undercooked cyprinoid fresh-water fish in clonorchiasis and opisthorchiasis and the eating of fresh-water crabs or crayfish in paragonimiasis or the ingestion of water caltrop, water chestnut and bamboo in fasciolopsiasis.

Yet, despite these variations, several general common features characterize the different epidemiological cycles:

1. The prevalences of the infections are highest in rural populations, frequently higher in males, commonly occurring in the younger age-groups and the distributions in man all follow the inverted binomial pattern, itself characteristic of those infections in which there is no replication of a parasite population within a human host.
2. An important feature of their propagation is the indiscriminate disposal of human faeces in areas deficient in sanitary provisions or in the use of "night soil" where this practice remains part of the prevailing agricultural pattern.
3. Transmission in all of these infections is via human behavioural variables— either obligatory water-contact in the case of the schistosomes, or age-old eating habits in the other trematodes— human attitudes and customs which are extremely difficult to alter and which are often resistant to conventional health education.
4. Animal reservoirs of infection are, with the exception of *S. haematobium* and to a lesser extent *S. mansoni*, extremely common.

It thus appears inherently improbable that complete eradication of these infections by the permanent interruption of transmission will be achieved on a global scale— at least in the immediate future and certainly not before the year 2000. The unique smallpox example, which possessed special biological characteristics and determinants cannot be used to extrapolate unrealistic prospects for the eradication of the majority of other bacterial, viral, protozoal, helminthic, rickettsial or fungal diseases. Most of the parasitic diseases are transmitted by vectors or intermediate hosts, the global control of which, in blunt terms, has been unsuccessful and has led to a general diminution of enthusiasm for the use of insecticides, pesticides or molluscicides on the very large scale necessary for success on a global scale.

All of these factors have slowly led to a generally accepted practical definition of "control" in both medical and epidemiological terms. "Control" means the reduction of the prevalence and intensity of parasitic infections to levels which do not constitute public health hazards and this achievement will imply the parallel reduction of infection incidence and, in turn, a decline in human morbidity and mortality produced by these infections.

Since schistosomiasis is the major globally-distributed example of the human trematode infections, it will be taken as an illustration of the linkage between epidemiological analysis and control strategy and will be dealt with in greater detail than the other trematode infections which, nowadays, are of greater regional than global significance.

SCHISTOSOMIASIS

Of all the human parasitic infections, schistosomiasis is one of the most widespread and is second only to malaria in socioeconomic and public health importance in tropical and subtropical areas.

Caused by a complex of parasites, transmission to man is through different species of

fresh-water snails in a wide variety of habitats. Five different parasites, at least, are epidemiological entities and affect different organ systems and functions of the body (*S. japonicum*, *S. mansoni*, *S. haematobium*, *S. mekongi* and *S. intercalatum*).

People maintain the life-cycle by contaminating the environment through indiscriminate defaecation or urination. In some areas, particularly where *S. japonicum* is endemic, infection in animals is important epidemiologically.

The infection is acquired through repeated contact with infected fresh-water; disease or morbidity due to schistosomiasis is caused basically by the heavy parasite loads in children who are in frequent contact with infected water. The chronic forms of disease observed in adults, including bladder cancer associated with *S. haematobium* infection, are sequelae to heavy infections acquired in childhood and repeated in adult life. Although mainly a disease of rural areas with high levels of poverty, poor housing, substandard hygiene and lack of sanitary facilities or adequate water supplies, some urban centres in endemic countries may show high prevalences of schistosomiasis. The risk of spread and the intensification of transmission of schistosomiasis is well recognized within expanding agricultural, hydroelectric and other water-resource development projects in endemic areas. In refugee settlements of South-east Asia and Africa, schistosomiasis is recognized as a public health problem.

Now endemic in 74 countries in the world, it is estimated that more than 200 million persons living in rural and agricultural areas are infected with schistosomiasis and that between 500 and 600 million people are exposed to infection because of poverty, ignorance, poor housing, substandard hygienic practices and the availability of few, if any, sanitary facilities.

In the earlier years of this century, *S. japonicum* infection in man occurred in six countries, but is found today only in China, Indonesia and the Philippines. Infection with *S. mekongi*, a close relative of *S. japonicum*, has been detected in two South-east Asian countries.

S. haematobium infections are endemic in 52 eastern Mediterranean and African countries, while *S. mansoni* occurs in 53 countries ranging from the Arabian peninsula to Brazil, Suriname, Venezuela and certain Caribbean islands. In 40 countries, double infections with *S. mansoni* and *S. haematobium* are endemic. *S. intercalatum* causes a form of human intestinal schistosomiasis reported infrequently from 6 central or West African countries. Reports of new locations of infection appear from time to time such as the appearance of *S. haematobium* in an irrigation development in Sao Tomé and Príncipe and the recent presence of *S. mansoni* in Niger and Oman. Even within ancient areas of endemicity, the spread of parasitism is not uncommon and a good example is the insidious advancement of *S. mansoni* from the Nile Delta up the river to the governorate of Aswan where cases, and snails, are found. This curious phenomenon is all the more intriguing since *S. mansoni* has never been detected south of Cairo from prehistoric times and the association in time of spread with the changes in water usage patterns induced by the construction of the Aswan High Dam Lake must make a causal role of the dam at least suspect, if not proven.

The epidemiology of schistosomiasis is not necessarily uniform within an endemic country and it cannot be compared between countries. For example, water-resource development schemes can change the epidemiology from seasonal and highly focal transmission into intense, widespread and continuous transmission in a surprisingly short space of time.

The summarized epidemiological profiles of the human element of the total picture,

which of course involves the snail distributions and species and the ecological backgrounds, are as follows:

In *S. mansoni* endemic areas, the prevalence of infection is greatest in the 10-24 year age-range. Prevalence in older age groups remains at higher levels than is the case in *S. haematobium* infections. A small proportion of the infected population excretes at least 50% of the total number of eggs contaminating the environment and most of these heavily infected people are between 10 and 15 years of age. A high proportion of children with elevated *S. mansoni* egg counts (over 800 eggs per gram of stool) have enlarged livers and/or spleens, irrespective of the endemicity of malaria.

In *S. haematobium* the peak prevalence and intensity of infection occurs in children aged 10-14 years with a rapid diminution in older age groups. As a generalization, 60-70% of all infected persons are in the age-range 5-14 years. In both children and adults, increasing haematuria and proteinuria parallel increasing intensities of infection with rising egg outputs. The well-known radiological changes which occur range from calcified bladders through ureteral deformities to hydronephrosis tend to be associated with heavy infections in children. In several studies haematuria detectable by reagent strips occurred in 98-100% of children with egg outputs of over 50 eggs per 10 ml urine, thus providing a useful field substitute for microscopy.

There is no typical age prevalence and intensity distribution in *S. japonicum* infection. Bimodal age prevalence curves with peaks in the 10-14 and 35-44 years age-groups have been reported.

A STRATEGY FOR CONTROL OF SCHISTOSOMIASIS

The major objective of the prevention and control of schistosomiasis is the reduction of human morbidity and mortality to levels below public health importance. Public health workers have frequently feared that unless schistosomiasis transmission has been stopped, a control programme cannot be declared a success. That this attitude is unrealistic is not in doubt; the high endemicity levels existing in many parts of the world, the socioeconomic deficiencies accompanying the widespread scarcity of sanitary facilities, the general lack of provision of rural potable water supplies and the pervading low standards of health education at even the most elementary levels make it plain that eradication of schistosomiasis is a non-realistic goal in the immediate future.

A strategy of control of morbidity caused by schistosomiasis can be implemented by increased emphasis on health education, large-scale population-based chemotherapy, provision of water supplies and sanitation and the integration of control activities into basic health services. Health education is promoted at the community level through the health services in coordination with the general education system. The effective, safe and well-tolerated drugs praziquantel, metrifonate and oxamniquine, all given by mouth, are now included in many national drug lists and drug policies. The capability for diagnosis of parasitic diseases, including schistosomiasis, should be an essential activity of peripheral health laboratories in endemic countries. In parallel with reductions in prevalence and intensity of infection, the role of snail control and environmental management, water supplies and sanitation are becoming more precisely targeted at an achievable level. Reductions of disease due to schistosomiasis can be attained within the known limitations of each endemic country. As the

epidemiology of schistosomiasis varies from one country to another, so will vary the managerial and operational structures of schistosomiasis control. The simplicity of the current microscopic diagnostic techniques, the ease and safety of standard dosage with orally given antischistosomal drugs and the limited use of snail control measures as required by epidemiological criteria derived from precise data collection and analysis permit schistosomiasis control activities to be adapted and introduced at any level of the health care delivery system.

The basic justifications for control of schistosomiasis, which are always demanded by financing bodies or decision makers at the political level are directed towards two primary concepts:

1. The direct reductions in human morbidity and mortality produced by a simple, well-tried technology which is affordable even by the poorest countries.
2. The use of the control of schistosomiasis as a tool in acceptance by rural populations for entry into other health-related activities, e.g. personal hygiene, environmental sanitation and improvement, health education, maternal and child care; in other words, the mechanics of primary health care. Considerable social benefits can be anticipated from control and, administratively, a not inconsiderable reduction in funds spent on medical care of infected people will benefit a national health budget, thus allowing a redeployment of resources towards other immediately pressing problems (Davis, 1989).

CHEMOTHERAPY IN THE CONTROL OF SCHISTOSOMIASIS

Since the most important and immediate control tool for the reduction of human morbidity in schistosomiasis is population-based chemotherapy, it is essential to consider its use within an epidemiological context and the appreciation that chemotherapy, although predominant in control, is certainly not the only public health intervention of value.

Whatever strategy variant is adopted, the next step is to proceed to the tactics of attack. Tactics are less a matter of medical practice than of medical administration within a national, regional or local health service background and this comprises the health delivery system to the public.

Success in an integrated approach to control depends essentially on an accurate ecological diagnosis, that is, a diagnosis of the human community, its epidemiological and parasitological characteristics, the physico-geographical environmental attributes, the biological properties of the transmitting snails in the broadest sense and man's behavioural attitudes and customs; these may be crucial to the success or failure of control.

The principles of community health care which can contribute to the control of schistosomiasis have been laid out (Davis, 1981) and comprise:

1. The use of accurate demographic and epidemiological survey methods to define the numerator of infections over the population denominator and to describe the age-specific prevalence and infection-intensity profiles.
2. The use of sensitive and specific parasitological techniques to demonstrate and quantify a specific infection. Nowadays, the cellophane thick smear, the Kato technique, or one of its numerous modifications, has become a standard diagnostic tool in epidemiological studies and has much to commend it in those schistosome infections where eggs are excreted in the faeces. In the diagnosis of *S. haematobium*, recent years have seen the

replacement of simple sedimentation or centrifugal techniques by filtration and currently urine samples are passed through filter paper, polycarbonate or polyamide by a variety of syringes or pumps. The principle common to all is that eggs are retained on the filter and can be stained and counted. On filters made from polycarbonate or polyamide, staining is unnecessary.

3. The necessity of community participation. The pioneering efforts of the Japanese Organization for International Cooperation in Family Planning, or JOICFP, in the control of intestinal parasites cannot be too highly praised for the example shown in mobilizing community participation.
4. The employment of population-based chemotherapy. The use of chemotherapy in control requires a clear definition of aims, selection of the most appropriate chemotherapeutic agent, decisions on the dosage and time-frame to be followed and the organization of the delivery system.

The aims of chemotherapy are twofold: to eradicate or control the infection in the patient as an individual and, in endemic areas, to benefit the community in which he lives. In the individual patient, successful treatment will prevent further deposition of eggs by female flukes and, since eggs are the pathogenic agents in the tissues, existing lesions will regress and future tissue damage will be prevented. For the community, the cessation of egg excretion will block the egg/miracidium/snail stage of the biological cycle, thus effectively reducing, or, on rare occasions, controlling transmission.

A quiet revolution has occurred in the treatment of schistosomiasis in the last twenty years. Up to the mid-1960's, trivalent antimony drugs were the cornerstone of antischistosomal chemotherapy. Since then, niridazole, metrifonate, hycanthone, oxamniquine and praziquantel have all come into clinical use and this advent of highly effective, well-tolerated chemo-therapeutic agents has provided physicians with flexibility and opportunities for curative treatment which were simply unheard of 20 years ago.

The major antischistosomal agents in current use are all on the WHO List of Essential Drugs. One important reservation must be noted; the success of this last generation of antischistosomals has had the paradoxical effect of reducing the efforts made by the pharmaceutical industry in research on new drugs against schistosomiasis. Two newcomers, amoscanate and oltipraz, although highly effective as schistosomicides, have failed to survive toxicological screens and there are no promising candidates on the horizon. This should be borne in mind for it cannot be claimed that resistance will not appear as a problem in future. In fact, although resistance to oxamniquine has been documented, fortunately it has not become a public health problem to date.

INDIVIDUAL ANTISCHISTOSOMAL DRUGS

Praziquantel:

Undoubtedly the most important advance of recent years in anthelmintic chemotherapy has been praziquantel. With few significant side effects, not adverse reactions on liver, renal, haemopoetic or other body functions, it is highly effective in all schistosome infections, the majority of other snail-borne trematode infections and a great variety of cestode infections.

Chemically (2-cyclohexylcarbonyl-1,2,3,6,7,11b-hexahydro-4H-pyrazino [2,1-alisoquinoline-4one), this broad-spectrum anthelmintic was derived from a novel heterocyclic

system. Extensive animal experimentation revealed high therapeutic activity over a wide range of helminths and currently, activity is known to exist in man against all schistosomes, *Clonorchis sinensis*, *Opisthorchis* spp., *Paragonimus* spp., *Metagonimus yokogawai*, *Fasciolopsis buski*, *Heterophyes heterophyes* and the cestodes, *Taenia solium*, *T. saginata*, *Hymenolepis nana*, *Diphyllobothrium latum* and *D. pacificum*. Of particular importance is its effect in human cysticercosis, both dermal and neurocysticercosis. A wide variation of therapeutic results have been reported against *Fasciola hepatica* and it is ineffective in the human secondary larval stage of *Echinococcus* infections.

In the customary pharmacological screening tests the profiles of action and toxicity were satisfactory in rats, beagle dogs, sheep and rhesus monkeys. In man, praziquantel is rapidly absorbed after oral dosage, and, after a pronounced first-pass biotransformation process, metabolites are excreted mainly in the urine. In healthy volunteers, maximum serum concentrations are reached in one to two hours. By the use of an isotope-measuring technique with ^{14}C -labelled praziquantel and a specific gas chromatographic assay, the elimination half-life of the drug from the serum was 1-1.5 hours and that for praziquantel plus metabolites was 4-5 hours. The renal elimination half-life for praziquantel plus metabolites was 4 to 6 hours and the cumulative renal excretion of praziquantel within 4 days was over 80% of the dose, 90% of which was eliminated on the first day after dosing (Buhning *et al.*, 1978; Leopold *et al.*, 1978).

The results of toxicological studies were reviewed comprehensively by Froberg (1984) who noted a lack of systemic toxic effects, a lack of adverse effects on mammals and their progeny and a lack of embryotoxicity. Extensive mutagenicity and full carcinogenicity studies failed to indicate any mutagenic or carcinogenic potential (Bartsch *et al.*, 1978; Ketkar *et al.*, 1982).

Praziquantel is active against schistosomes both *in vitro* and *in vivo*. In *in vitro* experiments, schistosomes instantly become immobile and undergo contraction on contact with the drug. A serum concentration of $0.3\ \mu\text{g/ml}$ is fully effective; one of $0.1\ \mu\text{g/ml}$ is without effect. When schistosomes are kept in culture media containing a little protein, all concentrations of drug above $0.04\ \mu\text{g/ml}$ are effective. It seems that the contraction of the schistosome musculature is due to an interference by praziquantel with inorganic ion transport mechanisms, resulting in a decreased influx of K^+ but an increase in influx of Ca^{2+} and Na^+ into the worms (Pax *et al.*, 1978).

In parallel with these biochemical studies, scanning and transmission electron microscopy of *S. mansoni* after *in vitro* exposure to concentrations of praziquantel ranging from $0\text{-}100\ \mu\text{g/ml}$ for times varying from 5 to 60 minutes has shown that the drug causes vacuolisation of the schistosome tegument, finally leading to the disruption of the apical tegumental layer (Becker *et al.*, 1980). This appears to be a direct and primary effect of praziquantel, not only on schistosomes, but also on cestodes which are sensitive to the drug. Glucose uptake of schistosomes, and hence lactic acid production, is reduced by praziquantel and the worm compensates by breakdown of its endogenous glycogen store. Egg formation in the female is inhibited at concentrations as low as $0.001\ \mu\text{g/ml}$ and totally inhibited at $0.01\ \mu\text{g/ml}$.

Thus the mode of action of praziquantel can be summarized as an extremely rapid and major alteration in energy support systems and neuromuscular functions of the worms at extremely low concentrations ($10^{-7}\ \text{M}$), followed by tegumental damage, an immunological

event which presents both internal metabolites and previously hidden and inaccessible antigenic sites to the enveloping blood stream. Phagocytes and granulocytes are attracted to the damaged tegument, fibroblastic encapsulation occurs and a rapid total disintegration of the schistosomes ensues (Senft, 1989). The precise molecular sequence of events remains under investigation.

Cooperative multicentre clinical trials of tolerance to praziquantel and of its therapeutic effect against the three common species of schistosome infecting man were conducted jointly by the Parasitic Diseases Programme of the World Health Organization and the manufacturing company (Bayer AG, Federal Republic of Germany) in Africa, Brazil, Japan and the Philippines. Double-blind trials of tolerance were followed by clinical trials of efficacy using a standard trial design and agreed technical protocols, although parasitological methods of therapeutic assessment varied with the species of infecting parasite (Davis and Wegner, 1979; Davis *et al.*, 1979; Ishizaki *et al.*, 1979; Katz *et al.*, 1979; Santos *et al.*, 1979).

In these trials, praziquantel was well tolerated, produced no changes of biological significance in a battery of haematological and biochemical monitoring tests or in serial electrocardiograms or electroencephalograms, and gave cure rates at 6 months after treatment of between 75 and 100% in the various samples of patients.

Virtually all subsequent trials have confirmed the absence of toxic effects of the drug on vital organs, systems, and functions. Side effects of treatment are generally mild and disappear within 24 hours. The most frequent symptoms reported are epigastric pain or diffuse abdominal discomfort, nausea, anorexia, loose stools or diarrhoea, dizziness, headache, pruritus or an urticarial-type of skin eruption and fever. Predictably, the proportion of those complaining of side effects varies with the ethnic origin of the patients. Abdominal pain has occurred in up to 50% of some series but is usually mild and only rarely accompanied by vomiting. With increasing experience of large-scale chemotherapy in the last few years when hundreds of thousands of patients have been treated, three groups of side effects can be distinguished as entities: (1) those related to the gastrointestinal tract as noted above and, in occasional patients with heavy infections with *S. mansoni* or *S. japonicum*, the passage of blood in the stools shortly after treatment (Polderman *et al.*, 1984). This is invariably short-lived and not aggravated by the giving of another dose of drug. (2) those symptoms related to the CNS, i.e. headache and dizziness, and (3) general symptoms of fatigue, fever, pruritus, etc. It should be stressed that in the vast majority of treated patients, side effects are mild and transient and rarely, if ever, require additional treatment.

After many years of experience, cure rates vary between 75 and 100% in different series where the characteristics of the treated groups may vary considerably and where there may be a very wide range of intensities of infection as assessed by excretal egg counts. The usual dosage used in large-scale campaigns for both *S. mansoni* and *S. haematobium* is one oral dose of 40 mg/kg; for *S. japonicum*, the current popular regimes are total doses of 60 mg/kg given either as 30 mg/kg in two doses in the day or 20 mg/kg given as three doses daily at four-hour intervals. It is noteworthy that advanced and complicated cases of *S. japonicum* or *S. mansoni* with ascites and portal hypertension tolerate the drug well.

The great majority of uncomplicated cases of schistosomiasis can be treated in the home, the out-patient clinic, the rural dispensary or the village or school— an immense advance from the practices of 20 years ago.

Other Antischistosomal Drugs:

Whilst praziquantel acts on all species of schistosome, there are two other drugs which are monospecific in their effects: metrifonate being active against *S. haematobium* only and oxamniquine against *S. mansoni* only. Metrifonate, an organophosphorus ester, was originally used as a pesticide and veterinary anthelmintic before its issue in pure form for therapeutic use in man. Its insecticidal action was due to enzymic inhibition of specific esterases in ganglionic synapses and neuromuscular junctions. In man, treatment is followed by depression of cholinesterases in both red cells and plasma but there is no correlation between cholinesterase depression and any post-treatment symptoms. It appears that metrifonate, in man, undergoes a chemical transformation, unrelated to enzymatic metabolism, into dichlorvos (DDVP 2,2-dichlorovinyl dimethyl phosphate) which is the actual cholinesterase inhibitory substance. Metrifonate acts as a slow-release mechanism for formation of DDVP. Although metrifonate has some activity against *S. mansoni* it is not normally used for the treatment of this species. It also has activity against hookworms, ascariasis, trichuriasis, creeping eruption, onchocerciasis and in cysticercosis but is rarely used since efficacy is inconstant. The sole activity for use is *S. haematobium* infection. Very widely used in millions of patients, it is well tolerated but suffers from having to be given in three doses at intervals of 14 days thus producing a large number of "incomplete treatments". Its virtues lie in its cheapness, its acceptance and a reasonable cure rate of 60-90% in different population samples.

Oxamniquine, the other monospecific schistosomicide, has been widely used against *S. mansoni*, the only indication for its employment. The therapeutic response varies with the age and thus the surface area of the patient and with the geographic origin of the infection, there being a distinct difference in response of schistosome strains of African and South American origin, the details of which need not concern us here. Highly effective, it was the mainstay of the major Brazilian campaign of the mid-1970's when many millions of treatments were given. It remains an interesting compound if only because it affects male worms rather than females and there is a distinct cut-off point in efficacy, it being totally without effect in man against *S. haematobium*, *S. mattheei* or *S. japonicum*.

POPULATION-BASED CHEMOTHERAPY AND THE DELIVERY SYSTEM

Mass, selective and targeted chemotherapy

It is clear that for the immediate future and perhaps even for decades, emphasis in the control of schistosomiasis in man will be placed on the reduction of human morbidity and mortality implemented through population-based chemotherapy. It is also clear that chemotherapy is the only agent available for the cure of the countless numbers of individual patients presenting themselves for health care.

Population-based chemotherapy is, as the phrase implies, based on target human populations, the hosts of the schistosomes. These populations must be viewed as epidemiological units and may be composed of total area populations, or several varieties of sub-populations, e.g. a population of children in a specific age-range, a whole village population, a population of plantation workers, etc. Although the term "community" is frequently used as an alternative description of a population, the latter is preferable in reminding us of the essential statistical rigour with which sampling and data analysis must be conducted. Conceptually,

at this stage, the population itself is the referral unit and not the individual human targets within the population— as is the case when reference is made to “targeted” chemotherapy.

Population-based chemotherapy is implemented via 2 main pathways: through mass chemotherapy or, alternatively, through what has become known as selective population chemotherapy or SPC.

Mass chemotherapy is the treatment of everyone in a population whether infected or non-infected. Since it is rarely practicable to examine everyone in a population except in small or moderate-size village levels or in school surveys, mass chemotherapy as a control tactic is usually applied after various survey sampling procedures and the subsequent action is based on decisions made on pre-determined rates of infection and/or levels of intensity of infection, which naturally vary in the numerous heterogeneous epidemiological settings encountered. Where prevalences and/or intensities of infection are very high, or where there is clear evidence of associated morbidity and/or mortality, this is a perfectly feasible tactic for morbidity control since, as we have seen, the modern antischistosomal drugs are highly effective and their toxicity to man is many orders of magnitude less than the compounds used even as recently as the 1960's, and population acceptance is good.

The alternative population-based chemotherapeutic approach, selective population chemotherapy, is the treatment of those infected members of a population only, i.e. selection is by the demonstration of infection, qualitatively, quantitatively, or both, depending on the objectives of the programme, the techniques and measurements used in examinations and the criteria adopted to indicate success— or lack of success! This approach implies the measurement, or in this case the diagnosis, of each individual member of a population (or “community”) and the delineation of those infected in contrast to those non-infected.

There are many variants of selective population chemotherapy, e.g. it can be applied to sub-targets of infected populations in the so-called targeted chemotherapy of high-intensity infections where the risk of developing manifest disease is greatest, or to particular age-ranges where prevalences are known to be higher than in the rest of the population; this is sometimes termed “selective group treatment”. Yet even these variants remain basically a form of selective population chemotherapy. In certain situations, a combined approach would constitute the most effective strategy; after mass chemotherapy has lowered prevalence and intensity rates, then selective population chemotherapy could be used in those individuals exhibiting the residual prevalence on follow-up examination.

Whatever strategy of chemotherapeutic control is adopted, and this will depend on the epidemiological survey data, its analysis and the subsequent projections of epidemiological transmission dynamics, the one essential tactical element will be repeated drug administration. Whereas mathematical models can point to the utility or otherwise of generalized tactics, the frequency of administration of drugs, the anticipated rates of population coverage, the duration of the attack phase, the timing and duration of surveillance and the maintenance of reduced prevalence and intensity levels tend to be area-specific, epidemiologically-specific, health service-specific and even species-specific in the various schistosome infections.

The essential components of any chemotherapeutic delivery system are personnel, diagnostic technologies and their associated materials, drugs, transport, logistical support, data recording and management apparatus and that elusive characteristic, motivation. Whilst the optimum method of drug delivery will vary with local conditions; the existing

infrastructure and its associated personnel should be used whenever possible.

Costs loom large in any strategic or tactical considerations and the proportionate components of each of the steps in the chemotherapeutic delivery system never fail to induce surprise, whether the calculations are based on numbers of specimens examined, yield per survey or cases detected, costs per person protected or treatment costs— which include fixed costs of salaries of personnel, field allowances, overtime, costs of materials, vehicular transport and maintenance, and costs of drugs. It is, for example, axiomatic that the lower is the prevalence, the higher is the cost of case-detection and it is obvious that the best returns in terms of value for money are in those situations where prevalences and intensities of infection are so high that even a restricted sampling procedure followed by mass chemotherapy is indicated.

There is certainly room for an expansion of practical modelling on chemotherapeutic delivery costs for the actual purchase prices of drugs are but a small fraction of the whole cost element. Even drug costs themselves are amenable to price reductions through bulk purchase schemes, competitive tenders, importation of bulk raw supplies for local tableting and a competent storage and distribution system at local and national levels (Davis, 1985, 1989).

Thus the introduction of new, safe, efficient and well-tolerated drugs has made chemotherapy the most potent currently available tool in the control of schistosomiasis. This principle can also be extended to the control of the other snail-borne trematode infections and large-scale chemotherapeutic campaigns with praziquantel are already in use in Thailand against opisthorchiasis and against clonorchiasis in Korea.

Although all of the principles enunciated for schistosomiasis control are applicable to the other trematode infections the outlook is likely to be less favourable since the complicating human behavioural variables of eating habits are much more difficult to eradicate as age-old customs. Additional complicating factors mitigating against success in control are the numbers of secondary intermediate hosts; Yoshimura (1965) tabulated 89 species of fresh-water fish or crustaceans in 10 families existing in China, Korea, Japan and Taiwan, and the large numbers of animal reservoirs including many mammals although their role in contributing to transmission dynamics is less than clear cut.

One terminological warning on the use of the term “drug-efficacy” should be borne in mind. Estimates of the antischistosomal activities of the drugs in use at the population level are frequently optimistic. The terms “cure rate” or “parasitological cure” have time-honoured and specific meanings in clinical usage and are applied usually to the individual patient.

They imply in this case the termination of an existing schistosome or other trematode infection with the permanent cessation of excretion of eggs from the body. This clinical state can be confirmed only after repeated parasitological examinations, often using concentration techniques, over an extended time period. In population-based chemotherapy programmes it is not possible to undertake repeated parasitological excretal examinations for logistic reasons and estimates of “cure rates” are thus usually based on the findings of a single post-treatment examination; in other words, the estimates are to be used as a guide and not as an absolute statistic, particularly when a once daily dose of an active drug may not represent the best pharmacological usage but is instead a compromise forced by the necessity to ensure the largest population coverage within logistic constraints.

An alternative technical term used in the assessment of drug efficacy in all helminthic

infections is the "egg reduction rate" expressed as a population-mean figure or in age-specific terms. This simply represents the calculation of a post-treatment egg count of either a population or a sample and its comparison with the pre-treatment egg load of the same common denominator, all based on a common unit weight of faecal material or the same volume of urine examined by the same technique on the two occasions. Although this technique is frequently used, it suffers, in parallel with the term "cure rate", from several disadvantages, principally because of the numerous variables that influence egg production and excretion and observer variation in microscopic assessment. It is therefore a rather indirect reflection of biological events. Neither index can be regarded as totally satisfactory and great care must be taken in the evaluation of claims of efficacy advanced after clinical or epidemiological trials, especially where methodological variation existed.

If neither the prevalence nor the intensity of infection is reduced after chemotherapy, an evaluation should be conducted to explore the possibility of (1) drug "failure", i.e. therapeutic failure; (2) lack of compliance; (3) "resistance" of the parasite to the drug—virtually unknown to date, or (4) "operational failure", an all-embracing term covering many different sins of omission or commission. Programme design and evaluation procedures usually require the assistance of an experienced epidemiologist, statistician and parasitologist (WHO, 1987). Finally, it should be recalled that experience during the last two decades has shown that the major constraining management problems in parasitic disease control are rarely technical but usually administrative and financial (Mott and Davis, 1986).

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PLASMODIUM BERGHEI AND YOELII: A CORRELATION OF SURVIVAL PERIODS AND IMMUNOLOGICAL PARAMETERS IN BALB/c MICE

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Abstract: After inoculation with *Plasmodium berghei* NK65, BALB/c nu/nu mice survived longer than normal BALB/c mice. No such difference was found after infection with *Plasmodium yoelii* 17X. The difference in survival periods was not due to a difference in parasitemia level; studies of several immunological parameters revealed that the mice that survived longer showed an increased ability to generate interleukin-2 and cytotoxic T lymphocytes from their spleen cells. The survival period had no relationship with the amount of anti-malarial antibodies nor the formation of immune complexes. T cell functions were generally decreased and natural killer cell activity was raised in all mice regardless of their different survival periods.

INTRODUCTION

Different species of rodent malaria parasites induce different immunological reactions in the host. The resulting pathological effects range from mild self-limiting diseases to rapidly fatal complicated infections. There is evidence to show that after infection, some species of malaria hosts with T cell dysfunction can survive longer than hosts with normal T cell functions. BALB/c mice die earlier than nude mice after inoculation with *P. berghei* NK65 (Waki *et al.*, 1977) or *P. berghei* ANKA (Finley *et al.*, 1982). Neonatally-thymectomized or anti-thymocyte serum-treated golden hamsters survived longer after infection with malaria than did normal hamsters (Wright *et al.*, 1968; Wright *et al.*, 1971). Malnourished children were found to suffer more from the less virulent form of *P. falciparum* infection than well-nourished children (Edington *et al.*, 1967). All these findings suggest that intact T cell functions are deleterious to the host after infection with certain species of malaria parasites. In order to elucidate the immune mechanisms involved in this phenomenon, we first tried to find experimental malaria models which could be used to demonstrate the role of T cell functions in malaria. Secondly, several immunological reactions were measured to determine any correlation with the severity of the disease.

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MATERIALS AND METHODS

Mice

BALB/c or BALB/c nu/nu mice were inoculated through the tail vein with 10^7 red blood cells infected with *P. yoelii* 17X (lethal) or *P. berghei* NK65. To determine the effect of different T cell functions on the severity of the illness, we studied the duration of survival and the mode of increase in parasitemia level among the different groups. For cellular immunological tests, the mice were sacrificed by cervical dislocation, and the spleen cells then collected aseptically. For serological tests, blood samples were collected by cardiac puncture and the samples stored at -70°C for simultaneous assay at a later date.

Serological assays

Anti-malarial IgG and IgM titres were measured by indirect fluorescence antibody technique (Kuvin *et al.*, 1962). Estimation of CICs was performed by Clq solid-phase radioimmunoassay using radio-iodinated protein A (Hay *et al.*, 1976) and purified Clq from pooled human serum (Yonemasu *et al.*, 1971).

T cell functions

For mitogen response, the mice were sacrificed 3 days after inoculation, and the spleen cells then cultured in the presence of $25\ \mu\text{g/ml}$ of PHA or $5\ \mu\text{g/ml}$ of Con A or $25\ \mu\text{g/ml}$ of LPS. The mitogen reactivity was determined by measuring the incorporation of ^3H -thymidine into DNA using 96 well microtitre plates. MLR was performed in the same way using mitomycin C-treated stimulator cells of C57BL/6J (H-2^b) or C3H (H-2^k) mice. BALB/c spleen cells (H-2^d) were used as a control. The same stimulator cells were used for CTL induction. Stimulated cells were cocultured with the target cells EL4 (H-2^b), X5563 (H-2^k) and P815 (H-2^d) at different ratios. Percentage cytolysis was determined using the ^{51}Cr release assay method.

Interleukin 2 production

For IL-2 production, spleen cells were stimulated with Con A for 24 hours. The supernatant was assayed for the presence of IL-2 activity by its ability to support the growth of an IL-2-dependent cell line, CTLL-2 (Baker *et al.*, 1979). To measure NK activity, spleen cells were passed through a nylon wool column to remove B cells. The resulting cells were cocultured with different proportions of YAC-1 cells. Percentage cytotoxicity was measured using the ^{51}Cr release assay method.

RESULTS

Nude mice survived longer than BALB/c mice after *P. berghei* infection ($p < 0.001$) but no such difference existed after *P. yoelii* infection. The early death was not attributable to a rapid increase in parasitemia level (Fig. 1). There appeared to be no relationship between anti-malarial IgG, IgM, and CIC levels in the different groups and the death of the host (Fig. 2). Mice after infection showed decreased responses in both mitogen and allogeneic stimulation, except that of BALB/c response to LPS after *P. berghei* infection. These changes also show no correlation with the survival pattern (Figs. 3 and 4).

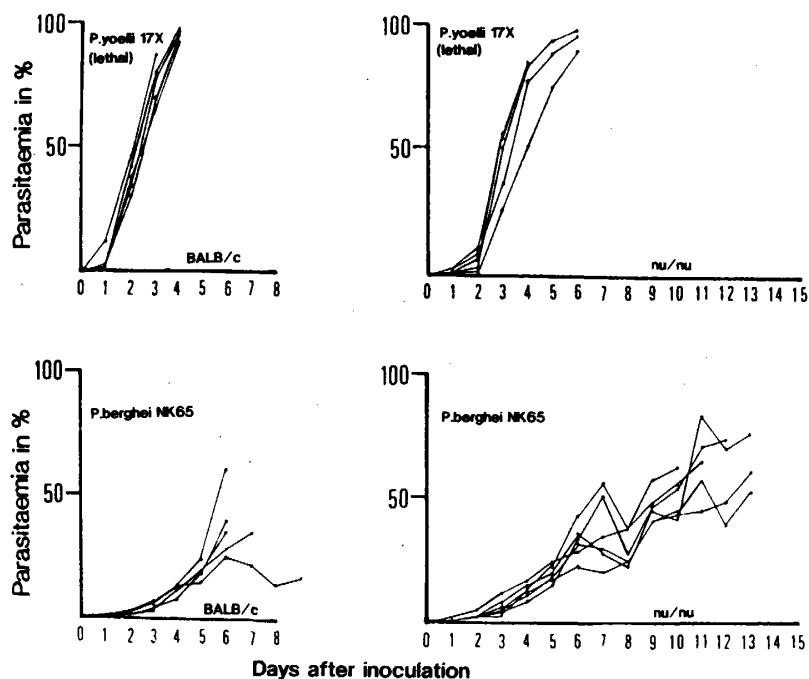


Figure 1 Parasitaemia levels of different groups of mice from the study of survival periods. Outstandingly prolonged survival period of the nude mice infected with *P. berghei* is obvious.

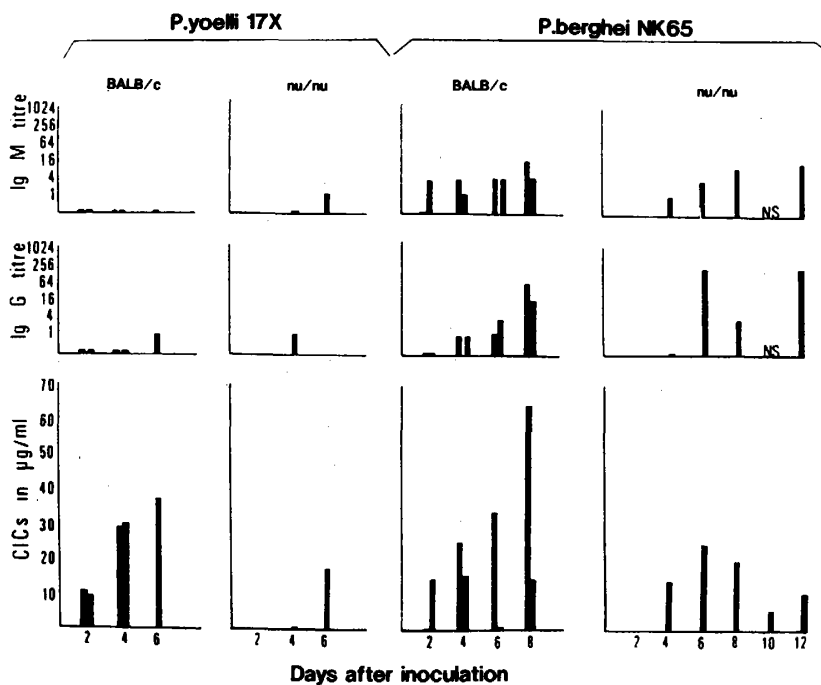


Figure 2 Composite diagram showing the relationship of antibody titres and CIC levels (NS: not sufficient for the tests).

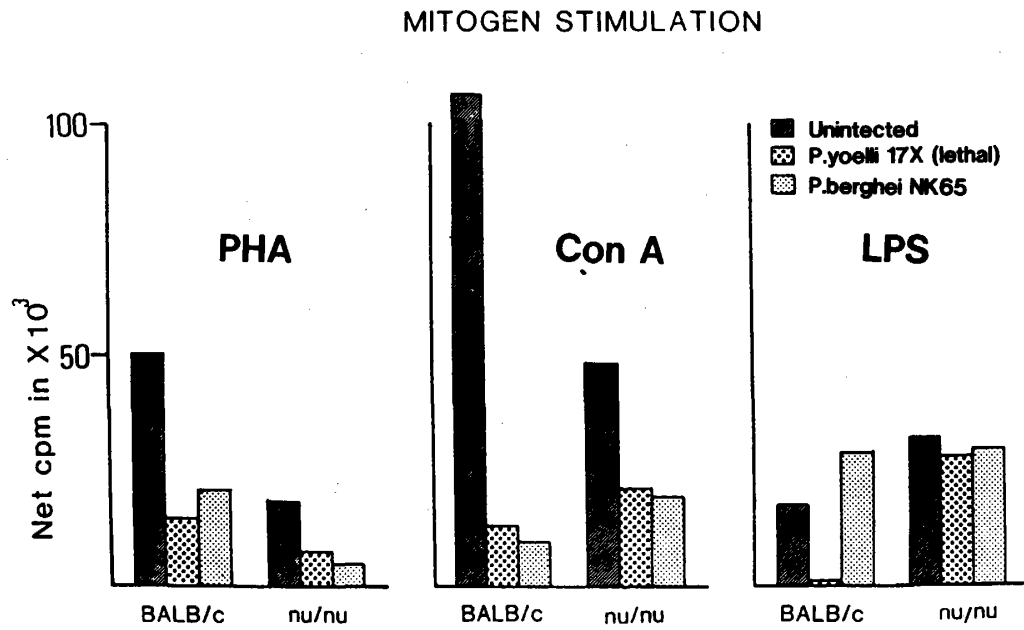


Figure 3 Response to mitogens expressed as net count per minute (cpm) calculated by subtracting the background counts of the culture wells without mitogen from those of the stimulated wells.

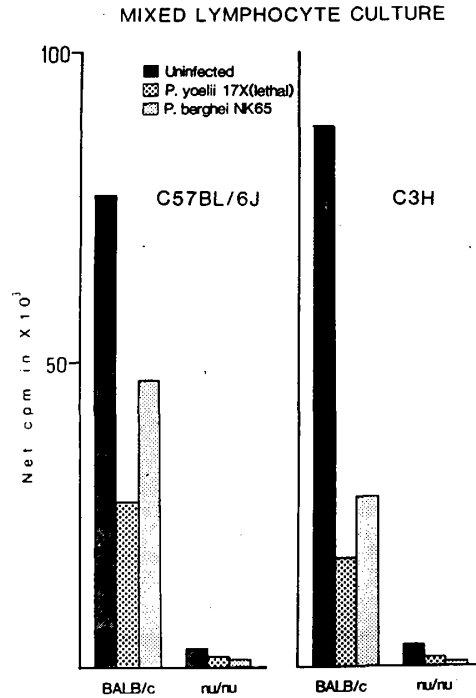


Figure 4 MLR results after C57BL/6J and C3H stimulation shown as net count per minute (cpm) calculated by subtracting the auto-stimulated background counts from those of the stimulated wells.

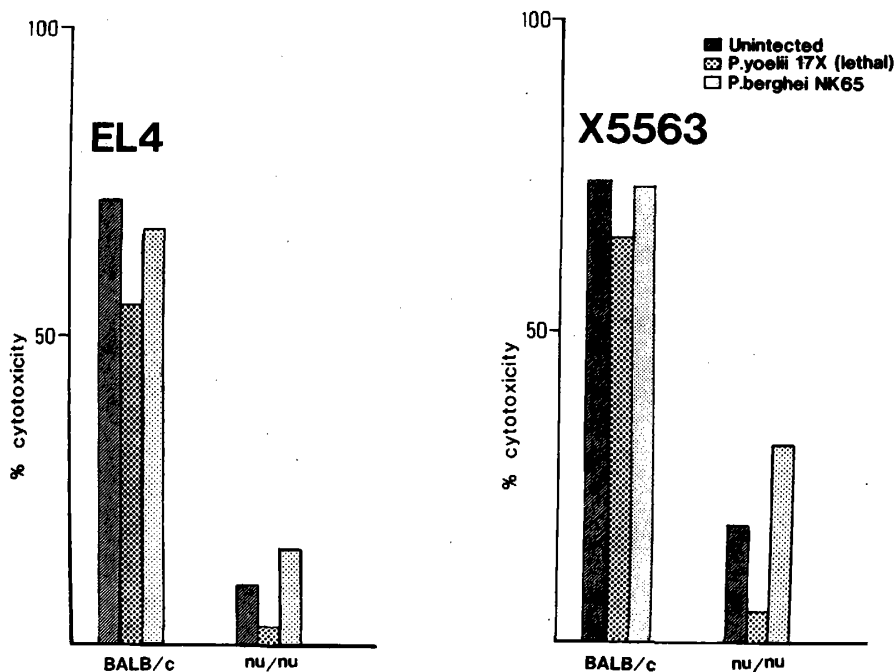


Figure 5 Generation of CTLs against H-2^b (C57BL/6J) and H-2^k (C3H) is shown as cytotoxicity to the target cells EL4(H-2^b) and X5563 (H-2^k).

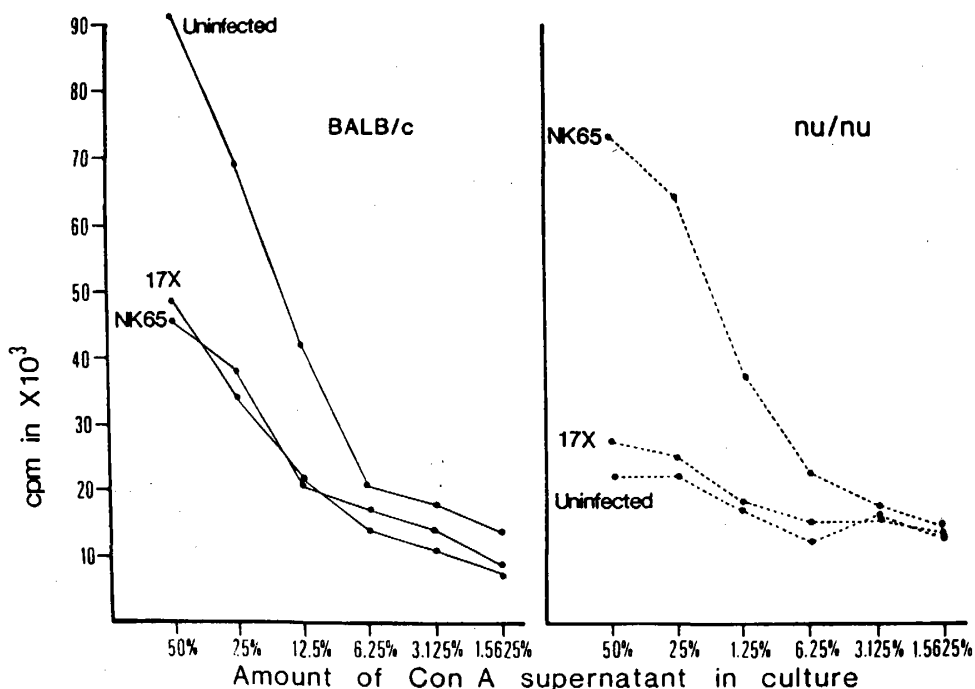


Figure 6 Con A-induced IL-2 production is demonstrated as the ability to support the growth of CTLL-2 cell line. A marked increase in the cell growth is seen only in those wells containing a high percentage of the Con A supernatant obtained from the nude mice infected with *P. berghei*.

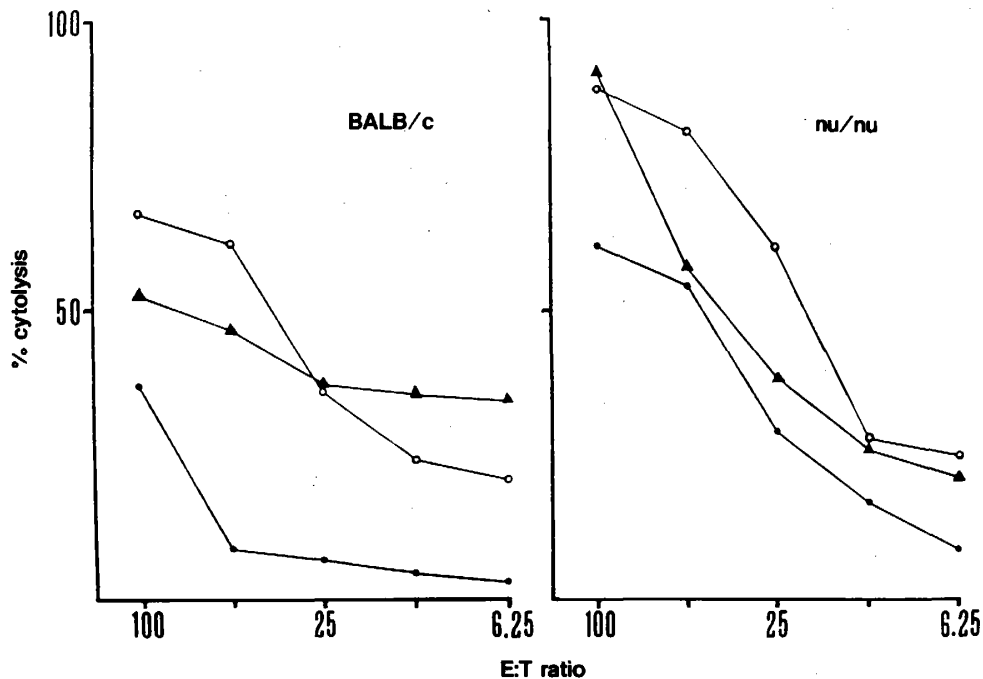


Figure 7 NK activity is shown as the degree of cytotoxicity against the target cell line YAC-1 at various effector: target (E:T) ratios: $\circ-\circ$, NIC 65 infected; $\blacktriangle-\blacktriangle$, 17X infected; $\bullet-\bullet$ uninfected.

A mild reduction in the generation of CTLs was observed in all the *P. yoelii*-infected mice. By contrast, among the *P. berghei*-infected group, nude mice showed an increased generation of CTLs whereas normal BALB/c mice showed a reduced response (Fig. 5). Thus, there seems to be a correlation between the increased ability to induce CTLs in the nude mice and their longer survival. In addition, Con A-induced IL-2 production was also markedly raised in the same group, whereas reduced levels were found in all other groups (Fig. 6). NK cell activity was raised in all the groups, there being no difference between long-lived and short-lived groups (Fig. 7).

DISCUSSION

Many explanations and speculations had been put forward regarding the prolonged survival of T cell-deprived hosts after some types of malarial infections, but many of the hypotheses did not fit with our findings. The results concerning anti-malarial antibody levels contrast with the previous thinking that the lack of T-dependent agglutinins in T cell-deprived hosts was responsible for their longer survival (Wright *et al.*, 1968; Wright *et al.*, 1971). CIC measurements in relationship to survival pattern excluded the possibility of immune complex-mediated injury (June *et al.*, 1979; Rest *et al.*, 1979; Adam *et al.*, 1981). Reduced mitogenic and allogeneic responses agreed with the previous findings of immunosuppression (Lelchuk *et al.*, 1980; Weidauz *et al.*, 1982).

Nude mice, having a higher NK activity (Herberman *et al.*, 1978), were presumed to

have a resistance to malarial infection. A correlation was demonstrated between susceptibility to malaria and NK activity (Eugui *et al.*, 1979). However, in our experiment, NK activity seemed to play no role in the resistance to malarial infection. Increased NK activity has previously been noted (Ojo-Amaize *et al.*, 1981; Ojo-Amaize *et al.*, 1984).

In contrast, the ability to produce IL-2 after Con A stimulation was markedly increased in the group that survived longest. This group also gave more CTLs in response to both H-2^b and H-2^k antigens. Increased IL-2 productivity may in some way confer a protection against the malignant pathological effects of *P. berghei* in nude mice. Raised CTL activity may be the result of the high IL-2 secretion because IL-2 has been known to induce the generation of specific CTLs particularly in nude mice (Gillis *et al.*, 1979; Smith *et al.*, 1984). The exact mechanism by which the high level of IL-2 confers protection needs to be further investigated.

Macrophage hyperactivity in mouse malaria is well documented (Zukerman *et al.*, 1977). Increased IL-1 production by activated macrophages resulting in an increased IL-2 production and then subsequent increase in CTL generation is a possible sequence, which needs to be confirmed by measuring the IL-1 productivity of adherent cells.

Our results pave the way to further observations of the varying pathological effects of different *Plasmodium* on human patients. Falciparum malaria can cause cerebral complications with rapidly fatal outcome whereas vivax infection is benign and uncomplicated. It will be interesting to observe whether such a difference is associated with an inequality in IL-2 productivity and/or CTL activity.

Our findings of raised IL-2 production is further evidence of the presence of functional T cells in nude mice. Despite the well known fact of their lack of the thymus, nude mice were found to exhibit some T cell functions if a sensitive assay method was used or after an intense immunologic stimulus (Loor *et al.*, 1973; Langhorne *et al.*, 1983; Ikehara *et al.*, 1984).

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Plasmodium berghei および *yoelii* 感染 BALB/c マウスの
生存率と免疫学的パラメータの解析

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Plasmodium berghei NK65 を、BALB/c ならびに BALB/c nu/nu マウスに感染させて寿命を比較すると、胸腺のない nu/nu マウスの方が長生きした。しかしながら *Plasmodium berghei* 17X の感染実験では、寿命に差はなかった。寿命の差は、血中の parasite 数によるのではなくて、host の IL-2 の産生能ならびにキラー T 細胞の誘導能の差によることが判明した。

さらに寿命は、抗マラリア抗体価とも血中の免疫複合体値とも相関しなかった。感染後いずれのマウスも、T 細胞機能は一般に低下したが、NK 細胞活性は上昇した。

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症例報告

マラリア患者の血液所見, 特に貧血について

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はじめに

貧血は, マラリアに特徴的所見であるといわれている。しかしマラリア患者は輸入例を散発的にみただけでなので, 感染原虫別に貧血の程度を分析することは難しい。過去24年間に経験したマラリア患者の血液検査所見を検討し, 特に熱帯熱マラリアの貧血とその対策について述べる。

患者資料

患者は1966年から1989年3月まで我々が直接, あるいは間接に関与したものである。同一患者が再発, あるいは再燃のため複数回入院治療を受けたときは, 別の症例として分析した。重複感染例では, 1つの原虫種が優勢で他の原虫種は少数しか感染していないので, 優勢種を感染原虫として集計した。

患者総数419人のうち男395人, 女24人で, 21-40歳の男性が約75%を占めていた。病名は熱帯熱マラリア170, 三日熱マラリア220, 卵形マラリア23, 四日熱マラリア6であった。

熱帯熱マラリア患者のなかには, 意識障害, DIC, 腎不全, 血色素尿, 肺水腫, 強度の黄疸などを合併した瀕死の症例が24人あり, そのうち14人が死亡した。その他のマラリアでは, 重症と判定されたものはなかった。

臨床検査と感染原虫数の算出

1. 血液検査異常値の基準: 下記の数字を異常値

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とした。赤血球: 1 μ l 当たり男399万, 女349万以下, 血色素: 男12.9, 女10.9 g/dl 以下, 白血球: 1 μ l 当たり3,900以下と9,600以上, 血小板: 1 μ l 当たり11万以下。

2. 原虫数の算出: 血液1 μ l 当たりのマラリア原虫数は薄層標本を, 1/50M, pH7.2-7.4のリン酸緩衝液を用いて染色して検査した。白血球100-200コを数えるうちに現われるマラリア原虫数Pを求め, 1 μ l 当たりの白血球数wにp/100, あるいはp/200を掛けて求めた。感染原虫数が多いときは, 赤血球1,000コに対する感染原虫数から1 μ l 当たりの原虫数を算出した。マラリア原虫数は, 10数コから2,000,000を越えることがあるので, 統計学的分析には原虫数の対数をとって比較したが, 表には実数で示した。

3. 統計学的処理: 各項目についての統計学的処理, 特に平均値と異常値を示すものの頻度の比較検討は, 脇本ら(1984)の統計学的解析用ソフトウェアを用いて行った。

結 果

各検査項目について, 平均値, 異常値を示すものの割合, それらの感染原虫種による差の検定結果(危険率1%), および異常値の最高あるいは最低値を表1に示した。各検査項目については, 累積百分率をもってその分布を図示した。以下各項目について説明する。

1. 感染原虫の種類と最大感染原虫数 (/ μ l)

マラリアで最も大切なのは, 血液内原虫数である。原虫数は, 通常治療前に最高値を示すが, と

Table 1 Comparison of parasite count and blood cell components in falciparum, vivax and ovale malaria

Illness	falciparum malaria			vivax malaria			ovale malaria			comparison of mean of each group	comparison of % of abnormal values
	mean	max.or minim.	% ab-norm.	mean	max.or minim.	% ab-norm.	mean	max.or minim.	% ab-norm.		
pc ¹ ×10 ³	18.2	2,138		3.24	13.8		0.35	2.4		Pf>Pv>Po	
rbc ² ×10 ⁶	3.50	0.98	69	3.81	1.91	63	4.12	3.23	28	Pf<Pv<Po	Pf≠Pv>Po
Hb ³ g/dl	11.0	3.2	74	12.4	5.8	62	13.6	11.4	41	Pf<Pv<Po	Pf≠Pv≠Po
wbc ⁴ ×10 ³	5.98	16.2 2.2	25	55.8	21.3 2.3	17	4.83	8.3 2.8	40	Pf≠Pv≠Po	Pf≠Pv≠Po
pltlt ⁵ ×10 ³	76	226	78	85	359	81	143	196	33	Pf≠Pv	Pf≠Pv

1,pc=parasite count, 2,rbc=red blood cells, 3,Hb=hemoglobin, 4,wbc=white blood cells, 5,pltlt=platelets.

The unit for pc, rbc, wbc and pltlt is number per μ l, and that for Hb is g/dl.

In the column of max. or minim., the figures for pc are the maximum values, the figures for rbc, Hb and platelets are the minimum values, and the figures for wbc are both maximum and minimum values.

The percent of abnormal values for wbc includes both abnormally high and low values together.

The sign \neq indicates no significant difference between the two groups.

きに治療開始1—2日後に最高値を示すことがある。血液1 μ l中原虫数の平均値は、熱帯熱マラリア18,200, 三日熱マラリア3,200, 卵形マラリア350で、統計学的に有意な差が認められた。

最小値は熱帯熱, 三日熱および卵形マラリアで1 μ l当たり15, 12, 10。最大値はそれぞれ2,138,000, 138,000および3,800で、熱帯熱マラリアにおける原虫数の多いことが注目に値する。

10,000以上の値を示したものは、熱帯熱マラリア61%, 三日熱マラリア24%, 卵形マラリア0%であった。100,000を越えるものは、熱帯熱マラリアが25%に対して、三日熱マラリアでは1%にしか見られなかった。以上の比率は、統計学的に有意である。卵形マラリアでは、20人中5,000を越えるものは1人もなかった。

図1には、3種マラリアにおける血液1 μ l当たりの最大原虫数の分布を示す。熱帯熱マラリアでは、原虫数が少ないものから100万以上(対数値で6)に広く分布していることがわかる。四日熱マラリアは、4人しか定量的に検査されていない。最高値は6,760, 最小値は500であった。

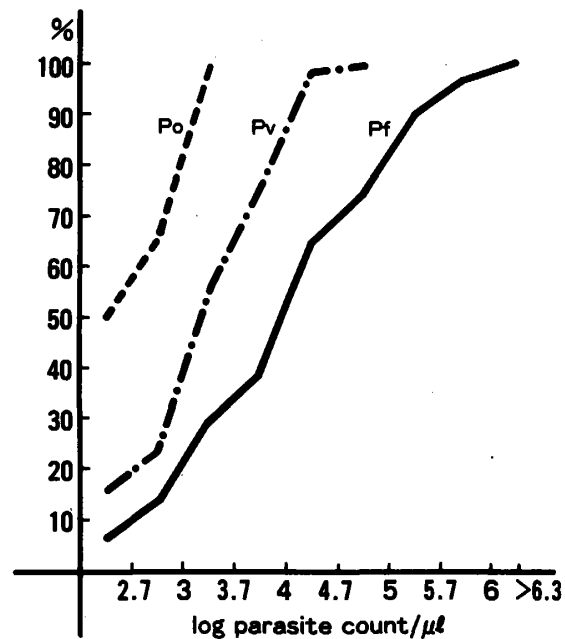


Figure 1 Cumulative percentage of the highest parasite count in malaria.

Parasite density is expressed in log units. Log 3, 4, 5 and 6 correspond to 1,000, 10,000, 100,000 and 1,000,000 per μ l. Pf, Pv and Po are abbreviations of *Plasmodium falciparum*, *P. vivax* and *P. ovale*.

2. 最小赤血球数 ($/\mu\text{l}$)

マラリア原虫増殖の直接の影響を受けるのは、赤血球の減少である。入院直後、あるいは治療開始前の赤血球数は、血液濃縮のためかえって増加しており、治療開始数日後の方が低値を示すことが多い。何回かの検査の最小値を、その患者の代表値とした。治療前1回しか検査していないものは、それを用いた。

赤血球数の平均値は、熱帯熱<三日熱<卵形マラリアの順に多くなり、その差は有意であった。熱帯熱マラリアの最小値は98万、熱帯熱マラリアにおける貧血の強さが明らかである。299万以下の強い貧血を示すものの割合も、熱帯熱の方が三日熱より多く、卵形と四日熱マラリアでは0であった。瀕死の重症と分類した熱帯熱マラリア患者は、赤血球数が299万以下になったものに多かった。

図2 Aに、3群の最小赤血球数の分布を示す。低値を示すものが、熱帯熱マラリアに多いことが明らかである。四日熱マラリアは、卵形マラリアとほぼ同様の値を示した。

なお赤血球、および次に述べる血色素いずれもマラリア原虫消失後は、貧血の程度により1-3

月以内に正常値に戻った。

3. 最低血色素量 (g/dl)

平均値は熱帯熱<三日熱<卵形マラリアの順に多くなり、各群の間にはいずれも有意の差があった。熱帯熱マラリア患者の最低値は3.2で、この患者は赤血球も98万で最低値を示した。治療前マラリア原虫は最高728,500に達し、クロロキン療法で減少しつつあったが、突然血圧降下をきたして死亡した(海老沢, 1981)。

血色素量が9.9以下の低値を示したものの割合は、熱帯熱>三日熱>卵形と四日熱マラリアの順に多く、その差は有意である。図2 Bには熱帯熱、三日熱および卵形マラリアの最低血色素量の分布を示す。赤血球の分布に類似した曲線を示している。四日熱マラリアでは、最小と最大値が8.3と14.2で、三日熱マラリアと近似した値であった。瀕死の重症例になる頻度も、血色素が10以下に下がるものに多い。

4. マラリア患者に対する輸血の問題

熱帯熱マラリアでは、赤血球が299万以下になったものは27%、血色素が10以下に下ったものは31%あった。輸血実施の目安は、全身状態と肝炎

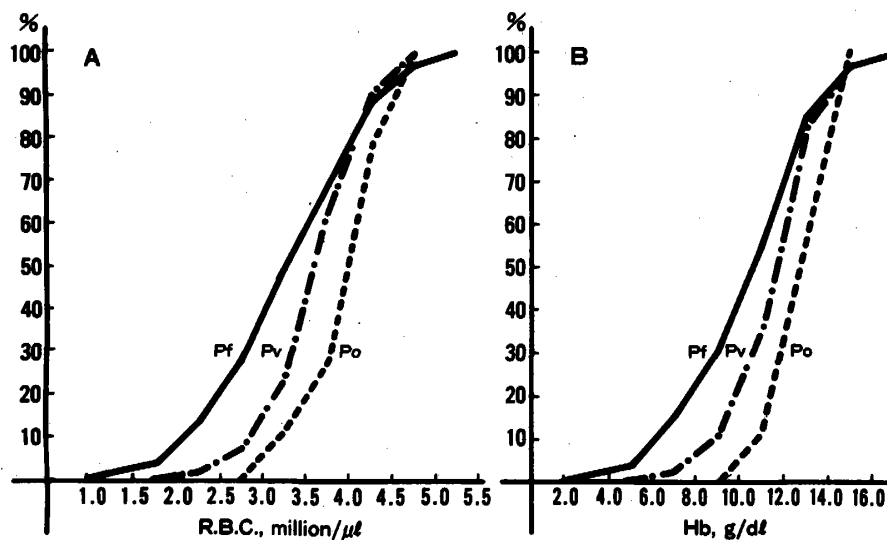


Figure 2 Cumulative percentage of the lowest red blood cell counts (A) and hemoglobin concentrations (B).

See Fig. 1 for abbreviations Pf, Pv and Po.

Table 2 Falciparum malaria patients treated with blood transfusion

Case No.	Age & sex	minim. rbc 10 ⁶ /μl	minim. Hb g/dl	max. pc per μl	minim. pltlts per μl	lost days*	main complications
1	26 F	0.85	3.2	728,500	16,000	11	DIC, ren.f., shock, death
2	45 M	1.60	5.4	21,550	22,000	8	cereb., ren.f., lng ed.
3	23 M	2.09	6.1	829,910	29,000	6	cereb., conv., ren.f., sev.jndc.
4	41 M	2.31	6.9	727,100	33,000	8	cereb., NANB hepatitis
5	29 M	2.46	6.7	44,500	40,000	8	None
6	39 M	2.60	8.7			16	Anemia, edem in legs
7	24 F	2.63	8.4	12,400	34,000	17	DIC, cereb., parapl., dementia
8	35 M	2.71	8.0	1,536,000	28,000	5	DIC, cereb., ren.f., sev.jndc.
9	52 M	2.85	8.8	3,520	32,000	6	DIC, cereb., ren.f., sev.jndc., death

See footnote to Table 1 for abbreviations rbc, Hb, pc and pltlts.

*The lost days indicate the number of days passed before treatment was started after onset of illness.

DIC=disseminated intravascular coagulation, ren.f.=renal failure, cereb.=cerebral malaria, lng ed=lung edema, conv.=convulsion, parapl.=paraplegia, sev.jndc.=severe jaundice.

合併の危険を考慮して、決定しなければならない。検討した症例のうち9例が輸血をうけている(表2)。赤血球数はすべて285万以下、血色素は8.8以下であった。瀕死の重症と判定されたものは、7人あった。発病から治療開始までの日数、すなわち損失日数(表2脚注参照)は5-17日で、8例が熱帯熱マラリア治療開始に安全な5日以内を過ぎてから治療を受けている。輸血を受けたが2例死亡、1例が輸血後かなり重症なNANB肝炎に罹患した。

死亡した症例1は、マラリアの治療にはほぼ成功したが、輸血の時期が遅過ぎた(海老沢, 1981)。症例9はマラリア治療開始の遅れ、DICなどが重なって死亡した。

5. 最小血小板数 (/μl)

血小板の減少は、マラリアでは頻回に見られる。血小板数が11万以下になったものは、熱帯熱と三日熱マラリア両群とも約80%であるが、3万以下になったのは前者が29%、後者が8%で統計学的に有意であった。最低値は前者が6,000、後者が16,000であった。血小板数の平均値にも、両群の間に有意の差はなかった。

卵形と四日熱マラリア患者は合計8人で、最低は64,000、最高260,000であった。血小板数はマラリア原虫が流血中より消失すると、1週間前後で速やかに正常値にもどった。熱帯熱、三日熱および卵形マラリアにおける最小血小板数の累積百分率は、次の報告で示す。

6. 白血球数 (/μl)

白血球数の増減は、マラリアでは一定していない。診断確定時、あるいは治療開始までの白血球数の最高値をとって検討した。3種マラリアの白血球数の平均値に有意な差はなかったが、異常値を示すものの割合(9,600以上と3,900以下)は熱帯熱、三日熱、卵形マラリアの間で有意な差があった。熱帯熱マラリアでは、増加するものと減少するものの比は1:2、三日熱マラリアでは1:5、卵形マラリアでは異常者8人が全部減少を示した。最小値は、熱帯熱マラリア患者の2,200、最大値は三日熱マラリア患者の21,300であった。重症熱帯熱マラリアでは、白血球増加例が多かった。

考 察

マラリア患者の血液内原虫の多寡は、感染原虫の赤血球の日齢に対する選択性に左右されるが、熱帯熱マラリア原虫は、赤血球の日齢を問わないのが特徴である。

マラリア原虫数の統計学的分析で注目されるのは熱帯熱マラリアで、最高2,138,000の値を示して死亡した例を見ると、本症の危険さを痛感させられる。しかし熱帯熱マラリアでも原虫数が10~50の少ない例があったことも、記録しておく必要がある。瀕死の重症と判定されたものや、極端な貧血例はすべて熱帯熱マラリアに限定されたもので、治療上は本症を最も重視すべきである。

感染赤血球の崩壊に直接影響される赤血球数と、血色素量は同じ順序で減少したが、血小板の減少は感染原虫の種類に関係なかった。しかし、その数が異常に少なかったものは、熱帯熱マラリアに多かったことは、本症でDICが起きやすいことと関連がある。

初診時は脱水のため、血液は濃縮している。さらに血液内マラリア原虫の分布は不平等で(海老沢, 1974)、静脈血より毛細血管内により多くのマラリア原虫が潜在する。抗マラリア薬で原虫が死滅するとき、感染赤血球も破壊されるので、抹梢血液所見から推定するより多くの赤血球が失われる。マラリア患者の貧血に関して、感染赤血球の崩壊の他に、免疫学的機序の関与と、脾網内系の機能昂進による非感染赤血球の破壊が推定されている(Perrin *et al.*, 1982) 一因であろう。

小児の熱帯熱マラリアにおける貧血(Abdalla *et al.*, 1980)に関しては、治療開始後1週間前後で最低値を示す急性初感染型、はじめから強い貧血を示す慢性型とその中間型が記されている。我々の症例は大部分成人で、ほとんど第1の初感染型に属していた。入院・治療後マラリア原虫が消失する頃には、初診時よりも50~100万くらい赤血球が減少することもある。

マラリア患者の貧血に対する輸血の時期について定説はないが、赤血球数が250万前後になったら、全身状態を考慮して輸血を考慮すべきである

う。検討した9例の輸血例のなかには、それが不必要であったと考えられるものもあった。輸血後肝炎合併の危険を考え、早期診断と即効性キニーネの点滴静注により、速やかにマラリア原虫を駆除することに先ず力をいれるべきであろう。

マラリアでは白血球は減少することが指摘されており(Perrin *et al.*, 1982)、三日熱マラリア患者で一時的に骨髓低形成による汎血球減少を併発した症例も報告されている(山川ら, 1989)。我々のマラリア患者全体では、白血球減少を示したものは16%であった。白血球減少の頻度は三日熱と熱帯熱マラリアで同様であり、卵形マラリアだけが40%の高率を示した。

白血球増加は、熱帯熱と三日熱マラリアいずれにも見られた。白血球増加と予後に関しては死亡例を含む瀕死の重症例で42%、それ以外のものでは2.6%であり有意な差が見られ、Tani *et al.* (1984)の報告を確認した。しかし瀕死の重症例でも、白血球減少例が2例あったことも記載に値しよう。

マラリア患者血液には異型リンパ球が出現するが(Kueh and Yeo, 1982)、予後には関係がない。

結 語

- 1) マラリア患者の最大原虫数は、熱帯熱マラリア>三日熱マラリア>卵形マラリアの順に多い。熱帯熱マラリアでは最高2,138,000に達した。
- 2) 赤血球数と血色素量の減少の割合は、これと同じ順序で大きい。両者の最低値は1 μ l当たり98万と3.2であった。
- 3) マラリア患者の貧血に対する輸血の時期については、赤血球が250万、血色素が9近くになったら考慮すべきであろう。
- 4) 血小板は感染原虫の種類に関係なく減少するが、極端に減少するものは熱帯熱マラリアに多かった。
- 5) 白血球数の平均値は、上記3種マラリアで差がない。白血球減少は全体の16%に認められ、増加例もあった。

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HEMATOLOGICAL FINDINGS IN MALARIA WITH A NOTE ON BLOOD TRANSFUSION IN SEVERELY ANEMIC PATIENTS

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Parasite count and hematological studies were made on 170 falciparum, 220 vivax and 23 ovale malaria patients to see whether hematological parameters differ in malaria infected by three different species of malaria parasites, *P. falciparum* (P.f.), *P. vivax* (P.v.) and *P. ovale* (P.o.) The mean and percentage of abnormal values of each parameter were analyzed statistically. The parasite count was significantly large in the order of P.f.>P.v.>P.o. The maximum parasite count of P.f. was 2,138,000 per μ l of blood. The mean parasite count for the 3 species was 18,200, 3,240 and 350 per μ l of blood. The red blood cells (rbc) and hemoglobin (Hb) decreased significantly in the same order and the minimum rbc count was 0.98 million per μ l and the lowest Hb concentration was 3.2 g/dl in falciparum malaria. The mean r.b.c. count in P.f., P.v. and P.o. malaria was 3.50, 3.81, and 4.12 million per μ l and the mean Hb concentration was 11.0, 12.4 and 13.6 g/dl, respectively. The changes, either increase or decrease, in white blood cells and the decrease of platelets were not significantly different in P.f., P.v. and P.o. malaria. Nine cases of falciparum malaria were given blood transfusion, and its lifesaving merits in severely anemic patients and demerits of NANB hepatitis were discussed. Early treatment, within 5 days of the onset of illness, with rapidly acting antimalarial drug was emphasized.

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症例報告

マラリア患者の血液生化学的所見

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はじめに

マラリアでは貧血のほか治療開始時期が遅れると急性腎不全, DIC, 強度の黄疸, 脳症など重い合併症を起こす。前報(海老沢ら, 1990)に引き続きマラリア患者の血液生化学的所見を分析, 特に熱帯熱マラリアにおける極端な異常所見を報告する。

の通りである。LDH: 500 u/l 以上, 総ビリルビン: 1.4 mg/dl 以上, 尿素窒素 BUN: 21 mg/dl 以上, クレアチニン: 1.6 mg/dl 以上, SGPT: 36 u/l 以上, SGOT: 41 u/l 以上, 血清総コレステロール: 129 mg/dl 以下, 血清総タンパク6.3 g/dl 以下。

検査所見

患者資料, 検査項目とその異常値の基準

患者資料は前と同じ, 各検査項目の異常値は次

前報と同じ要領で各検査項目の平均値と異常値を示すものの割合, および感染原虫種による差の検定の結果を表1に示す。さらに異常値の最高,

Table 1 Biochemical parameters of blood in falciparum, vivax and ovale malaria

Illness	falciparum malaria			vivax malaria			ovale malaria			comparison of mean of each group	comparison of % of abnormal values
	mean	max. or minim.	% ab-norm.	mean	max. or minim.	% ab-norm.	mean	max. or minim.	% ab-norm.		
LDH	1,168	15,292	68	539	5,142	35	425	550	22	Pf>Pv≡Po	Pf>Pv
TBil	6.2	42.3	59	1.3	6.4	37	1.1	1.4	17	Pf>Pv≡Po	Pf≡Pv
BUN	36.5	204	33	15.1	26	9	13.4	23	8	Pf>Pv≡Po	Pf>Pv=Po
Crt	2.4	16.9	30	1.1	1.9	1	1.0	1.1	0	Pf>Pv≡Po	Pf>Pv
SGPT	57.5	455	48	29.6	260	16	22.3	58	22	Pf>Pv≡Po	Pf>Pv
SGOT	70.3	653	44	24.9	180	7	23.0	58	11	Pf>Pv≡Po	Pf>Pv
Cholesterol	119	50	68	119	51	65	109	79	78	Pf≡Pv≡Po	Pf≡Pv≡Po
Tp	6.1	3.2	53	6.7	5.2	31	6.8	6.1	7	Pf<Pv≡Po	Pf>Pv≡Po

See text for units of each biochemical parameters. In the column of maximum or minimum, minimum values are shown for cholesterol and total protein. The maximum values are shown for other biochemical parameters. ≡ indicates no significant difference between the two groups.

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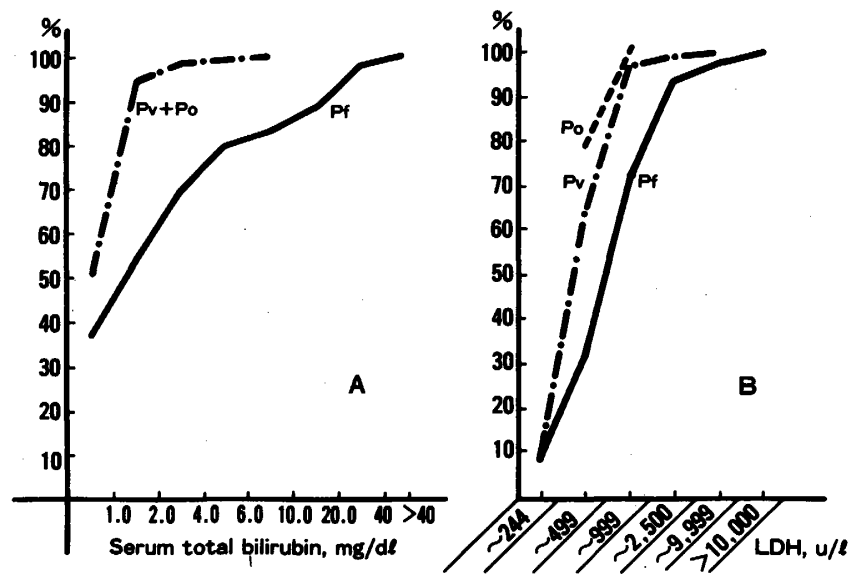


Figure 1 Cumulative percentage of the highest serum total bilirubin (A) and LDH (B) concentrations in malaria patients. Pf, Pv, Po represent *Plasmodium falciparum*, *P. vivax* and *P. ovale*. Pv+Po indicate that data of both groups of patients are mixed together.

あるいは最低値も表示した。各検査項目の分布は、感染原虫ごとに累積百分率をもって図に示した。以下各項目について説明する。

1. 最高 LDH 値 (u/l)

赤血球中に多量に含まれる LDH は、赤血球の崩壊により血清中に多量に放出される。LDH の平均値および異常値を示すものの割合は、熱帯熱の方が三日熱マラリアより高いが、三日熱、卵形および四日熱マラリア間には差がなかった (図 1 B)。LDH 最高値が15,290に達した熱帯熱マラリア患者は、11病日に治療を開始された例で、原虫数は824,100に達し、腎不全を合併、腹膜透析を行ったが死亡した (表 2, 症例 1)。

2. 最高血清総ビリルビン濃度 (mg/dl)

血清ビリルビンの測定は全員に行われず、熱帯熱マラリアでは肉眼的に黄疸が認められたのでその検査を行った例があり、症例の選択に偏りがあったことは否めない。

血清ビリルビンの平均値は熱帯熱の方が三日熱マラリアより高かったが、三日熱、卵形、および四日熱マラリアでは差がなかった。熱帯熱マラ

リア患者のビリルビン量が、広い範囲にわたっているのが特徴的である (図 1 A)。しかし異常値を示したものの割合は、熱帯熱と三日熱マラリアで有意の差はなかった。ビリルビン最高値が42.3に達した患者は、生前マラリアを全然考慮に入れず、急性肝・腎不全として全血交換などの治療を受け11病日に死亡した。死後剖検を断られ、生検針による肝の屍検により熱帯熱マラリアと診断された例である (表 2, 症例 2)。なお総ビリルビンが異常高値を示した例では、直接および間接ビリルビンも上昇していた。

3. 最高尿素窒素 BUN 濃度 (mg/dl)

熱帯熱マラリアでは、腎不全は予後に関係する重要な合併症である。BUN の平均値および異常値を示すものの割合は、熱帯熱の方が三日熱マラリアより多かったが、三日熱と卵形マラリアでは差がなかった (図 2 A)。

BUN が最高204に達した例は、LDH も最高値を示した前述の熱帯熱マラリアの例である。四日熱マラリアで4人中1人33の値を示したものがあつた。本例は36年間四日熱マラリア原虫に感染

Table 2 Synopsis of falciparum malaria patients with abnormally high or low biochemical parameters

Case	1	2	3	4	5	6	7
age, sex	27 M	43 M	45 M	39 M	37 M	40 F	24 M
prognosis	died	died	cured	cured	died	cured	cured
pc ¹	24,100	?	215,500	259,900	253,700	655,800	8,000
lost days	11	∞	8	7	9	6	8
rbc ²	2.22	2.89	1.60	3.18	4.30	2.65	3.20
Hb ³	6.6	8.5	5.4	10.3		7.6	11.1
wbc ⁴	11,600	5,500	5,000	4,700	10,500	12,000	5,700
LDH	15,290	1,750	900	956	1,568	1,130	780
TBil	5.7	42.3	0.8	0.3		6.5	
direct Bil	4.3	20.3	0.2	0.2			
BUN	204	177	201	21	163	56	14
Crt	12.8	6.7	16.2	1.2		2.4	1.1
SGPT	138	118	63	455		117	11
SGOT	491	270	53	222	653	151	15
Tp	6.1	4.7	6.4	4.6		3.2	
Cholesterol	145		191	59	333	62	50

Abbreviations: 1. pc=parasite count, 2. rbc=red blood cells, 3. Hb=hemoglobin, 4. wbc=white blood cells. The units for pc, rbc and wbc are number per μ l. The unit for Hb is g/dl. ∞ =untreated.

していた例で、クレアチニンも2.1に上昇、腎結石も合併した症例 (Tsuchida *et al.*, 1982) である。

4. 最高クレアチニン濃度 (mg/dl)

平均値および異常値を示すものの割合は、いずれも熱帯熱の方が三日熱マラリアより多かった。しかし三日熱と卵形マラリアの間には、有意差はなかった。熱帯熱マラリアにおけるクレアチニンの分布は、BUN と類似した分布を示している (図 2 B)。

クレアチニンが16.2で2番目に高かった例は、BUN も201で2番目に高かった。本例の原虫数は215,500に達し、腹膜透析を12回繰り返して救命できた (三木ら, 1979) (表 2, 症例 3)。

5. 最高 SGPT (u/l)

マラリア患者にはしばしば黄疸が見られるので、肝機能障害の有無は注目されている。SGPT の平

均値および異常値を示すものの割合は、いずれも熱帯熱の方が三日熱マラリアよりも高い値を示した。最高値はそれぞれ455と260で肝炎患者に見られるような高値ではなかった (図 3 A)。SGPT が最高値を示した熱帯熱マラリア患者は腎機能障害が起きず、順調な経過をとって治癒した (表 2, 症例 4)。

6. 最高 SGOT (u/l)

SGOT の平均値および異常値を示すものの割合は、いずれも熱帯熱の方が三日熱マラリアよりも高い。最高値はそれぞれ653と180である (図 3 B)。SGOT が最高の653を示した症例は、マラリアの治療を受けず 9 病日に死亡、原虫数は253,700に達した。解剖で心筋毛細血管内に成熟マラリア原虫が感染した赤血球が、充満していた (海老沢, 谷, 1980) (表 2, 症例 5)。

7. 最低血清タンパク濃度 (g/dl)

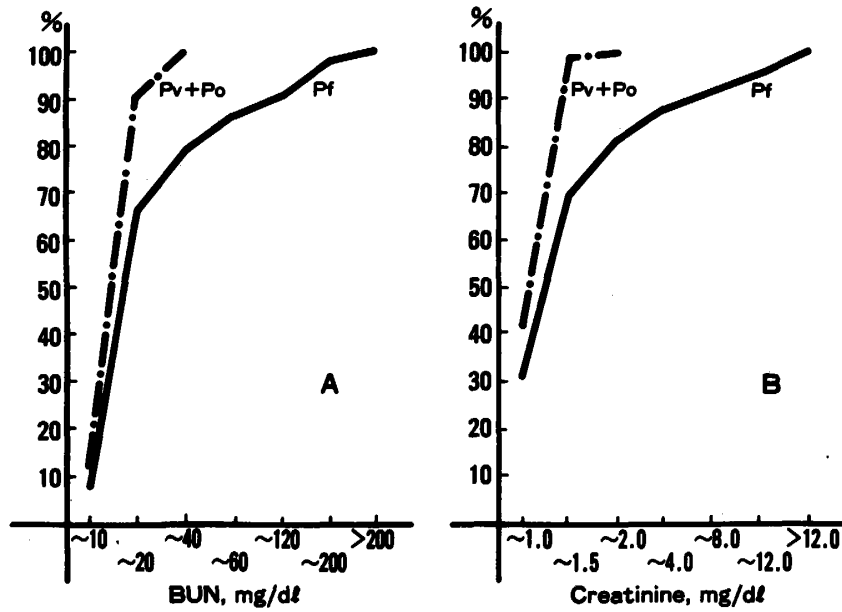


Figure 2 Cumulative percentage of the highest BUN (A) and creatinine (B) concentrations in malaria patients. See footnote to Fig. 1 for abbreviations Pf and Pv+Po.

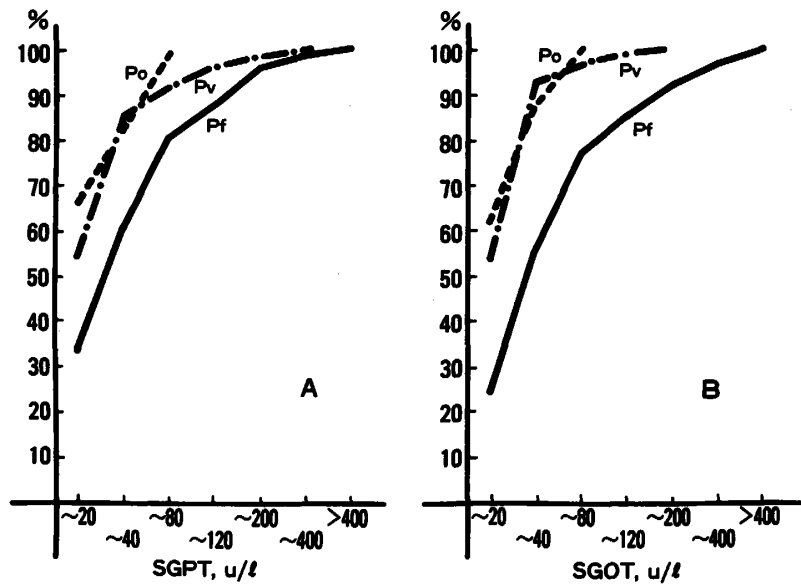


Figure 3 Cumulative percentage of the highest SGPT (A) and SGOT (B) activities in malaria patients. See footnote to Fig. 1 for abbreviations Pf, Pv and Po.

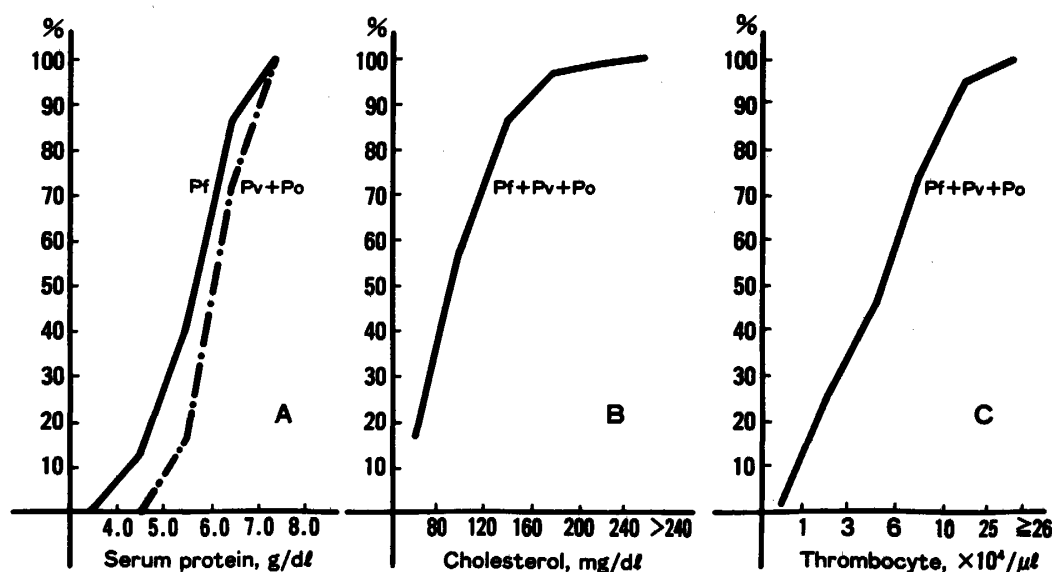


Figure 4 Cumulative percentage of the lowest serum protein (A) and cholesterol (B) concentrations and thrombocyte counts (C) in malaria patients.

See footnote to Fig. 1 for abbreviations Pf and Pv+Po. Pf+Pv+Po indicate that data of 3 groups are mixed together as cholesterol and thrombocyte count were independent of infecting parasites.

平均値は熱帯熱の方が三日熱より低く、異常値を示すものの割合は、熱帯熱の方が三日熱マラリアよりも高い。三日熱と卵形マラリアの患者間には差が見られない (図4 A)。

3.2の最低値を示した熱帯熱マラリア患者はインドネシアで感染した女性で、発病当初下痢が持続、原虫数は655,800に達し意識不明になった(杉山ら, 1989年)。クロロキン、ファンシダールおよびファンシメフの内服で全治したが、経過中全身浮腫と肺水腫を起こした (表2, 症例6)。

8. 最低血清全コレステロール (mg/dl)

マラリアでは、一時的なコレステロールの低下はよく見られる。しかし熱帯熱、三日熱および卵形マラリアでは平均値も、異常低値を示すものの割合も差がなかった(図4 B)。コレステロールが最低値50を示した熱帯熱マラリア患者は腎機能が侵されず、順調な経過をとった (表2, 症例7)。

考 察

マラリアの主たる臨床病態は、マラリア原虫感染赤血球の崩壊と、成熟した原虫感染赤血球による毛細血管の一時的閉塞で、これは特に熱帯熱マラリアに強く起こる。これらが重なってDICと強い血色素血症が起こる。腎糸球体血管も、成熟マラリア原虫感染赤血球により閉塞され、急性腎不全が起こる。毛細血管の閉塞は、この他に全身の臓器で起こる。

以上の病態生理学的機序を、直接あるいは間接に反映する検査所見LDH、総ビリルビン、尿素窒素、クレアチニン、SGPTとSGOTおよび血清総タンパク量は、感染原虫数が多くなる熱帯熱マラリアの方が、三日熱や卵形マラリアより異常値を示した。これに反してコレステロールと、前報で述べた血小板は感染原虫種に関係なく減少した。ただし極端な異常値は、コレステロールや血小板の検査でも熱帯熱マラリア患者に多く見られた。

以上の生化学的検査所見を見て、マラリアのう

ち最も危険なのは熱帯熱マラリアであり、生化学的検査の中ではBUNとクレアチニンが予後を占う上で、最も都合よい指標であると考えられる。腎不全を起こした例では、キニーネの点滴静注によるマラリアの治療と同時に、腹膜あるいは血液透析を行わねばならない。しかも患者の血液は、感染の危険がある病原体を多量に含んでいる。マラリア治療に経験あるものと、腎不全対策に慣れている医師達の共同が必要である。このような患者はまたDICを合併していることがあり、その対策も必要である。

SGPT, SGOTの増加に関しては血管内溶血と、血清ビリルビンの増加を起こしやすい疾患であるから、肝機能障害の指標として容易に理解できよう。今回の調査では発病当初だけでなく、全経過中の最高値をその患者の代表値とした。そのため用いた薬剤、例えばファンシダール(サルファドキシシンとピリメサミンの合剤)(Reisinger *et al.*, 1989), キニーネの点滴静注などの影響も考慮に入れるべきであろう。既存のアルコール性肝障害があったため、これらの値が高くでた症例も何人かあった。岩田ら(1982)が指摘したように、SGPT, SGOTいずれもウイルス性肝炎患者に見るような高い値は示さなかった。熱帯熱マラリア患者のSGPTとSGOTが、200を越えるものはそれぞれ3.7と7.3%しかいなかった。これらの成

績は、マラリア死亡例や回復期患者の肝生検所見で肝組織の構築が障害されていないことによって裏づけられよう。

結 語

- 1) 赤血球の崩壊に直接ないし間接的に関係する生化学的検査項目LDH, 総ビリルビン, 尿素窒素, クレアチニン, SGPT, SGOTは、感染原虫数が多くなる熱帯熱マラリア患者の方が三日熱マラリア患者より高い値を示したが、三日熱と卵形マラリア患者の間には有意差はなかった。
- 2) 血清総タンパク量は、熱帯熱マラリア患者の方が三日熱マラリア患者より低い値を示したが、三日熱と卵形マラリア患者の間には差がなかった。
- 3) コレステロール量は減少はしているが原虫種による差は見られなかった。
- 4) 熱帯熱マラリアの検査異常最高値はLDH (15,290), 総ビリルビン (42.3), BUN (204), クレアチニン (16.9), SGPT (455), SGOT (653), 異常最低値はコレステロール (50), 総タンパク (3.2) が示すように、特に溶血と腎機能障害の強さが著明である。熱帯熱マラリアでは、早期治療、特に重症患者では即効性静注用キニーネ使用の必要性を痛感する。

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BIOCHEMICAL ABNORMALITIES IN MALARIA

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Biochemical parameters of blood were analyzed statistically in the same way as in the groups of malaria patients mentioned in the accompanying paper. The parameters which directly or indirectly reflect intravascular hemolysis, i.e., lactic dehydrogenase (LDH), total bilirubin (TBil), blood urea nitrogen (BUN), creatinine (Crt), serum alanine aminotransferase (SGPT) and serum aspartate aminotransferase (SGOT) were elevated in malaria patients infected by *P. falciparum* (P.f.) significantly more than in malaria patients infected by *P. vivax* (P.v.) or *P. ovale* (P.o.). The differences in the biochemical parameters of the last two groups were not significant. The total protein (Tp) levels also showed the same order of decrease. Cholesterol (Chol) was decreased equally in malaria patients irrespective of the infecting parasite species. The maximum values of LDH (15,290 u/l), TBil (42.3 mg/dl), BUN (204 mg/dl), Creat (16.9 mg/dl), SGPT (455 u/l), and SGOT (653 u/l) and the lowest figures of Chol (50 mg/dl) and Tp (3.2 g/dl) in Pf malaria indicate the seriousness of this infection. The same parameters in vivax malaria are LDH (5,140), TBil (6.4), BUN (26), Creat (1.9), SGPT (260), SGOT (180), Chol (51) and Tp (5.2). The early treatment of falciparum malaria, within 5 days of the onset of illness, is emphasized to avoid serious complications.

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Note

THE ORTHODOX MODEL OF HEALTH CARE DELIVERY SERVICES AND THE FATE OF NIGERIA'S 64 MILLION RURAL DWELLERS: A SEARCH FOR A VIABLE HEALTH SUPERMARKET

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Abstract: This paper is purely theoretical in orientation and seeks to make the point that the archtype capitalistic orthodox model of health care delivery services currently operated in Nigeria, constitutes the greatest clog to human development in the rural area. In order to bring the discussion to bear, we examined the provisions made for health in the three national development plan and established how the perpetuation of this model limits opportunities in the rural area. The paper winds up making a number of suggestions on how the health status of these 64 million Nigerians can be improved.

INTRODUCTION

The potential for development is inherent in all human societies, what differ is the historically determined pool of strategies and tools which the members are able to mobilize in certain dimensions (Anikpo, 1984).

It will be proper to begin this paper by operationalizing the key variables in our somewhat rude title. Such explanations are however rendered within the context of this paper.

Orthodox medicine refers to the present model of health care delivery services with all its curative emphasis. We then arrived at the figure 64 million, by finding 80% of our present estimated population size of 80 million.

PREAMBLE

Not many scholars will dispute the fact that the ideological leaning of Nigeria takes after that of her capitalist oriented colonial master-Britain. Capitalism like any other political ideology favours asymmetrical allocation of resources between the rural and urban areas; with an unambiguous tilt towards the latter (Anikpo, 1984).

The implication of this for economic planning, is that in situations where -as in Nigeria- few urban centres exist and where the vast majority live in the rural areas, the gains of economic planning will continue to be elusive. A focus on the health sector afforded the

demonstration of this. On the whole, the paper built on the assumption that a healthy nation is contingent on healthy citizenry.

It therefore, limits itself to showing how our health planners limit the opportunities in the rural areas by perpetuating the orthodox model which encourages uneven allocation of health resources. Therein lies the thrust of this paper. The paper winds up by looking at how the health status of the Nigerian rural dweller can be substantially improved.

THE DEFINITION OF HEALTH

The World Health Organization (1964) defined health as "... a state of complete physical, mental and social well being, not merely the absence of disease or infirmity". Commenting on this definition, Lewis (1953) argued that "... in practice, it is the presence of disease that can be recognised, not the presence of health". Continuing, he noted that there are no positive indications of health that can be relied upon and on the basis of this, declared healthy, everyone who is free from any evidence of disease or infirmity.

Nigeria is a former colony of Britain and like her colonial master, operates the orthodox model of health care delivery services, with all its curative emphasis.

The unfortunate thing about this model is that it has led many third world nations who were former colonies of these western nations and who still retain the capitalist ideology; into formulating over-ambitious health policies that not only fail to capitivate their world view, but also considered wasteful in terms of cost and in the light of social epidemiological reports. It should however be stressed that such a model of development which seems to assume that Nigeria needs replica 'infrastructure' to be as developed as their Euro-American counterparts is, to use Anikpo's word, a product of 'misguided paternalism' and it is neither limited to the health sector of our socio-economic life, nor typical of Nigeria. The implication of the perpetuation of such a false model of development for the health sector, has been a gross insurfficiency in the health care delivery serices of these nations, while the mass of the people continue to live in squalor and consequently in disease (Olugbile, 1981; Hill, 1970).

NATIONAL PLANNING

It is a common knowledge that the goal of economic planning in developing nations like Nigeria is for the realization of a high standard of living, for a substantial proportion of the population (Rodney, 1972). Similarly, Erinoshio (1981a) has argued that: health planning for developing countries is aimed at ensuring for the average citizen in the population, access to medical care and other basic facilities, which would enable him/her to attain a resonably high health status and long life-expectancy.

While the authenticity of this goal is not in doubt, analysts have continually stressed that the modalities employed are always influenced by the ideological orientation of such countries. A look at the Nigerian economy will facilitate this.

THE NIGERIAN ECONOMY

The economy of Nigeria hinges on an ideological orientation which emphasises a capitalist mode of production (Onimode, 1983). Capitalism like socialism or communism

Table 1 Sectorial distribution of investment spending, First National Development Plan, 1962-1968 (Secondary source: Anikpo, 1984)

Sector	Rural	Urban	Rural-Urban*
Trade & industry	2.6	97.1	0.3
Electricity	0.6	97.7	0.5
Communications	0.0	91.4	8.6
Health	3.9	76.2	19.9
Information	0.0	37.8	62.0
Social welfare	9.2	90.8	0.0
Water supply	39.6	58.5	1.9
Total	4.9	91.7	3.4

* Under this heading are public expenditure items disaggregated into rural and urban component.

Table 2 Sectorial distribution of investment, Second National Development Plan, 1969-1974 (Secondary source: Anikpo, 1984)

Sector	Rural	Urban	Rural-Urban
Industry	4.7	5.3	0.0
Commerce & finance	1.6	8.4	0.0
Electricity	11.0	89.0	0.0
Communications	0.0	100.0	0.0
Health	6.6	43.1	50.4
Information	0.0	53.0	46.1
Labour & social welfare	28.2	66.1	5.7
Water & sewage	14.7	60.8	24.6
Town & country planning	0.1	81.4	9.4
Total	8.0	79.6	12.5

breeds industrialization and the latter in turn breeds unequal allocation of resources (Anikpo, 1984). Be that as it may, it is the contention of this paper, that capitalism, more than any other system limits opportunities in the rural area by championing rural neglect. A look at the sectorial distribution of investment in the First, Second and Third National Development Plan will reveal this.

Table 1 depicts the sectorial distribution in investment spending in the First National Development Plan, 1962-1968. Even a cursory look will reveal the factor of inequality between the allocation for rural and urban areas. It is of note to point out that a total of less than 5% went to the rural sector. This pattern highly contradicts the goals of the First National Development Plan, which was to raise the rate of economic growth and to have the nation's economy (Olatunbosun, 1975). A look at Tables 2 and 3 will show that this trends has continued unabated.

It will be inconceivable, given the level of our industrialization and the fact that agricul-

Table 3 Sectorial distribution of investment spending in the Third National Development Plan (Source: Anikpo, 1984)

Sector	Rural		Urban		Rural-Urban	
Industry	3.4	8.9	96.7	91.0	0.0	0.0
Commerce & finance	4.9	2.2	86.7	96.8	8.4	1.0
Electricity	21.9	23.9	78.1	76.1	0.0	0.0
Communications	0.1	0.1	97.5	98.4	2.3	1.5
Health	13.3	7.2	50.0	75.7	36.7	17.1
Information	0.0	0.0	67.4	53.2	32.6	46.8
Social welfare	0.4	0.5	68.3	84.8	31.3	14.7
Water supply	23.6	20.0	68.3	70.6	8.2	9.4
Sewerage & drainage	0.0	0.0	100.0	100.0	100.0	0.0
Town & country planning	2.5	1.3	88.7	89.3	8.8	9.4
Cooperative & supply	9.9	16.4	16.5	9.0	75.6	74.4
Community development	74.2	84.3	7.0	15.7	18.7	0.0
Labour	0.0	0.0	100.0	100.0	0.0	0.0
Housing	0.0	0.0	100.0	100.0	0.0	0.0
General administration	0.7	0.0	84.5	41.8	14.8	58.2
Defence security	0.0	0.0	39.0	9.2	61.0	90.8
Total	4.1	4.6	78.4	58.1	17.5	37.3

The first column under each sector shows planned budget allocation (%), while the 2nd column shows actual spendings.

ture formed the economic mainstay of Nigeria, during the First National Development Plan period, to suggest that industrialization influenced the minds of our economic planners. But let us assume for the purposes of analysis, that it is difficult to establish the extent to which industrialization influenced their minds. What it boils down to is that we have been able to authenticate the fact that capitalism like socialism or communism favours lopsided allocation of resources between the rural and urban areas.

It therefore, becomes clear that a look at the sectorial distribution alone cannot uphold our contention that capitalism, more than any other political ideology, limits opportunities in the rural areas by promoting urban bias and rural neglect in resource allocation.

What is needed is an examination of the policy implications for urban bias and rural neglect, of any aspect of our socio-economic life, the choice of which is highly influenced by our ideological leaning and least by industrialization. For the purposes of this work, we shall pick on the health sector. This choice is deliberate.

THE HEALTH SECTOR

The Nigerian medical system is organised along the capitalistic Euro-American model. And like an all-time capitalist oriented countries, the economies of the United States, Britain and Sweden are predicated on a regulated free enterprise. In the United States, health care is left wholly in the hands of entrepreneurs, who act as fronts to the various insurance

companies which exist to provide coverage for all aspects of medical care. Under such dispensation, Erinosh (1981b) noted that the citizenry is left at the mercy of those insurance companies which obviously derive great human and material benefits from the sale of health policies. The physicians in this country also derive high income in their practice, whilst the highest quality care is reserved for the highest bidder.

Health care delivery services in Britain and Sweden on the other hands, take the same form as that of the United States, except that in the latter, some powerful pressure groups who feel strongly about state participation in some aspects of their socio-economic life, have persuaded their governments to introduce a National Health Insurance Scheme. It is of note to say that this scheme has made it possible for the poor and the rich to have access to a heavily subsidized health care delivery services (Erinosh, 1981b).

In Nigeria, orthodox medicine exist side by side with traditional medicine, event though the latter is older and yet to be accorded official recognition.

As a practice that was borne out of the colonial experience, it emphasizes curative, rather than preventive health services; whereas, social epidemiological researches have made it clear that most prevailing diseases in Africa are preventable. Furthermore, orthodox medicine is founded on science and like an archtype scientific practice, limits its explanation of diseases causation to physical or biological discontinuity, whereas, the African view of it, incorporates the physical as well as the psyche realm (Chilivumbo, 1976; Mbiti, 1976; Ndeti, 1976; Oke, 1982).

Two third of the recognised health institutions in Nigeria are owned by the federal government (Sunday Tribune, 1985). While the other one third is made up of private

Table 4 The capital programme by activity (health) in the Third National Development Plan (million)

Government	Hospital programmes	Basic health services programmes	Training programmes	Supporting health programmes	Total
Federal	212.000	51.000	24.000	26.960	314.160
Benue Plateau	12.040	12.980*	3.500	2.150	30.670
East Central	36.622	17.600	4.000	4.399	62.621
Kano	8.289	18.850*	4.000	1.300	32.430
Kwara	11.000	12.100	3.500	1.900	28.500
Lagos	41.501	7.700*	4.100	0.600	53.901
Midwestern	20.700	10.570*	3.750	4.670	39.690
North Central	5.200	15.050*	3.500	0.060	23.810
North Eastern	6.750	22.000	5.000	9.150	42.900
North Western	11.357	14.310*	4.000	0.883	30.550
Rivers	22.150	6.450*	3.500	2.703	34.805
South Eastern	11.500	7.700	3.500	0.150	22.250
Western	7.310	22.865*	3.500	9.366	43.041
Total	406.410	219.175	70.050	64.293	759.928

* Allocation includes cost of projects concerning the control of communicable diseases and other preventive activities.

hospitals.

Despite such massive participation by the government, the extent to which treatment is subsidized is highly questionable given the fact that most of the hospitals are without the necessary facilities (Newswatch, 1986).

Other problems centre around the urban based nature of orthodox medicine, which encourages the few number of personnel she parades to cluster around urban centres, high cost of training paramedical staff etc. A focus on the provision for health under the Third National Development Plan will establish the above claims.

Table 4 depicts capital programme by activity (health) in the Third National Development Plan period. A total of 759.928 million was allocated to programmes in health sector during this planning period. Of this sum, a staggering sum of 406.410 million was spent on hospital programmes by both the federal and the then 12 states in the federation. Of the remaining 540.753, a total of 219.175 was spent on basic health services programmes: 51 million by the federal government and 168.075 spent by the federal and state governments on training and supportive health programmes respectively.

For the purposes of clarification, let us quickly say that hospital programmes involve the building, expending or re-activation of existing hospitals, clinic, maternity etc., while basic health services programmes are devoted to the eradication of communicable and other preventable diseases. Training programmes involves both the provision of training facilities and the actual training of paramedical personnel. Supportive programmes on the other hands, are "chiefly concerned with pharmaceutical and drug manufacturing laboratories, medical stores, purchase of special vehicles and accomodation for both junior and senior officers" (see 3rd NDP).

We have seen from Table 4 that the greater proportion of the health budget for the 3rd National Development Plan period was devoted to executing hospital programmes. These hospitals are mainly concentrated in the urban areas, where only 20% of Nigeria's 80 million people live. A look at the 1969 United Nations estimate will corroborate this.

Table 5 shows the 1969 United Nations estimate of the total population of rural dwellers and urban dwellers in Nigeria by year. It is readable from the Table that a total of 89.8% of Nigeria's 30.4 million people lived in the rural area in 1953, as opposed to 10.2% who resided in the urban areas. A decade later, she again estimated 80.7% and 19.3% from a population of 55.7 for the rural and urban dwellers respectively. Despite the reservations people have expressed about these estimates, which they claim was based on the 1953 and 1963 controversial head count, many analysts are agreed today, that at least 80% of Nigerians live in the rural areas (Olugbile and Oyemade, 1981; Newswatch, 1986; Times International, 1986).

Table 5 The rural and urban population of Nigeria in 1953 and 1963 (Ekanem, 1972)

Year	Total Nigerian population	Total rural population	Total urban population	No. towns with 20,000
1953	30,402,000	27,307,000 (89.8%)	3,101,000 (10.2%)	54
1963	55,672,000	44,943,000 (80.7%)	10,729,000 (19.3%)	183

A look at the location for hospital programmes during the Third National Development Plan period, will authenticate the fact that they are mainly urban based. In line with this, studies have shown that at least 2/3 of the population of Nigeria's doctors are concentrated in 7 cities, 6 of which are locations for the older universities; while more than 1/2 of the remaining 30% of available doctors are concentrated in the big towns in the country. The same urban concentration is also true for all other categories of western trained health personnel (Ademuwagun 1969).

The irony of the perpetuation of the orthodox model, is that even our very colonial orthodox-approach-oriented health planners are aware that 95% of our killer diseases are preventable (3rd NDP).

IMPLICATIONS

The implication of perpetuating the present health model with all its curative emphasis, and numerous urban based hospitals and health personnel was driven home by Erinsho (1981a) when he noted that under such an arrangement; the real issue, namely, the provision of medical care for a substantial proportion of the people in the population inevitably assumes secondary place in the scheme of things.

Indeed, a situation in which 80% of our 80 million live in the rural areas and are ill-provided with medical facilities, cannot be said to be healthy. This view tallies with that expressed by Anikpo (1984) when he noted that given the biases in the sectoral distribution of investment in the Third National Development Plan: Nigeria's present underdevelopment seems less surprising since even from a purely economic point of view, the development of over 80% of the population was never part of the planning process.

Furthermore, if we accept the truism that a healthy nation is contingent on healthy citizenry and will allow Hill (1970) to persuade us that poverty breeds diseases and vice versa then we cannot but come to the sad conclusion that the very life-blood of the 'neglected' 64 million rural dwellers in Nigeria are by the perpetuation of orthodox model, wittingly or unwittingly sucked, and each of them turned into a misfit agent of development. The implication of this for the economic rating of this country, is that we shall continue to remain a developing nation.

DISCUSSION

I have demonstrated in the course of this work, that health planning under capitalism cannot guarantee adequate health need for a substantial part of the population. This is because capitalism generally promotes the interest of the few at the expense of the majority.

What is needed therefore is for us to adapt an ideology under which we can evolve a health care model that will be geared towards achieving for the average citizen in the population, access to medical care and other basic facilities, which would enable him or her to attain a reasonably high health status and long life expectancy. This ideology is the African ideology.

African ideology is solely based on African spiritual communalism. It is neither socialism nor welferism, it is an ideology which embodies the indigenous African principles of live and let live, collective sharing, common concern for one another; sense of belonging together;

social justice; economic progress and viability for all . . . (Onwuachi, 1977).

It can be argued that Nigeria is still a face-to-face society, where relationships with kins and neighbours matter a lot. This is in line with the values of African spiritual communalism. An effective way of incorporating the values of African ideology into our health planning, is for us to formulate health policies that are geared towards the mass of the people.

We can best achieve this by relying on social epidemiological reports, which have continually shown that by far the greater, proportion of the prevailing diseases in tropical Africa, are preventable.

It will therefore be a step in the right direction to increase the emphasis on primary health care scheme while de-emphasizing the orthodox model, with all its curative emphasis, expensive urban based hospital scheme and huge cost of training paramedical personnel (see 3rd. NDP).

Analysts like Hill (1970), Olugbile and Oyemade (1981) have demonstrated that the control of diseases is dependent on the extent to which we can successfully improve the quality of our environment. To this end, it will be wise for us to divert funds that would have been going into new hospital scheme, to the provision of pipe borne water, electricity, drainage, waste disposal and adequate shelter -for our rural population, who presently lack these things (Newswatch, 1986).

It will serve a useful purpose to educate our people, both in the rural and urban areas, on the need to keep a clean environment. Here, the rebirth of the environmental sanitation by the present administration is a welcome development. However, we may still have to train health educators to meet this end. A major aspect of the duties of these health educators, will be to demonstrate to the people, especially these is the rural areas, that most diseases have cultural origins and for them to co-operate with health workers, to abolish such cultural practices which limit rather than promote life.

It will also help if the government can recognize and integrate the traditional healers into the mainstream of our health care delivery services. This is the only rational way out. I therefore agree with Olatunbosun (1975), when he noted that: the choices before us are clear; either we have a meaningful rural development plan based on equity and social justice, or we must forfeit a golden opportunity to achieve a decent level of living for all men, whether in the urban or rural areas.

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