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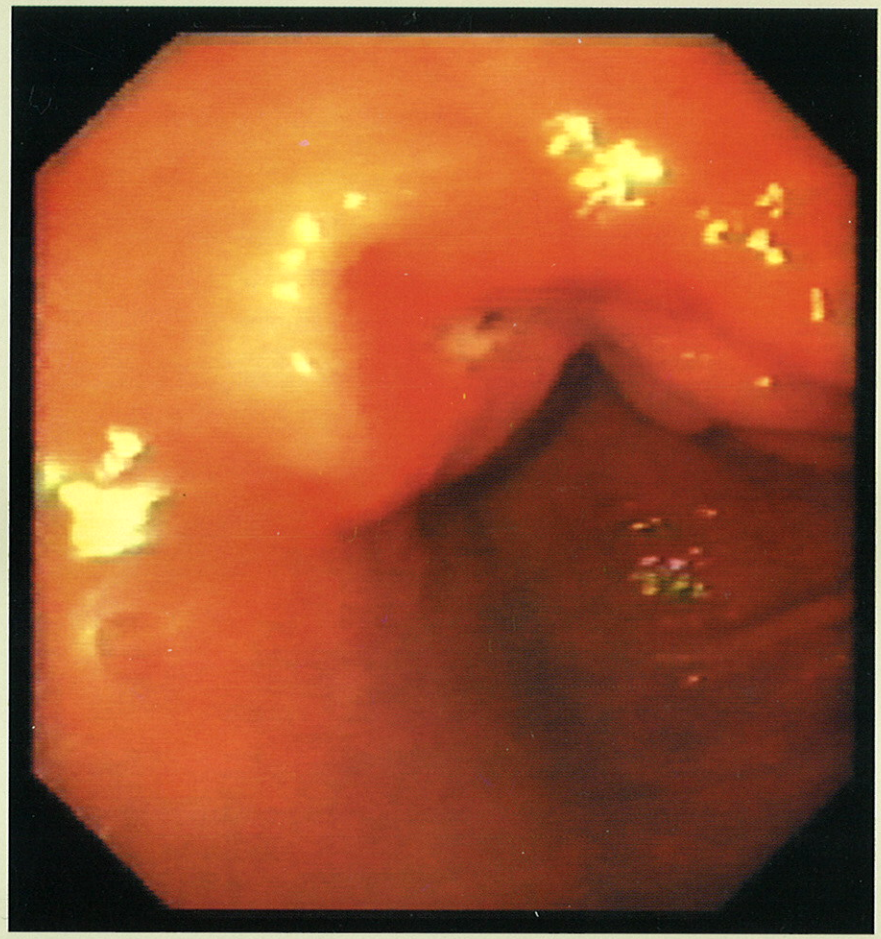

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Duodenal ulcer seen on a gastroscopy

(Courtesy of Professor K L Goh, Department of Medicine, University of Malaya Medical Centre)

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MALAYSIAN SOCIETY AND HEALTH: ISSUES AND CHALLENGES IN THE 21ST CENTURY

Introduction

Health is complete physical, mental, social well-being and not only the absence of illness of an individual.
WHO/Allopathic Practitioner

Health is not simply a physical or a mental state. Health is a state of balance in the body, the family, the village, the country, and the world.
Sri Lankan Ayurvedic Practitioner

In a new era, Malaysia may be well on the road towards achieving developed nation status. To some extent and in comparison to neighbouring countries, Malaysian society today enjoy relatively high standards of living, above-average health status, political and economic stability. Yet, we must not become complacent. With the dawning of the new millennium, there are also numerous challenges to our society, not least of which is ensuring the availability of sustained quality health care and services. The recent economic and financial climate pose serious challenges to the Malaysian health care system and our above-average health status. There is also the need to continually improve the management of our health care system to cope with changing demography, rapid social change due to modernisation/urbanisation, newly emerging as well as re-emerging diseases previously well-controlled.

Health status

Access

Malaysians today enjoy greater accessibility to health services as indicated by the proportion of doctors per 10,000 population that had trebled from 2.6 in 1980 to 6.8 in 2000. Eighty-eight percent of the urban poor and 77% of the rural population are within 9 km of either a Government or private clinic. It is important to point out that these milestones towards achieving good health status had been gained with relatively low health expenditure. The 1996 National Household Health Expenditure Survey (NHHES) found that although private healthcare costs were higher, private facilities were the most frequently utilized sources of care for acute conditions. However, for inpatient care, the low-income group tended to utilize services provided by the public or government health sector (Eighth Malaysia Plan 2001-2005).

Mortality

It is an undeniable fact that Malaysians enjoy a relatively good health status as reflected in our selected health indicators (see Table 1). Increasing life expectancy and the sustained decline in infant (IMR) and maternal mortality rates (MMR) are significant indicators of the above average health status of Malaysian society. Male life expectancy has been increasing from 66.7 years in 1980 to 70.2 years in 2000, while Malaysian women today are expected to live up to 75 years. As shown in Table 1, the sharp decline in the Malaysian infant mortality from 19.7 per 1000 livebirths in 1980 to 9.5 per 1000 livebirths in 2000 is an impressive achievement, comparing to that for middle-income and high-income countries. However, IMR rates for Sabah and Sarawak are not comparable to that in the Peninsula because of under-reporting, lower level of development, and higher proportion of births delivered by untrained birth attendants (WY Low *et al*, 1996).

Over these last 20 years, maternal deaths had not only been significantly reduced, from a MMR of 0.6 per 1000

Table 1. Selected Indicators of Health Status

Health Status Indicator	1980	1985	1990	1995	1997	2000[P]
Life Expectancy: Male	66.7	67.9	69.0	69.3	69.6	70.2
Female	71.6	73.0	73.5	74.0	74.5	75.0
Crude birth rate (per 1,000)	30.9	31.7	28.4	28.0	25.5	24.5
Crude death rate (per 1,000)	5.3	5.0	4.7	4.4	4.6	4.4
Doctors per 10,000 population	2.6	3.2	3.8	4.5	6.6	6.8
Dentist per 10,000 population	0.5	0.7	0.7	0.9	0.9	0.8

Source: Sixth Malaysian Plan; Vital Statistics Malaysia 1997; Social Statistics Bulletin Malaysia 2000.

Note: P – preliminary figures

livebirths to 0.2 per 1000 livebirths, but the latter has been sustained since 1995. Once again, we need to take note of the regional and social class differences. For instance, while the rate of decline seems more rapid for Peninsular Malaysia, it has appeared to have stabilized in the eighties period due to the lag in development in Sabah (0.4 per 1000 livebirths in 1998). In Sabah, the implications of migrants from poorer neighbouring countries have to be considered, that is, their lower socio-economic status impacting upon infant and maternal mortality (MOH, May 2000).

Morbidity

As has been mentioned earlier, Malaysian society experience both infectious and chronic diseases due to the health or epidemiologic transition that we find ourselves in today.

Communicable/Infectious Diseases

Malaysia has been successful in controlling communicable diseases through child immunization programmes, provision of safe water supply, proper sanitation and waste disposal, and food quality control. For example, the immunization program in 1999 achieved 100% coverage for BCG, 94.1% for the triple antigen vaccine (diptheria, pertussis and tetanus), 86.2% for measles, and 93.4% for poliomyelitis. Indeed, Malaysia was declared a polio-free area in October 2000. The incidence rate for malaria declined from 286.1 per 100,000 population in 1995 to 60.8 in 1999 (Eighth Malaysia Plan 2001-2005). Outbreaks of dengue haemorhagic fever occur periodically, more so in urban areas. A seasonal variation in dengue outbreaks has been identified, with increased rates during the dry season (May to September) (Sekhar & Ong 1992/93). Malaysian society was recently shaken by the emergence of the Nipah Virus outbreak. Learning from this experience, efforts to establish the Infectious Disease Centre were started in 1999; and rapid response and greater collaboration efforts were established through the inter-ministerial committee and networking with international bodies, such as, WHO and the CDC in Atlanta (Eighth Malaysia Plan 2001-2005). Full coverage of piped water supply was achieved for urban areas and 84% for rural areas in 2000. These efforts contributed to a reduction in the incidence of water-borne disease from 3,500 in 1995 to 2,100 in 2000. The rural sanitation program covered 99% or 1.7 million households in the same year (Eighth Malaysia Plan 2001-2005).

Malaysian society ought to wake up to the HIV/AIDS epidemic in our midst impacting on everyone – men, women, adults and adolescents, and not confined only to intravenous drug users. The data point to a dramatically increasing trend since the first cases were identified in 1986. The HIV/AIDS incidence rate increased steadily over the ten years, from 0.01 per 100,000 population in 1987 to 2.43 per 100,000 population in 1997. Whilst the mortality rate of AIDS followed a similar increasing trend from 0.02 per 100,000 population in 1988 to 1.88 per 100,000 in 1997 (Abu Bakar Suleiman & M Jegathesan, undated). From 3 HIV cases in 1986, the number escalated to 4692 cases in 1999, with a cumulative total amounting to 33,233. The cumulative total for AIDS cases was 3,554 in 1999. Ninety-four percent of these were men and six percent were women. The upward trend for women is noticeable since 1995 and this is worrisome. Forty-two percent of the HIV+ cases were below 29 years of age and 30 per cent of AIDS cases were found within this cohort. Although a relatively small proportion (4 per cent) of known AIDS cases were adolescents (13-19 years), 22 percent of them were between 20-29 years. This latter group may have first contracted HIV during their teens, given the possibly lengthy period between viral infection and appearance of disease symptoms. Indeed, data showed that the Heterosexual category had the second highest proportion of HIV+ and AIDS cases, following after the intravenous drug user category (Malaysian AIDS Council, 2000).

Table 2. Principal causes of hospitalisation in government hospitals, Malaysia, 1998

Principal causes	Number of discharges
Total	1,552,845
Normal delivery	305,380
Complications of pregnancy	186,994
Injury and poisoning	162,170
Diseases of the circulatory system	103,512
Certain conditions originating in the perinatal period	83,022
Diseases of the respiratory system	101,123
Diseases of the digestive system	72,006
Signs, symptoms and ill-defined conditions	63,120
Infectious and parasitic diseases	116,703
Diseases of the urinary system	68,590
Diseases of the blood and blood forming organ	10,749
Others	279,476

Source: Social Statistics Bulletin 2000

In terms of programs, the Ministry of Health Malaysia began monitoring and surveillance since 1985 of the numbers afflicted by instituting mandatory reporting under the Prevention and Control of Infectious Diseases Act (1988). In 1995, a Malaysian AIDS Charter was launched by the Minister of Health, a document formulated by nearly 80 government and NGO agen-

Table 3. Deaths by medically certified and inspected cause, Malaysia, 1994-1998

Cause of death	Year				
	1994	1995	1996	1997	1998
Total deaths	38,223	41,395	41,694	44,154	43,514
Pneumonia	1,245	1,492	1,433	1,670	1,865
Tuberculosis	525	524	573	569	573
Septicaemia	1,980	2,399	2,641	2,741	2,923
Malignant neoplasm of tranchea, bronchus and lung	832	884	821	909	941
Malignant neoplasm of female breast	260	320	297	339	339
Malignant neoplasm of cervix uteri	165	142	146	129	177
Diabetes mellitus	720	734	677	807	729
Hypertensive disease	275	285	362	530	450
Acute myocardial infarction	3,166	3,383	3,306	3,426	3,328
Other ischaemic heart disease	899	931	932	1,039	1,062
Cerebrovascular disease	3,136	3,349	3,271	3,355	3,367
Atherosclerosis	5	5	2	1	1
Other diseases of circulatory system	3,274	3,664	3,621	3,830	3,902
Motor vehicle traffic accidents	2,039	2,289	2,693	2,985	2,577
Suicide and self-inflicted injury	36	52	92	177	200
Homicide and injury purposely inflicted by other persons	47	44	74	117	141
Other violence	2,303	2,534	2,429	2,300	2,115

cies involved in AIDS-related activities, in consultation with people with HIV/AIDS, representatives from various groups, including religious leaders and sex workers. This Charter explicitly states the rights and responsibilities of individuals, organisations and government bodies pertaining to AIDS, and addresses significant issues such as testing, confidentiality and access to information and education (WY Low *et al*, 1996).

Among the principal causes of hospitalisation at government hospitals in 1998 in Malaysia, excluding normal birth deliveries and pregnancy complications, injury and poisoning and infectious and parasitic diseases were prominent causes (Vital Statistics Malaysia 2000).

Data on deaths by medically certified and inspected cause in Table 3 show that septicaemia, pneumonia and tuberculosis were the most common fatal infections in 1998, accounting for 6.7%, 4.3% and 1.3% of total deaths (35,612), respectively. Moreover, there was an increasing trend for all three diseases for the period 1994 to 1998 (Vital Statistics Malaysia 2000).

Chronic Diseases

Chronic diseases have become more prominent in this country with time. Part of the increase in chronic ailments is due to improved longevity among Malaysians as mentioned earlier. At the same time, economic progress and increased affluence have been accompanied by changes in lifestyle, including diet, which have also contributed to this change in disease pattern.

The Second National Health Morbidity Survey showed increasing incidences of non-communicable or chronic diseases amongst the Malaysian population, such as, hypertension, diabetes, and obesity as well as mental disorders (Eighth Malaysia Plan 2001-2005). A review of hospital deaths also revealed the relative importance of adult non-infectious diseases related to lifestyle, occupation and environmental risks such as cardiovascular diseases, cancers, injuries, and accidents. While deaths due to communicable/infectious diseases and fevers have seen marked reductions in all age-specific groups, deaths from accidents, cardiovascular related diseases, and cancers have increased in almost all age-specific groups between 1982 – 1996 (Abu Bakar Suleiman & M Jegathesan, undated, pp 409-410).

Table 3 shows the increasing prominence of non-communicable illnesses, such as heart disease and cerebrovascular disease, compared to infectious diseases such as pneumonia over the period 1994 - 1998. The most common certified cause of death continues to be cardiovascular, particularly acute myocardial infarction, and cerebrovascular disease. As a group (hypertensive disease, myocardial infarction, ischaemic heart disease, cerebrovascular disease, artherosclerosis and other diseases of the circulatory system), these conditions constitute about 27% of total deaths in 1998 (Social Statistics Bulletin 2000).

Malignant neoplasms have increased as a contributor to total deaths in this country, particularly malignant

neoplasms of trachea, brochus and lung (see Table 3). In 1999, the annual prevalence of cancer in Malaysia was estimated to be 230 per 100,000, and the annual incidence was estimated to be 30,000. The incidence of cancer is expected to rise with an increasingly ageing population. A regional cancer registry has shown that the ten leading cancers among men were lung, nasopharynx, stomach, urinary bladder, rectum, non-Hodgkin's lymphoma, larynx, liver, colon, and the oesophagus. While the ten leading cancers among women were cervix, breast, ovary, lung, nasopharynx, oesophagus, thyroid, colon, rectum, non-Hodgkin's lymphoma (Social Statistics Bulletin 2000; Ministry of Health, 1999, pp 219-220). It is important to note here that cancer of the lung is the most common killer amongst malignancies.

Mental Health

Until very recently, relatively little attention has been paid to mental health issues in this country despite the growing manifestations. Hence, it is timely to take note of this problem here. Mental health problems tend to bear the stigma of shame and embarrassment for family members, and hence, are kept concealed. Skilled manpower resources, such as psychiatrists, psychologists, counsellors and behavioural scientists, capable of dealing with mental health issues are very much lacking in this country in this stage of its development. It is alleged that traditions, religious beliefs, and social behaviours have important influences on suicide in every country, as illustrated in the consistently low rates in Islamic countries and rising trends in societies experiencing rapid social change (Ministry of Health, 1999).

As an indicator of mental health, the number of deaths due to suicides and self-inflicted injuries had increased from 36 or 0.1% in 1994 to 200 or 0.4% in 1998 (see Table 3). While data collected from the Ministry of Health hospitals from all states showed that there were 2,931 suicide cases in 1996 and 2,738 cases in 1997. In Malaysia, the suicide rate is 3 per 100,000 population which is relatively low as compared to a rate of 20% in France (1990). The suicide rate prevalent in a society is said to be one of the important indicators of its socioeconomic structure and status and is determined by various psychological, socio-economic and cultural factors. There seemed to be a gender difference in suicide rate, as shown in data on suicide and parasuicide from public hospitals in the country whereby the rate among women was higher than that among men for the years 1995, 1996 and 1997 at 59.9%, 63.3%, and 60.8% respectively (Ministry of Health, 1999). Data on attempted suicides admitted to a major public hospital in the capital city showed that the majority were women of lower income, low education, Indian ethnicity, and younger age (<39 years) (Mohd Hussain *et al* 1992/ 1993). There were twice as many women as men among the cases. Depression caused by maladjustment to psychosocial stressors, particularly financial problems and interpersonal conflicts with spouses, friends and family members, was the main predisposing factor involved in the suicide attempt.

Health Issues and Challenges

Despite the tremendous health gains and above-average health status that Malaysians now enjoy as described above, we are compelled to take stock of the emerging health issues as well as to handle serious challenges to our health in the 21st century. These include changing trends in diseases due to demographic and health transitions, environmental health, migration influxes and health, effects of gloablisation on health, mental health and wellness as well as fundamental access and equality in health care.

Demographic and Health Transitions – Impact on Morbidity Patterns

The changes in the Malaysian demographic profile that will warrant attention from the health sector are our gradually ageing population, urbanization/modernization, the nuclear family structure, and a population that is increasingly health conscious (Abu Bakar Suleiman & M Jegathesan, undated). In the foregoing discussion on diseases, some of the recorded changes in the pattern of morbidity have been due to changes in the age composition of the population. At the same time, modernisation has also influenced society's values and behaviour with an impact on both communicable and non-communicable diseases. For example, demographic changes have led to an increase in the number of adolescents and young adults being exposed to the related rise in the risk and prevalence of sexually transmitted diseases. Moreover, changing attitudes towards sexuality might also influence sexual behaviour and the transmission of disease. Thus, how sex education can impact positively on sexual behaviour in the future and how to prevent or diminish the incidence of disease will be one of the future challenges. Although generally Malaysia has been successful in controlling communicable diseases, some of these, such as, HIV/AIDS , dengue, and tuberculosis will continue to be a challenge together with non-communicable diseases such as cardiovascular-related diseases, cancers, and accidents. Thus, we would need to be vigilant in sustaining the health successes and gains and not be lulled into complacency.

Environmental degradation and Health

The Ministry of Health has identified environmental factors to be the major contributors to the health problems of Malaysian society in the future. Environmental degradation is becoming a great concern for the coun-

try because it will undermine the sustainability of social and economic development and health. The three areas pertinent to environmental consideration and public health are water pollution, air pollution, and the management of solid waste. The MOH alleged that the observed rise in cardiovascular diseases, cancer, and accidents should not attributed entirely to individual lifestyle changes or viral infections. Instead, environmental and occupational hazards such as industrial conditions, crowded roads and pollution are major causes of injuries, respiratory disease, linked cardiovascular disease, and cancer. The impact is more marked in males in the 30-63 years age group, particularly in relation to accidents, cancers, and heart attack rates. It is important to note the MOH views seriously the effects of urbanisation on the environment and health. The urban areas, with the "built environment", are now faced with a host of new problems arising out of atmospheric and water pollution, accidents, urban housing, town planning as they relate to mental, social, and physical health (Abu Bakar Suleiman & M Jegathesan, undated; WY Low *et al*, 1996).

Migration and Health

Here, we are concerned with the issue of foreign migrant workers in particular. As Malaysia's relative favourable socioeconomic conditions have drawn a large pool of foreign workers, it has also created a whole set of health and social issues and problems, especially in the introduction and transmission of diseases and different value systems that need to be addressed. In 1994, foreign workers represented 35.4% (118 cases) of the total reported cases of leprosy nationwide. With regards to tuberculosis, they constituted 10.5% (1,230 cases) of the total, and they made up 12.6% (7,421 cases) of new cases of malaria. Foreign workers constitute a large proportion of the urban poor living in unhealthy and crowded squatter/slum conditions, leading to problems of violence and disease infection (Abu Bakar Suleiman & M Jegathesan, undated).

Globalisation

With the fervour about globalisation raging around us, it is also increasingly acknowledged as a force that is changing our lives, including our health, far beyond financial markets and international trade. Changes in trade and markets, the movement of people, goods and services including trade in legal and illegal substances, contaminated foodstuffs, inappropriate medical technology and in military arms are being facilitated by the globalisation process. It is, thus, a concern that continuing globalisation reduces the control that governments have over a growing number of health determinants that derive from the international transfer of health risks (Abu Bakar Suleiman & M Jegathesan, undated).

Mental Health & Wellness

As it has been mentioned earlier that mental disorders are one of the chronic diseases that have been on the rise. However, the issues of early recognition and detection in the form of depression and anxiety illnesses are being taken seriously only recently. Another issue is the failure to link the relationship between mental health and physical illness, and hence the inadequate as well as ineffective treatment being given to mental health patients. For instance, while millions of dollars are spent on reduction of cigarette smoking, there are few attempts to relate smoking behaviour to mental health factors in the smoker. Similarly, in health promotion efforts to reduce obesity so as to decrease incidence of non-insulin dependent diabetes and cardiovascular diseases, mental factors are seldom, if ever, taken into account in looking into the causes of diet, eating habits and obesity (Deva MP, 1999, p 58).

Although as has been discussed earlier that the suicide rate in Malaysia is relatively low compared to other countries, it is doubtful that this low trend will continue as our society is now going through rapid and unprecedented social changes mentioned previously. It is pertinent to stress, here, that studies have indicated that approximately 80% of parasuicide cases have no underlying psychiatric disorders, thus emphasising the need for increasing awareness of general public and health care practitioners on the association between risks of suicide and mental health (Malaysia's Health, 1999). Thus, for the immediate and now, specific services to promote mental health and to help people cope with such traumatic social and structural changes are greatly needed. Whilst, for the long run, preventive approaches such as Wellness programs are also equally important. The fundamental concept of wellness or healthy lifestyle dates back to the concepts of "holistic health". Wellness refers to a lifestyle that one chooses and designs to maximise one's potential for well-being through a balanced life that gives a sense of purpose, inner peace, and satisfaction. Wellness involves eight dimensions, each an important facet of life: the social, physical, spiritual, emotional, nutritional, intellectual, occupational and the environment. It is also a framework that can be used in many ways to help in organising, understanding, and balancing human growth and development towards a more proactive, responsible, and healthier existence. The Eighth Malaysia Plan has specifically stated that the expansion of the wellness program will be one of the strategies for the country's health sector development (Eighth Malaysia Plan 2001-2005).

Equity Health Care

The Ministry of Health has acknowledged that although progress in the health status of the general Malaysian society is evident, the number of people living in pov-

erty and poor conditions of nutrition and health is significant. Indeed, it has been alleged that the issue of equity in health care will be the most challenging of all. Equity in health care refers to equal access to available care for equal needs, equal utilisation for equal need and equal quality of care for all. Closely associated with equity health care is the appropriateness of care, availability of affordable care and quality of care. The MOH has stressed that any future health system should ensure the delivery of dependable and high quality care which is based on need and not on the ability to pay (Abu Bakar Suleiman & M Jegathesan, undated). Fundamental and complex issues of health costing and health financing, thus, arise and many are still in the process of being debated: health reform, privatisation, national health insurance, public-private mix and so forth. In essence, the debate has revolved around whether health financing is a social responsibility or it is a private matter to be left to market forces. It has been argued that usually the pursuit of free price setting and consumer choice (market forces) is in conflict with concerns for equity, efficiency and budgetary constrains (Abu Bakar Suleiman & M Jegathesan, undated).

Future Prospect

In view of the above health issues and challenges facing Malaysian society today, pressure is building for health care reform and transformational changes are taking place. It has been alleged that this can only occur if the MOH is successful in its mission of building partnerships in health and the creation of health as an asset. It is hoped that Malaysia will continue its emphasis in upholding and conforming to the principles of Primary Health Care. At the same time, both the Vision for Health and the Health for All strategy should remain on Malaysia's health agenda in the new millennium. As pressures on resources increase, health care decisions have to be made explicitly and publicly, warranting a basic scientific approach to health care management (Abu Bakar Suleiman & M Jegathesan, undated).

Thus, the strategies for health sector development during the Eighth Malaysia Plan period will include the following:

- Improving accessibility to affordable and quality healthcare
- Expanding the wellness programme
- Promoting coordination and collaboration between public and private sector providers of health care
- Increasing the supply of various categories of health manpower
- Strengthening the telehealth system to promote Malaysia as a regional center for health services
- Enhancing research capacity and capability of the health sector
- Developing and instituting a healthcare financing scheme, and
- Strengthening the regulatory and enforcement functions to administer the health sector, including traditional practitioners and medical products

Concluding Remarks

Being pro-active, resilient, and innovative, Malaysian society would forge ahead towards our Vision for Health in this new era. That is, to be a nation of healthy individuals, families, and communities, through a health system that is equitable, affordable, efficient, technologically appropriate, and environmentally adaptable, with emphasis on quality, innovation, health promotion and respect for human dignity, and which promotes individual responsibility and community participation towards an enhanced quality of life.

Professor Dr Mohd Amin Jalaludin
Dean, University of Malaya Medical Centre
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ROLE OF ENDOTHELIAL DYSFUNCTION IN CARDIOVASCULAR DISEASE: A REVIEW

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Introduction

Cardiovascular disease remains to be the chief cause of death in industrialized countries. Although the cause of cardiovascular disease remains unknown, it is now clear that an impairment of tissue perfusion represents the primary problem. Three main factors contribute to the impairment of tissue perfusion, which are: enhanced vasoconstrictor responses, increased interaction of circulating blood cells and structural changes of the arterial intima.

Endothelium, due to its strategic anatomical location between the circulating blood and vascular smooth muscle is a primary target and mediator of cardiovascular disease. The importance of endothelium in modulating the activity of vascular smooth muscle and therefore in regulating vascular tone was first recognized by the pioneering studies of Furchgott and Zawadzki (1). Functional integrity of the endothelium is crucial for the maintenance of blood flow and antithrombotic capacity because, endothelium releases humoral factors that control muscle relaxation and contraction, thrombogenesis and fibrinolysis and platelet activation and inhibition.

Physiology of the endothelium

Stimulation of intact monolayer of endothelial cells by neurotransmitters, hormones, and substances derived from platelets and the coagulation system causes release of a substance, that in turn induces relaxation of the underlying vascular smooth muscle. Furthermore, shear forces generated by circulating blood induce endothelium-dependent vasodilation, which is an important adaptive response of the vasculature during exercise. This endothelium-derived relaxing factor (EDRF), a diffusible substance with a half-life of a few seconds has been identified as the free radical, nitric oxide (NO). Nitric oxide is formed from L-arginine by oxidation of the guanidine-nitrogen terminal (2). The NO-synthesizing enzyme exists in several isoforms in endothelial cells, platelets, macrophages, vascular smooth cells, nerves and the brain (3). The activity of NO synthase can be inhibited by the circulating amino acid, asymmetrical dimethylarginine (ADMA) indicating that endogenous substances also regulate the activity of L-arginine NO pathway.

Endothelium-dependent relaxations due to NO involve an increase in cyclic 3',5'- guanosine monophosphate (cGMP) in vascular smooth muscle via the soluble enzyme guanylyl cyclase (4) (Fig 1). Soluble guanylyl cyclase is also present in platelets and, if activated by NO, increases cGMP in platelets and in turn reduces adhesion and aggregation. NO induced endothelium-dependent relaxation can be pharmacologically inhibited by analogues of L-arginine such as L-NG-monomethyl arginine (L-NMMA) or L-nitroarginine methylester (L-NAME), which compete with the natural precursor L-arginine at the catalytic site of the enzyme (3). When infused, L-NMMA induces long lasting increases in blood pressure indicating that the vasculature is in a constant state of vasodilation due to continuous basal release of NO by the endothelium.

In addition to NO, endothelial cells release two other relaxing substances (Table 1). Prostacyclin increases cyclic 3',5'-adenosine monophosphate(cAMP) in smooth muscles and platelets. Its platelet-inhibitory effects play a greater physiologic role than its contribution to endothelium-dependent relaxation. NO and prostacyclin synergistically inhibit platelet aggregation suggesting that both the mediators are required for maximal inhibition of platelet aggregation. In the epicardial coronary circulation, inhibitors of the L-arginine pathway do not prevent all endothelium-dependent relaxations (5). Because vascular smooth cells become hyperpolarized during NO-independent relaxation, the existence of endothelium-dependent hyperpolarizing factor (EDHF) has been proposed (6,7). EDHF appears to activate ATP-sensitive K+ channels and/or Na+-K+-ATPase in smooth muscle cells (8).

Soon after EDRF was discovered, it became clear that endothelial cells can also mediate contraction. Endothelium-derived contracting factors (EDCF) include the 21-aminoacid peptide endothelin-1 (ET-1), vasoconstrictor prostanoids such as thrombaxane A2 and prostaglandin H2, and components of the rennin-angiotensin system such as angiotensin 2. Translation of messanger RNA generates preproendothelin, which is converted to big endothelin that is further converted by endothelin-converting enzyme to the mature peptide

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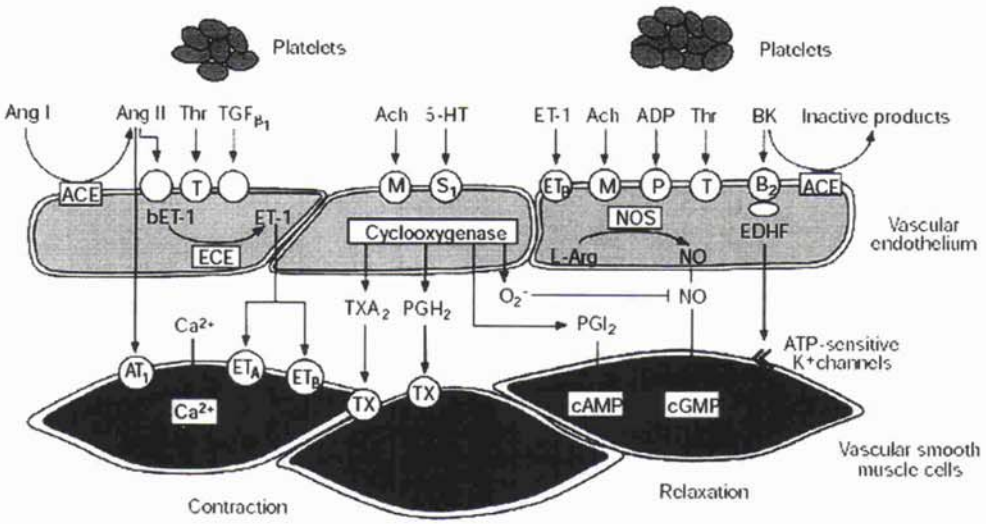

FIG. 1 Vasoactive mediators released by the endothelium. The endothelium produces factors that promote both relaxation (right) and contraction (left). Ang = angiotensin, ACE = angiotensin-converting enzyme, Ach = acetylcholine, ADP = adenosine diphosphate, ATP = adenosine triphosphate, Bk = bradykinin, cAMP/cGMP = cyclic adenosine/guanosine monophosphate, ECE = endothelin-converting enzyme, EDHF = endothelium-derived hyperpolarizing factor, ET = endothelin-1, 5HT = 5-hydroxytryptamine (serotonin), L-Arg = L-arginine, NO = nitric oxide, NOS = nitric oxide synthase, O_2^- = superoxide, PGH_2 = prostaglandin H_2, PGI_2 = prostacyclin, $TGF\beta_1$ = transforming growth factor β_1, Thr = thrombin, TXA_2 = thromboxane A_2. Circles represent receptors (AT = angiotensinergic, B = bradykinergic, ET = endothelin receptor, M = muscarinic, P = purinergic, S = serotonergic, T = thrombin receptor, TX = thromboxane receptor).

Fig Source: TF Luscher *et al.*,Clin Cardiol.Vol.20(Suppl 2),1997

Table 1. Relaxing and contracting factors released by endothelium

Relaxing factors	Contracting factors
1. Endothelium derived nitric oxide	1. Cyclo-oxygenase dependent endothelium derived constricting
2. Prostacyclin (PGI2)	2. Endothelin 1
3. Endothelium-derived hyperpolarizing factor (EDHF)	3. Thromboxane A2
4. Atrial natriuretic peptide	4. Prostaglandin H2
5. Adrenomedullin	5. Angiotensin 2

ET-1. Expression of messenger RNA and release of ET-1 are stimulated by thrombin, transforming growth factor beta, interleukin-1, epinephrine, angiotensin 2, arginine vasopressin, calcium ionophore and phorbol ester (9,10). Endothelin-1 causes vasodilation at lower concentrations but marked and sustained contractions at higher concentrations (9). The cyclooxygenase pathway also produces endothelium-derived vasoconstrictors. Agonists such as arachidonic acid, acetylcholine, histamine and serotonin can evoke endothelium-dependent contractions mediated by thromboxane A2 or prostaglandin H2. In addition, endothelium also plays an important role in regulating the activity of renin-angiotensin system.

Endothelial dysfunction: marker or mediator ?

An imbalance between endothelium-derived contracting and relaxing factors results is endothelial dysfunction. It may be the cause or consequence of vascular disease and is a hallmark of known cardiovascular risk factors. Endothelial dysfunction precedes structural vascular alterations indicating a protective role of the functionally intact endothelium.

Endothelial dysfunction and atherosclerosis are particularly common in epicardial coronary arteries and large arteries such as the aorta and iliac artery while others such as internal mammary artery appear to be protected. This difference could be related to selective alterations in endothelial function in different areas of the vascular tree or due to pulse pressure alterations. Atherosclerosis and plaque rupture are associated with endothelial cell denudation in late stages. Such morphological changes in endothelium are invariably associated with functional alterations and intimal thickening, accumulation of vascular smooth muscle cells and white blood cells and fibroblasts and matrix deposition.

Endothelial dysfunction in Hypertension

Hypertension is associated with functional and morphological alterations of the endothelium (11). In hypertensive blood vessels, endothelial cells have an increased volume and bulge into the lumen. The subintimal space exhibits structural changes with increased fibrin and cell deposition. And the interaction of endothelium with platelets and monocytes is increased in hypertensives compared with normotensives.

Studies have shown that patients with essential hypertension (EH) have impaired response to acetylcholine,

an endothelium-dependent vasodilator (12,13) and a normal response to sodium nitroprusside, an endothelium-independent vasodilator. These results indicated that patients with EH have a specific deficit in the endothelium-derived nitric oxide system and this defect could partly be responsible in determining both the increased vascular resistance and the impaired response to endothelium-dependent agents in these patients. Subsequent studies have shown that blunted endothelium-dependent vasodilator responses in essential hypertensives is largely due to reduced bioactivity of nitric oxide (14), is not related to decreased availability of the natural NO precursor, L-arginine (15), is not due to impaired responsiveness of the vascular smooth muscle to nitrovasodilators (12,13) and is not related to abnormolaties of any specific intracellular signal transduction pathways (16).

A recent study has demonstrated the presence of impaired endothelial function in normotensive subjects with a family history of hypertension (17) and also in the offsprings of EH patients (18). This shows that the onset of endothelial dysfunction may be an important pathogenic event preceeding the development of clinically evident vascular disease.

Endothelial dysfunction in congestive heart failure

The pathogenesis of heart failure is determined by the ventricular and vascular responses to myocellular injury. Studies indicate that vascular endothelium may play an important role in modulating the progression of ventricular and vascular remodeling in heart failure. Abnormalities of vascular endothelial function characterized by increased basal vasomotor tone and decreased vasodilatory reserve could be of particular relevance to the pathophysiology of congestive cardiac failure (19).

Endothelium-dependent vasodilation has been investigated in various experimental models and clinical studies of congestive heart failure. In experimental studies on rats and dogs with induced heart failure, agonist-stimulated and flow-stimulated nitric oxide-mediated vasodilation was found to be decreased in both conduit and resistance vessels compared with normal controls (20). Similarly in clinical studies, endothelium dependent vasodilation in response to hormonal agonists and increased flow were impaired in the coronary and skeletal muscle circulations of patients with heart failure compared to normal subjects (20). Studies have also shown that endothelin-1, an endothelium-derived contracting factor is increased in both experimental subjects and clinical heart failure patients compared with normal control subjects (20). These findings demonstrate that heart failure is associated with generalized endothelial dysfunction, which is partly described by impaired nitric oxide-mediated vasodilation and increased plasma concentration of endothelin-1.

Increased peripheral vascular resistance is known to be a hallmark of congestive cardiac failure. The impaired functional capacity of peripheral blood vessels to dilate in response to sheer stress is a major determinant of the degree of exercise intolerance, which is an important clinical feature in patients with heart failure (21,22). This deficit in peripheral vasodilator capacity that results from attenuated vascular endothelial function has been attributed to the loss of ability of the endothelium to release nitric oxide in response to physiologic stimuli (23,24).

Immunologic and inflammatory responses may also play a role in the development of heart failure (25). Elevated circulating levels of pro-inflammatory cytokines such as interleukin-1, interleukin-6 and tumour necrosis factor-alpha, as well as certain chemokines has been noted in patients with congestive heart failure (26-28). These cytokines cause endothelial dysfunction either directly or through the generation of free radicals (29,30). In addition, changes in regional flow and pressure patterns seen commonly in patients with heart failure may also contribute to increased free radical production (31) providing a potential link between endothelial dysfunction and congestive heart failure. A very recent study has shown that the serum of patients with congestive heart failure potently induced apoptosis of endothelial cells through the activation of caspase cascade, thus providing another possible mechanistic clue in the pathogenesis of endothelial dysfunction in these patients (32).

Endothelial dysfunction in atherosclerosis

Endothelial injury, either physical trauma or more subtle cellular damage, is now regarded as an important initial event in atherogenesis (33,34). Physical damage to the endothelium has been shown to cause atherosclerotic lesions even in normocholesterolemic animals (35). Hypertension has been shown experimentally to disrupt endothelial integrity (36). Hyperhomocysteinemia, that causes chemical endothelial injury, is associated with premature atherosclerosis and thrombosis (37). The finding of these insults associated with the clinical progression of vascular disease, being related to endothelial injury has added more glamour to the "response to injury" hypothesis proposed by Ross and Glomset (38).

The consequences of endothelial damage that initiate fatty streak and plaque formation include increased adherence of monocytes, increased permeability to monocytes/macrophages and lipoproteins that accumulate in the vessel wall, increased platelet adherence and increased smooth muscle cell migration and proliferation (39). Endothelial dysfunction may also be accompanied by decreased availability of local NO. This may be due to decreased endothelial production of NO or to excess production of superoxide anions or both with consequent degradation of NO before it can reach its target tissues. Because NO is a local vasodilator that

also inhibits platelet adherence and aggregation, smooth muscle proliferation and endothelial cell leucocyte interactions, reduced NO activity may also contribute to the initiation and progression of atherogenesis (40). In hypercholesterolemia, superoxide production is enhanced with consequently decreased bioavailability of NO (41). Studies have shown that supplementation with oral L-arginine, the precursor of NO has profound antiatherogenic effects in cholesterol-fed animals (42) and was associated with decreased platelet aggregation (43) and monocyte/endothelial cell adhesion (44) in humans.

Endothelial dysfunction has been demonstrated in asymptomatic children and young adults with risk factors for atherosclerosis (45). Hypercholesterolemia is associated with endothelial dysfunction in children as young as 7 years old, with significant correlations between the degree of endothelial impairment and the levels of lipoprotein (46). In the coronary circulation, endothelial dysfunction is not only observed at the sites of obstructive stenosis, but has also been documented in angiographically smooth arteries of subjects with risk factors for atherosclerosis (47,48). However no longitudinal studies in humans have yet shown that those young subjects with endothelial dysfunction will go on to develop advanced atherosclerosis. Traditional risk factors (Table 2) interact to damage the endothelium in symptomatic subjects in the same way, as they are known to interact in determining the clinical cardiovascular end points (49).

Table 2. Common conditions associated with endothelial dysfunction

Atherosclerosis	Type 1 and 2 diabetes mellitus
Hypercholesterolemia	Hyperglycemia
Low HDL cholesterol	Active and passive cigarette smoking
Hypertension	Heart Failure
Aging	Family history of coronary disease
Insulin resistance	Postmenopausal status

HDL = high-density lipoprotein

In coronary arteries, endothelial dysfunction occurs first at branch points and precedes occlusive arterial disease in both the experimental models and in human heart transplant recipients (50,51). Studies have shown that impaired endothelium-dependent dilation at the site of coronary plaques may result in paradoxic vasoconstriction during exercise or mental stress. This phenomenon was first demonstrated by Ludmer *et al.* in human coronary arteries where, stenotic arteries showed paradoxic vasoconstriction in response to intra coronary acetylcholine (52). Endothelial dysfunction has also been noticed in the coronary microcirculation and may play a significant role in the pathogenesis of myocardial ischemia (53). The clinical correlate of endothelial dysfunction in the coronary arteries may be episodic myocardial ischemia, either with or without chest pain. Taken together, these data from in vivo human studies indicate the importance of impaired endothelial function in both the early and late stages of atherosclerotic disease.

Assessment of endothelial dysfunction

A large number of studies have assessed arterial endothelial function in health and disease over the past two decades. The ability of normal endothelium to release the vasorelaxing factor NO in response to physiologic or pharmacologic stimuli was tested in most of these studies. Although this is only one of many endothelial functiuons, NO release is particularly important because of its actions on platelets, monocytes and smooth muscle cells.

Coronary artery testing. In vivo assessment of coronary endothelial function was first reported in humans in the mid 1980s (52). Coronary artery diameter was measured by quantitative angiography before and after intracronary infusion of acetylcholine. In normal arteries, acetylcholine stimulated the endothelial release of NO, resulting in vasodilation, whereas in subjects with endothelial dysfunction, vasoconstriction was observed due its direct smooth muscle constrictor effect. This response was contrasted with the response to nitroglycerin, an exogenous source of NO and therefore an endothelium-independent vasodilator. Invasive testing of coronary microvascular endothelium was also described by measuring the response of coronary flow to administration of endothelium-dependent and endothelium-independent small vessel-dilator substances using Doppler wires or catheters (54). The potential for reversibility of endothelial dysfunction in the coronary arteries has been assessed using this technique to assess novel therapeutic strategies such as angiotensin-converting enzyme inhibition and cholesterol-lowering therapy (55,56). The major disadvantage of intra-coronary testing is its invasive nature and is therefore generally unsuitable for use in children and adults who are at risk atherosclerosis but with no clinical signs or symptoms of the disease.

Peripheral artery testing. Non-invasive detection of endothelial dysfunction in the brachial and femoral arteries was first described in 1992 (45). In this technique, arterial diameter is measured in response to an increase in shear stress, which causes endothelium-dependent dilation and in response to sublingual nitroglycerin, an endothelium-independent dilator. This technique has been shown to be reproducible (57) and to correlate well with invasive testing of coronary endothelial dysfunction (58). Endothelial function has also been investigated in the forearm microcirculation by intra-arterial infusion of endothelium-dependent and inde-

pendent vasodilator substances, followed by measurement of forearm flow using plethysmographic techniques (59,60). These techniques have provided important insights into the risk factors for atherogenesis in children and in young adults and are being used in various studies of endothelial dysfunction in asymptomatic subjects.

Reversibility of endothelial dysfunction

Studies over the past decade have demonstrated that endothelial dysfunction can be attenuated by a variety of therapeutic interventions. To date, most interventions attempting to improve endothelial dysfunction have targeted one or more of the numerous risk factors that can cause endothelial damage: hypertension (ACE-inhibition), hypercholesterolemia (lipid-lowering agents), cigarette smoking (cessation), sedentary life style (increased physical activity), menopause (hormone replacement therapy), and diabetes mellitus (control of associated metabolic abnormalities). Several pharmacologic agents have been suggested to achieve vascular protection through various mechanisms. Beneficial changes to the endothelium might result from promotion of vascular relaxation, inhibition of vasoconstriction, reduction in the production of free radicals, or other mechanisms that protect the endothelium from injury.

Lipid lowering agents. Cholesterol lowering therapy has been associated with a decreased risk of coronary ischemic events and an improvement in coronary endothelial function (61). Reduction of LDL cholesterol alone failed to improve vasodilation in coronary arteries but was significantly improved with the addition of antioxidant therapy (62), thus highlighting the importance of oxidative stress in the pathogenesis of endothelial dysfunction. Improvement in the vasomotor response to acetylcholine was significantly greater in the combined therapy (lovastatin and probucol) group than with diet or LDL cholesterol lowering alone. Tamai *et al.* demonstrated that endothelial vasodilator function could be improved immediately after plasmapheresis in patients with familial hypercholesterolemia (63).

Angiotensin-converting enzyme (ACE) inhibition. The role of rennin-angiotensin system in endothelial dysfunction relates primarily to angiotensin 2 as a potent endothelium derived contracting factor. One of the first studies to demonstrate an improvement in endothelial dysfunction with an ACE inhibitor was the Trial on Reversing Endothelial Dysfunction (TREND) (64). This trial demonstrated significant improvement in endothelial vasomotor function in normotensive patients with coronary heart disease treated with an ACE inhibitor (quinapril 40g/day). The beneficial mechanisms of quinapril in this trial probably relate to the effects of ACE inhibition on both angiotensin2 and bradykinin, which is a potent vasodilator. In the TREND study quinapril improved endothelial dysfunction without altering lipids or reducing bloodpressure (64). More recently, the Heart Outcome Prevention Evaluation (HOPE) trial has shown favorable effects with ramipril in highrisk group of patients with preexisting vascular disease (65).

Antioxidants. Because oxidation of low-density lipoprotein (LDL) cholesterol contributes to endothelial dysfunction, investigators have reasoned that a diet rich in antioxidants may be protective. However results of clinical studies have not consistently shown a benefit. Levine *et al.* reported that vitamin C reversed endothelial dysfunction in the brachial circulation of patients with coronary artery disease (66).

Hormone replacement therapy. The finding that estrogen receptors are localized on endothelial and smooth muscle cells of several mammalian species has suggested that the hormone may directly influence vascular function (67). Estrogen receptor expression has also been demonstrated in human endothelial cells suggesting, estrogen may act directly on human vascular tissue (68). Estrogen therapy has been shown to have a beneficial effect on endothelial function in postmenopausal women with atherosclerotic coronary arteries (69). This protective effect of estrogen may be due to an antioxidant effect, or an estrogen-induced enhancement of NO synthase expression.

Other interventions. Augmentation of NO production by L-arginine supplementation has been shown to improve vascular relaxation in certain conditions (70). A recent study demonstrated improved brachial artery flow mediated dilation (FMD) in hypercholesterolemic subjects after four weeks of oral L-arginine supplementation (71). Future longterm oral studies will clarify the usefulness of L-arginine in modulating endothelial dysfunction.

Conclusion

Over the past decade, knowledge regarding the versatile functions of the endothelium has advanced enormously. Experimental and clinical evidence suggest that endothelial dysfunction is a major determinant for the development and progression of cardiovascular diseases. A major goal of therapy in these patients should be to improve or preserve endothelial function. Furthermore, since endothelial dysfunction occurs prior to structural vascular changes, therapy should be initiated early in patients at risk eg., familial hypercholesterolemia, hypertension, diabetes mellitus etc. Prevention or correction of endothelial dysfunction in cardiovascular disease with agents targeting the endothelium are likely to improve the clinical outcome in these patients and may have important public health benefits in the future.

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MEDICAL THERAPY FOR BLEEDING PEPTIC ULCER

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ABSTRACT: **The majority of patients with upper gastrointestinal bleeding due to peptic ulcers stop bleeding spontaneously. The remainder of patients who have persistent or recurrent bleeding will require surgical or endoscopic intervention. Medical therapy provides an attractive alternative to these two treatment options. The advent of H2 antagonists in the mid 1970s revolutionized the treatment of peptic ulcer disease as it provided good ulcer healing with a treatment course of 6-8 weeks. A more potent acid suppressing class of drugs: the proton-pump inhibitors (PPI's) were introduced in the late 1980s and provided even better and faster ulcer healing. It was natural that the acid suppressing drugs were also used for the treatment of ulcer bleeding. Intravenous H2 antagonist and more recently intravenous PPI's have routinely been prescribed in many hospitals as soon as a bleeding patient is admitted. Critical evaluation of the literature shows, however, that H2 antagonists are no more effective than placebo in stopping ulcer bleeding. The PPI's, on the other hand, have been shown in several clinical studies to have a beneficial effect. The action of acid suppression in stopping ulcer bleeding is believed to be due to its effect in the stabilization of an ulcer clot by providing a high pH milieu and to commence the process of ulcer healing.** *(JUMMEC 2000; 2:67-72)*

KEYWORDS: **Upper gastrointestinal bleed(UGIB), proton pump inhibitors(PPIs), H2 antagonists.**

Introduction

Upper gastrointestinal bleeding (UGIB) due to peptic ulcers remains a major medical emergency and important cause of hospital admission and death with mortality rates of 5-10% been consistently reported (1-3). What treatment options do we have? Up to 80% of patients with bleeding peptic ulcers, experience spontaneous cessation of the bleeding (4,5). These patients require no active surgical or endoscopic intervention and are treated medically with acid suppressing agents with or without Hp eradication therapy depending on their Hp status. In patients with persisting or recurrent bleeding, however, surgery remains the mainstay of therapy in many countries. Advances in therapeutic endoscopy techniques and timely endoscopic intervention have been shown to improve the overall morbidity and outcome of patients with ulcer bleeding. Where available endoscopic intervention should first be offered to patients. Does medical therapy help with cessation of ulcer bleeding in this group of patients? The advent of H2 antagonist in the mid 1970s revolutionized the treatment of peptic ulcers. It was a matter, of course, that these agents were used for treatment of ulcer bleeding as they were shown to be efficient ulcer healing agents. In the late 1980s, a more potent class of agents: the proton-pump inhibitors (PPIs) were introduced for treatment of peptic ulcers and again attention turned to its use in ulcer bleeding (6-12). Medical treatment of ulcer bleeding is a very attractive treatment option particularly in centres where surgical and endoscopic support facilities and expertise is lacking. If effective it obviates surgical intervention in a patient who is often critically ill. This paper reviews the role of medical therapy, chiefly the role of acid suppressing agents in the treatment of bleeding peptic ulcers.

History of medical treatment

One of the earliest medical treatments of UGIB in this century came from Hurst *et al.*. in 1924 (13) where they used alkali, belladona and olive oil after a 48 hour fast. It was believed that complete immobilization together with frequent morphine administration was important to prevent clot dislodgement. Although there were many followers of the "immobilization, morphine and starvation" regimen, others reported on the use of pure diets and liberal use of milk and water for patients with haemetemesis or maelena (14).

The major breakthrough came along in 1930s when intravenous infusion of large volumes of blood was developed and patients could be resuscitated effectively. During the following three decades, the es-

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sentials of medical treatment, consisted of alkalinazation of gastric contents and bland diets for ulcer healing.

The use of iced saline gastric lavage had been considered an essential part of therapy. Its use was first described by Wangensteen *et al.*. about half a century ago in an animal model (17-19). Gastric cooling to 10 °C was associated with a significant reduction in gastric blood flow and acid secretion. However, its use in humans was beset with multiple problems which included generalized hypothermia and ventricular dysrhythmias and which eventually led to its abandonment.

Adrenaline lavage had also been widely used in clinical practice in the past, but scientific evidence supporting its use has been largely based on retrospective and uncontrolled studies. Sarin *et al.*. (20) have published the only randomised, prospective, double blind placebo controlled study. However, the majority of his patients had variceal bleeding. Non-variceal bleeding ceased within 24 hours in four of five patients who received norepinephrine (8 mg in 100 ml of cold saline) as opposed to cessation in two of six patients who received placebo. Norepinephrine is promptly metabolised in the liver and thus systemic side effects are avoided; however its clinical efficacy remains to be validated in a larger study population with non-variceal bleeding.

Timing of endoscopy and endoscopic criteria of high risk bleeding peptic ulcers

It is well established that endoscopic intervention for bleeding peptic ulcer is successful in stopping active bleeding, reduce the risk of rebleeding, the need for blood transfusion and the length of hospital stay. While the benefit of endoscopic therapy for bleeding peptic ulcer is well proven, what is more controversial is the timing of the endoscopy.

The timing of endoscopy in patients with upper gastrointestinal bleeding has commonly been divided into urgent, emergent and elective. Urgent endoscopy is that performed prior to hemodynamic stabilization in patients with massive blood loss in whom the risk of exsanguinations outweighs the risk of performing urgent endoscopy. This is most commonly used in patients with massive variceal bleeding. Emergent endoscopy is that which is performed within 24 hours of admission and usually after hemodynamic stabilization has been achieved or during resuscitated efforts. This group comprises the vast majority of patients with bleeding peptic ulcer.

Elective endoscopy is reserved for those in whom there is no hemodynamic instability and the risk of bleeding is thought to be low. These patients are scoped at the convenience of the patient and the endoscopist.

Most studies evaluating endoscopic management of peptic ulcer bleeding have employed emergent endoscopy within 12-24 hours of admission. This approach is able to identify accurately the bleeding site, as well as the stigmata of recent haemorrhage and therefore, be able to predict the likelihood of continued bleeding. Therefore, early endoscopy (less than 24 hours) is an effective strategy to reduce the length of stay, hospital costs and identify the risk of recurrent bleeding and surgery in the high-risk patient.

The majority of patients (75-80%) with bleeding peptic ulcers will stop bleeding spontaneously. It is identification of the remainder 20% who is at high risk for rebleeding that is of interest. It appears that the best predictor of rebleeding in peptic ulcer is the endoscopic appearance of the ulcer. The presence of a 'sentinel clot' or a visible vessel in the base of the ulcer indicates a high likelihood of rebleeding. Similarly, ulcers with a clean base have a negligible risk. Flat, pigmented lesions and adherent clots of the ulcer base have an intermediate risk of continued bleeding. Laine and Peterson (1) summarized the available literature and stratified the risk of rebleeding by endoscopic criteria (Table 1).

Table 1. Risk of rebleeding and mortality in patients with peptic ulcer bleeding.

Endoscopic finding	Risk of rebleeding (%)	Mortality (%)
Active bleeding	55	11
Visible vessel	43	11
Adherent clot	22	7
Flat spot	10	3
Clean base	5	2

Patho-physiological rationale for the use of acid suppressing agents

The stability of a thrombus to seal the hole in a submucosal artery is acid labile. Peptic digestion of the thrombus is maximal in the pH range of 1-3.5 and pepsin 1 may continue to function up to pH of 5 (15). Platelet aggregation and disaggregation is also severely impaired at low pH *in viro*. As blood coagulation and platelet aggregation are abolished at pH lower than 5.4, the perceived failure of traditional antisecretory drugs to promote haemostasis in bleeding peptic ulcers may reflect inadequate pH control. This has provided the rationale use of more potent acid reducing agents such as proton pump inhibitors in the management of peptic ulcer bleeding.

Labenz *et al.* (16) randomised 20 patients with bleeding duodenal ulcers and 20 patients with gastric ulcers to receive ranitidine 0.25mg/h/kg after a bolus of 50 mg intravenously, or omeprazole 8mg/h after a bolus of 80mg

for 24 hours. Intragastric pH was monitored with a glass electrode placed 5 cm below the cardia. The fraction of time spent below a pH of 6 was 0.15% with omeprazole and 20.1% with ranitidine in duodenal ulcers (p=0.0015) and 0.1% with omeprazole and 46.1% with ranitidine in the gastric ulcer group (p=0.002). Thus, omeprazole infusion causes a more potent and persistent increase in intragastric pH.

Prostaglandins

Prostagladins are arachidonic acid derivatives found in a wide variety of mammalian tissues with varying roles in the modulation of end organ function. Prostagladins of the E and A origins are potent inhibitors of gastric secretion and appear to exert a protective effect on gastric mucosal integrity. These properties offer a theoretical potential for prostagladins to be used in peptic ulcer bleeding.

E-type prostaglandins have been used in clinical trials on peptic ulcers, on upper gastrointestinal bleeding, and on mucosal lesions induced by non-steroidal anti-inflammatory drugs. In nearly all trials, natural prostaglandin E2 as well as the synthetic prostaglandin analogues misoprostol, enprostil, rioprostil and rosaprostil accelerated the healing of peptic ulcers compared with placebo. However, in the treatment of acute upper gastrointestinal bleeding prostaglandin analogues are not more effective than placebo in spite of several case reports suggesting that prostaglandin analogues would be helpful in these situations (22).

Somatostatin

Somatostatin is one of the many hypothalamic regulatory peptides and is found throughout the entire gastrointestinal tract. Its main effects can be localized to the pancreatic islet cells and antral D cells. Somatostatin decreases basal and meal stimulated gastric acid secretion, serum gastrin concentration and inhibits pepsin secretion. In addition it also has a stimulatory effect on gastric mucus production and decreases sphlanchic blood flow. Basso *et al.* (24) in a randomised double blind trial comparing somatostatin to ranitidine and placebo for peptic ulcer bleeding noted that there was significant differences between the groups for rebleeding rates, emergency surgery, transfusion requirements and overall survival. In another study, Christiansen *et al.* (25) treated 241 patients with peptic ulcer bleeding with either somatostatin analogue, octreotide acetate or placebo and found no differences between the two groups with regard to cessation of bleeding or rebleeding rates.

Tranexamic Acid

Tranexamic acid is an antifibrinolytic agent similar in physiological action to aminocaproic acid. A large trial (26) compared tranexamic acid infusion (225 patients) to cimetidine (219 patients) in peptic ulcer bleeding. There were no significant differences in transfusion rates but it did show significant lower mortality rates (4%) as compared to the cimetidine group (11%, p=0.007). However, this decrease in mortality was not associated with a decrease in the frequency of recurrent bleeding or emergency surgery that would be expected. In fact, surgery was performed more frequently in the group with tranexamic acid infusion as compared to cimetidine group. At present there does not appear to be sufficient data to justify the use of tranexamic acid for the treatment of upper gastrointestinal bleed.

Histamine H2 antagonists

Histamine H2 antagonist and antacids has long been known to accelerate healing of peptic ulcers and has been used prophylactically to prevent bleeding in stress ulcers. However, the use of H2 antagonist and antacid in active bleeding ulcers or the prevention of rebleeding from an already established ulcer has yet to be proven.

Meta analysis examining 27 randomised trials of cimetidine or ranitidine (only 3 ranitidine studies) in the treatment of UGIB involving more than 2500 patients showed no significant difference between H2 antagonist therapy (21%) and placebo (23%). In fact, only one of the 27 individual trials reported a significant decrease in bleeding with an H2 antagonist therapy (21).

In a large American study published by Zuckermann *et. al.* (5), which compared H2, antagonist and/or antacids with placebo in a prospective, randomised, double blind controlled study. Patients with ongoing bleeding were given an intravenous infusion of a coded drug, which was either cimetidine 300mg or placebo every 6 hours. Endoscopy was not required prior to starting the coded drug. Two hundred and eighty five patients were evaluated in this study. Cimetidine failed to control active bleeding in 44 patients as compared to placebo 30 (Table 2). This failure rate is not significantly different. When specific bleeding lesions or areas were evaluated there was no statistical difference.

Table 2. Intravenous cimetidine versus placebo during acute gastrointestinal bleeding in 285 patients

	Treatment success	Treatment failure	Total
Cimetidine	109(71.2%)	44(28.7%)	153
Placebo	102(77.2%)	30(22.7%)	132

There is no conclusive evidence to show that H2 antagonist is of benefit in stopping active ulcer bleeding or preventing rebleeding from peptic ulcer.

Proton pump inhibitors (PPI's)

Proton pump inhibitor is a selective and long acting inhibitor of H+/K+-ATPase of the gastric parietal cells. Omeprazole was the first registered substance from this class to be used followed by other newer agents such as lansoprazole, pantoprazole and rabeprazole. Currently, only omeprazole, lansoprazole and pantoprazole are available in intravenous forms.

Many of the earliest studies used omeprazole either as intermittent bolus injections or continuous infusion in the treatment of acute gastrointestinal bleeding. Pharmacological studies have shown that intermittent bolus application cannot achieve the necessary intragastric pH because proton pumps are continuously being generated in the circulation. This implies that a proton pump inhibitor should be continuously available in the circulation to inhibit newly generated pumps and thereby inhibits gastric acidity for prolonged periods. Other studies have reported similar intragastric pH with omeprazole given in bolus injections and in continuous infusion (28-30).

In a meta-analysis by Gisbert *et al.* (27) comparing proton pump inhibitors with H2 antagonist, eleven studies fulfilled the inclusion criteria. When combining the results of the studies, it was observed that persistent or recurrent bleeding was less frequent with proton pump inhibitors (6.7%) than with H2 antagonists (13.4%)(OR 0.4; 95%CI:0.27-0.59%). The need for surgery and mortality rates did not reach statistical significant but showed a favourable trend towards PPI as it may be due to the low proportion of patients requiring surgery in the individual trials.

The use of PPIs is useful in patients with high risk (Forrest Ia, Ib and IIa) as opposed to low risk patients (eg clean based ulcers or flat pigmented spots). The risk of recurrent or persistent bleeding is much lower in the PPI group than with the H2 antagonists (13.3% vs 34.5%; OR 0.28: 95%CI: 0.16-0.48) when applied to high-risk patients.

Endoscopic therapy has been proven to be effective in the treatment of bleeding peptic ulcers especially in the high-risk group (Forrest Ia, Ib and IIa). However, when endoscopic therapy was performed in these patients the role of PPI over H2 antagonist as regards to recurrent or persistent bleeding was not significant. Studies that did not use any adjunct endoscopic therapy showed less incidence of recurrent or persistent bleeding with proton pump inhibitors than with H2 antagonist (4.3% vs 12%; OR 0.24). Because endoscopic therapy is routinely used for bleeding peptic ulcers in many centres the role of proton pump inhibitors may be beneficial mainly or exclusively for patients not having any adjunct endoscopic therapy.

Three studies have evaluated the use of high dose proton pump inhibitors in the management of ulcer bleeding without endoscopic therapy (7, 9, 12). Lanas *et al.* (9) randomised 51 patients with high-risk endoscopic stigmata seen at endoscopy to receive either IV ranitidine or IV omeprazole infusion. No endoscopic therapy was given prior to therapy. The rebleeding rate and surgery rate was higher in the ranitidine group, but there was no statistical significant difference.

Khuroo *et al.* (7) randomised 220 patients with bleeding ulcers with high-risk stigmata to receive oral omeprazole 40 mg BID versus placebo. The patients treated with omeprazole had lower risk of rebleeding and need for emergency surgery for haemostasis than did those in the placebo group.

Table 3. Outcomes of proton pump inhibitors in bleeding peptic ulcer

	No. Patients	Type of Treatment	Outcomes (with omeprazole)
Lanas *et al* 1995	51	No endoscopy therapy Ranitidine (iv) vs Omeprazole (iv bolus)	Rebleeding ↓Surgery
Khuroo *et al* 1997	220	No endoscopy therapy Oral Omeprazole vs placebo	↓Rebleeding ↓Surgery
Hasselgreen *et al* 1997	333	No endoscopy therapy IV Omeprazole vs Placebo	↓Rebleeding ↓Surgery (Infusion)
Lau *et al* 2000	240	Endoscopic therapy (Epinephrine & thermocoag) IV infusion omeprazole vs placebo	↓ Rebleeding & endoscopic Rx

Hasselgren *et al.* (12) randomised 333 patients over the age of 60 with high-risk stigmata in the ulcer to receive either continuous IV infusion with omeprazole versus placebo. The omeprazole group had statistically less rebleeding and need of emergency surgery as compared to placebo.

In another study from Hong Kong, the use of intravenous omeprazole following endoscopic therapy for ulcer bleeding resulted in significant reduction in rebleeding (5 in the omeprazole group and 24 in the placebo group, $p<0.001$) (23).

Intravenous pantoprazole has also been used in peptic ulcer bleeding. Fried *et al.* (31) compared pantoprazole infusion (66patients) with ranitidine (67 patients) in patients with Forrest Ia, Ib, IIa and IIb after undergoing endoscopic haemostasis with adrenaline or adrenaline with polidocanole. There was a tendency for lower rebleeding rate in the pantoprazole group as opposed to ranitidine (48 hour rebleeding rates were 10% and 17%, respectively)

One can conclude from the above data that if urgent endoscopic therapy is not available either due to lack of access or due to patient factors mitigating delayed endoscopy, then the use of proton pump inhibitors to suppress acid secretion should be used. However, routine use of PPIs before a delayed endoscopy will only increase hospital costs and length of stay in hospital and therefore cannot be recommended.

Recommendations

Based on current evidence, proton pump inhibitors have a beneficial effect in ulcer bleeding. No other agent has been shown to have any such effect. In patients with significant UGI bleed and no known history of previous variceal bleeding, intravenous PPIs is recommended. Following UGI endoscopy, patients with stigmata of recent haemorrhage should receive endoscopic haemostatic therapy and intravenous PPIs continued until bleeding ceases. Patients should then be switched to oral PPIs; patients diagnosed to have Hp infection should undergo Hp eradication therapy. High-risk patients on NSAID therapy following current recommendations should be continuously treated with PPIs.

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THE AETIOLOGY OF CHRONIC FATIGUE SYNDROME: A REVIEW

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ABSTRACT:: Chronic fatigue syndrome (CFS) is a chronic debilitating condition affecting both physical and mental functioning. It was first quoted as a 'new disease' spreading in the developed countries. It became a major issue by doctors, professionals and the media for the past 15 years. CFS was not only affecting the adults but childhood fatigue has also been noted. The CFS patients commonly described themselves to be perfectionists, highly driven, energetic and motivated before the condition started. Studies have been focused on the definition, diagnosis and management of CFS. However, the understanding of CFS and what cause it is still unclear and controversial. Thus the aetiological factors of CFS are reviewed in this article. *(JUMMEC 2000; 2:73-77)*

KEYWORDS: Chronic fatigue syndrome (CFS), Aetiology, Psychiatric disorders, Viral infection, Immunology

Introduction

Broadly defined fatigue appears to be very common in the community, at the primary care level and among the hospital attenders. Doctors, professionals and lay journals started to address fatigue syndrome as a major issue since 15 years ago. An operationalised criteria for chronic fatigue syndrome (CFS) has been developed in the western countries. Chronic fatigue syndrome is a severe chronic fatiguing condition affecting both physical and mental ability. The criteria may include somatic symptoms and require exclusion of serious medical illnesses and a number of psychiatric disorders (1). The current definitions are based on the observation of the symptom constellations rather than detailed knowledge regarding the aetiology or pathophysiology of fatigue syndrome.

Prevalence of CFS

The prevalence estimates for chronic fatigue syndrome varies between 0.07% and 1.8% (2). A population-based study ascertains the point prevalence of chronic fatigue syndrome as 0.37% (3). A survey based on Scottish general practices (4) reported the prevalence of CFS as 1.3%. While they achieved a better response rate, case identification depended largely on individual doctor's perception of CFS. Another study (5) based on the Epidemiologic Catchment Area (ECA) data, found that chronic fatigue syndrome appeared to be quite rare in that only one woman in the entire sample (13538) – 0.07%, fulfilled the criteria.

Aetiology

While there has been a growing consensus regarding the definition, diagnosis and management of CFS, the aetiology remains controversial. To date, studies have focused on a range of biological and psychosocial factors including the role of persistent viral infection, immunology, psychological disorders, neuroendocrine disturbances, structural and functional brain abnormalities, life events, personality traits and genetics.

Relationships between CFS and Psychological disorders

Studies in the community (6), primary care setting (7) and tertiary care fatigue clinics (8,9) have demonstrated a significant relationship between fatigue and psychiatric disorder with reported rates of psychiatric illness in (broadly defined) fatigue patients ranging from 60% to 75%. If one looks at studies relating to chronic fatigue syndrome specifically, reported rates of psychiatric disorder range from 40% - 75%.

Major depression appears to be the most common psychiatric diagnosis in CFS (9,10). Several studies looking at psychiatric features in CFS, and conducted using standardized diagnostic instruments, identified

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between 50% - 70% of CFS patients as suffering from major depressive disorder (11,12).

In addition to depression, it has recently become clear that the incidence of anxiety disorders in CFS was underestimated. For example, one study indicated that 20 per cent of a sample of chronic fatigue patients fulfilled criteria for one or more anxiety disorders (13). Somatization disorder also appears to be relatively common in CFS patients. Most studies find that between 5% and 10% of those seen in specialist CFS clinics fulfill established criteria for somatization disorder (8,14).

Viral infection

There have been many claims linking viral agents with CFS over the years. One reason is the consistent observation made by patients attending specialist units that their illness began with a viral infection, and that the symptoms of their persisting illness resemble those of viral infection (15). However, establishing any link between viral infections and CFS is far from straight forward. Firstly, symptoms of viral infection are not synonymous with evidence of an infective process. Secondly, viral infections are common - the average person has between three and four such infections a year and chance associations are thus hard to exclude. It is also possible that infection may follow, rather than cause fatigue (16).

A controlled, prospective primary care study (17), suggested that common viral infections do not have a causal role in CFS. Another study however, demonstrated a modest increase in chronic fatigue 6 months after presentation with symptomatic common viral infections to a general practitioner (18). In contrast, there is evidence that serious viral infections particularly Epstein-Barr viruses do trigger or precipitate CFS (19).

The link between enteroviruses with ME/CFS started after the Royal Free Hospital (1955) epidemic outbreak as poliomyelitis was seen as the major threat. This led to several studies to look at the association of enteroviruses with CFS. However, the results of the studies were not convincing (20,21). A prospective postal questionnaire follow-up study (22) of patients with viral meningitis and other viral infections found the prevalence of chronic fatigue syndrome was 12.6% which was higher than rates reported from primary care attenders. However, there was no difference in the rates of chronic fatigue between patients infected by enterovirus and the control group (i.e. those who were infected by non-CNS non-enteroviruses). Thus, in conclusion, even though enteroviruses are common, studies have not identified a link between enteroviral infections, persistence of the virus, and the development of chronic fatigue syndrome.

Immunology

The hypothesis that the pathogenesis of chronic fatigue syndrome has an immunologic basis remains tantalizing. Although advanced laboratory techniques have been applied to the study of immunologic function in CFS, no clear conclusions can be drawn from existing data. Some authors have suggested that observed immunological changes are not of pathological significance, but represent a normal immunological response to persistent viral infection (23). However there is frequent occurrence of abnormalities within the cellular and humoral immune system of patients with well-defined chronic fatigue syndrome (24). It was reported that a reduction in the absolute number of peripheral blood lymphocytes; specifically in the total T-cell (CD2), the helper/inducer T-cell (CD4) and the suppressor/cytotoxic T-cell (CD8) subsets which are likely to be associated with the persistence of viral antigens. Other laboratory findings showed depressed natural killer cell function and reduced numbers of natural killer cells; low levels of circulating immune complexes; low levels of several autoantibodies, particularly antinuclear autoantibodies and antithyroid antibodies; altered levels of immunoglobulins; abnormalities in number and function of lymphocytes; and modestly elevated levels of two Epstein-Barr virus-related antibodies, immunoglobulin G to viral capsid antigen and to early antigen (25). The pattern of these findings being typical of that seen in patients during the resolution of acute viral infection (26). However, a case-control study showed that the immunologic abnormalities in CFS patients are in accord with the growing body of evidence suggesting a chronic, low level of the immune system functioning in chronic fatigue syndrome.

As usual, nothing is so simple in CFS. It has not been possible to clarify whether the observed immunological changes are the cause or effect of chronic fatigue. The reported abnormalities are non-specific and similar abnormalities of immune function have also been reported in major depressive illness. In addition. The duration of CFS samples, the use of medications, mood and stress may all be possible confounders.

Hypothalamic-pituitary-adrenal (HPA) axis

Because of its role in the control of sleep, energy, mood and appetite, several authors have suggested a possible role for the hypothalamus as a final common pathway for symptom generation in CFS (27). Demitrack et al (28) studied the normal diurnal variation of cortisol activity and neuroendocrine changes following challenge with corticotrophin releasing hormone (CRF) and adenocorticotrophic hormone (ACTH). The findings

showed that free plasma cortisol levels and the basal evening cortisol levels were low in CFS patients in contrast to the hypercortisolism in major depression. However it is difficult to interpret these findings as similar effects have been noted in many conditions, some of which overlap with CFS (eg. eating disorders, post-traumatic stress disorder, seasonal affective disorder and fibromyalgia). In addition, sleep disturbance, depression and anxiety are all relevant to CFS and may have an impact on the results of neuroendocrine challenge tests. It is possible therefore that the reported neuroendocrine abnormalities in CFS may be epiphenomena of the clinical condition or, alternatively be related to the confounding effects of psychological distress, sleep deprivation or prolonged inactivity.

Serotonin function

Several studies have investigated central serotonin (5-HT) function in CFS. Results of a study compared central serotonin activity (using the response to buspirone, a 5-hydroxytryptamine (5-HT1A) receptor agonist) in CFS patients, with normal and depressed controls showed a significantly increased sensitivity of central 5-hydroxytryptamine receptors in chronic fatigue syndrome (27). These findings were later supported by a group who used d-fenfluramine, a more selective 5-hydroxytryptamine releasing agent, and showed that CFS may be associated with an increased 5-hydroxytryptamine function (29). However another study found neither significant difference in the prolactin response to d-fenfluramine between CFS patients and controls, nor any significant difference in peak prolactin concentrations achieved (30). This discrepancy in findings could reflect methodological differences in the selection of cases.

Disturbance of brain physiology

There have been several studies using modern neuroimaging techniques to study brain structure and function in CFS. The first MRI study of chronic fatigue was published in 1992 (31). They reported abnormalities in 78% of 144 patients. These abnormalities included foci of high signal intensity on T2-weighted images, typically punctate and occasionally larger patchy areas and which affected the subcortical white matter most often. However, these abnormalities were also found in 21 per cent of the controls and subsequent studies did not replicate these findings (32,33). Both CFS patients and psychiatric controls showed white matters hyperintensities; and no increase in MRI abnormalities.

Given the paucity of abnormal findings on MRI, researchers have begun to explore whether CNS dysfunction can be shown in chronic fatigue syndrome using functional neuroimaging. Single-positron emission tomography (SPET) has been used to measure cerebral blood flow and regional blood volume. Previous studies suggested a range of abnormalities either in the temporal, frontal or parietal areas, with no visible single pattern. It was reported that brainstem perfusion was significantly reduced in CFS subjects compared with controls, with depressed patients showing intermediate values (34). However, a question arises whether these findings were due to depression and/or anxiety, which also could alter the cerebral blood flow. This is because several studies found that the brain perfusion in CFS was similar to that observed in major psychiatric illness, particularly major depression. In conclusion, the neuroimaging findings are probably neither sufficiently sensitive nor specific to allow its use a diagnostic tool for CFS, although it may have a role in understanding the pathophysiology of the disease.

Life events

Ray et al (35) found, retrospectively, no relation between negative life events and fatigue severity in CFS, although negative life events were associated with more severe anxiety in these patients. Positive events, however, were protective against fatigue, anxiety, depression and general functional impairment. After EBV infection, life events were associated with a 5-fold increase in the risk of developing any psychiatric disorder, and a 10-fold increase in developing depression at 2- and 6-months follow-up. However, there was no association between life events with the development of post-infectious fatigue (36). Finally, the frequency of life events in CFS has been found to be no different from that in healthy controls or those with irritable bowel syndrome (37).

Personality

Study of the relationship between personality and CFS is in its infancy. It is a common perception that CFS patients seen in specialist clinics show characteristic type-A personality traits. The CFS patients would rate themselves as more hard driving prior to illness than the healthy controls (37). In addition, chronic fatigue patients tended to describe themselves as significantly more "action-prone" compared with neurotic or chronic organic patients (38). However, while there was "no unique" set of psychological characteristics which could be considered as necessary antecedents of CFS though high levels of emotionality or neuroticism may act as predisposing factors (39).

Genetic factors

If genetic factors are involved in the transmission of a disorder, the disorder should cluster in the families of affected probands at a higher rate than in the relatives of population controls. However, relatives who share a

number of genes also tend to share common environments, so familial clustering by itself does not necessarily implicate a genetic mechanism; family culture, infectious or other environmental agents may also be involved.

To date, there has been little exploration of genetic influences in the aetiology of chronic fatigue or chronic fatigue syndrome. However, two research groups have recently started to address the issue of genetic factors in chronic fatigue using twin study designs (40,41) and another study on family history of CFS (42).

Prolonged fatigue appeared to have independent genetic and environmental determinants (43). Interestingly, chronic fatigue syndrome was found to be a familial disorder and this similar finding was reported in childhood fatigue as well (41).

Conclusion

Range of aetiological factors have been focused in the reviewed articles. However, it remains controversial and non conclusive. It is still difficult to explain whether depression, viral infection and the observed immunological changes are the cause or effect of CFS. Furthermore, similar study findings in CFS patients have been observed in other psychiatric disorders mainly major depressive disorder. Another area that is interesting to explore in future is whether CFS is a culture bound syndrome since it is more established in the western countries.

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INTRODUCTION OF META-ANALYSIS: WHAT, WHY AND WHO

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ABSTRACT: **Meta-analysis is a method of review that summarises the results of previous research of the same particular issue in a systematic and quantitative way. A meta-analysis that properly combines results from different studies will average out differences caused by random variation and produce a more precise estimate of the true effect. It may also detect and investigate heterogeneity among studies thus providing a deeper understanding of clinical dilemmas and guidance on resolving them, in this way a meta-analysis will be a better guide to practice than an individual study. Meta-analysis also has its limitations as it is largely dependent on the quality of published data and requires careful planning and execution of a valid protocol, together with cautious interpretation of the results.** *(JUMMEC 2000; 2:78-84)*

KEYWORDS: **Quantitative Review, Critical Appraisal, Overall Effect, Publication Bias.**

Introduction

Huque defined meta-analysis as "a statistical analysis that combines or integrates the results of several independent clinical trials considered by the analyst to be 'combinable'" (1). A properly conducted meta-analysis will have a written protocol that clearly specifies the techniques for searching, selecting, appraising, combining, and finally presenting quantitative data of two or more independent studies. Data from several different comparable studies are reviewed quantitatively to explore relations between study characteristics and findings. If judged combinable the study results are then pooled to produce an overall estimate (Figure 1). An advantage of this approach is it provides more statistical power than that of the separate studies to detect treatment effects. Many clinicals can be subjected to meta-analysis. The technique has been applied to trials on the effectiveness of treatment, preventive or therapeutic interventions, to diagnostic procedures, to epidemiological risk-factor studies and to relationships in etiological research (2).

Reviews incorporating meta-analyses have appeared in medical journals in increasing numbers. The National Library of Medicine has included Medical Subject Heading (MeSH) "META-ANALYSIS" (1989), and publication type "meta-analysis" (1993) within the Medline indexing system (3). A search of MEDLINE database using the subject heading META-ANALYSIS (1985-1999) revealed a remarkable increase of papers published on meta-analyses in medical research in the past decade (Figure 2).

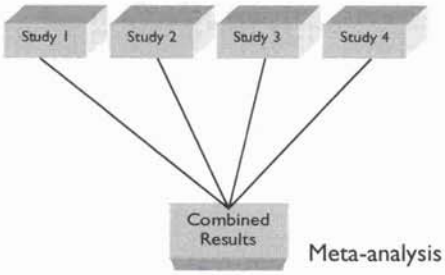

Fig 1. Meta-Analysis: Data from several different studies are combined, translated to a common metric, and produce a single estimate.

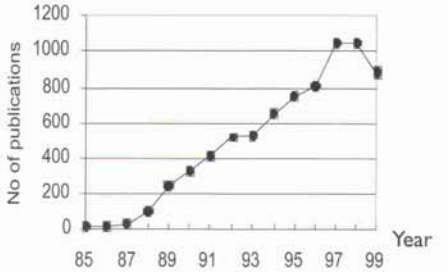

Fig 2. The number of publications about meta-analysis, 1985-1999, results from Medline search using text word and medical subject heading 'META-ANALYSIS'.

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History of Meta-Analysis

Efforts to pool results from separate studies are not new. The statistician Karl Pearson, was probably the first researcher who reported the use of formal techniques to combine data from different samples in 1904 (4). The first meta-analysis assessing the effect of a therapeutic intervention was published in 1955 (5). The development of more sophisticated statistical techniques, took place in the social sciences, particularly in education research, in the 1970s. Light and Smith were among the first to propose pooling original data from previously published research studies (6). In 1976, the psychologist Gene Glass was the first to use the term "meta-analysis" when referring to the statistical approach of pooling data from similar but disparate experiments (7). The prefix "meta" implying an analysis that is similar but more comprehensive, than the original ones. Other terms that are often used synonymously are overview, data pooling, literature synthesis, data synthesis, quantitative synthesis, and systematic review.

One of the earliest uses of meta-analysis in clinical trials was the study by Chalmers *et al* (8). The purpose of the study was to clarify the role of warfarin in patients. Chalmers reasoned that studies that showed statistically non-significant results, owing to inadequate sample size, could be pooled providing that they were of similar design. Such an expanded data set might overcome the lack of statistical power that precluded many of the individual studies from showing statistically significant results. The analysis showed that warfarin was superior to placebo in reducing long-term postinfarction outcome (8).

The Cochrane Collaboration (named after Archie Cochrane, a pioneer in the field of evaluation of medical interventions) is an international network of clinicians, epidemiologists, and other health professionals that aims to prepare, maintain and disseminate comprehensive and systematic reviews (meta-analyses) of the effects of health care (9,10). Since its establishment in Oxford in October 1992, the network has been growing rapidly, with the foundation of 15 other centres in Europe, North and Latin America, Africa, and Australia involving hundreds of individuals from all over the globe collaborating in review groups. Figure 3 is the Cochrane Collaboration logo (11).

The rationale of meta-analysis

The rationale of meta-analysis are summarized as (2,12,13):

1. To provide an overview of a complex literature in order to guide policy decisions and direct future research
2. To improve the precision of estimates of the effect size by increasing the number of observations
3. To assess and resolve apparent conflict in the literature by investigating heterogeneity in study design and results
4. To enable more reliable subgroup analyses to be performed
5. To answer questions not posed at the start of individual trials
6. To define new research questions and assist in the planning of future trials

Figure 3. The Cochrane Collaboration logo shows how pooling data reveals the significance of treatment effects.

Method of Meta-analysis

A meta-analysis should first begin with a protocol, which clearly states its aim and methodology. The objectives, hypotheses to be tested, proposed methods and criteria for identifying and selecting relevant studies, and extracting and analyzing information must be described clearly. Actual study search, selection and appraisal follows, which involves applying specified procedures for locating and appraising studies that meet specified criteria for inclusion. Data are extracted and checked to see if they can be quantitatively combined. This involves clinical criteria and statistical procedures to investigate relations among study characteristics and findings. A brief description of the steps follow, a complete description and evaluation would be beyond the scope of this review.

1) Formulating questions and locating studies for inclusion

The review should begin with a focused question. By formulating the question properly, the criteria that primary studies need to meet to be included become clear. The investigators then must try to find every relevant report. This usually begins with a computerized search of MEDLINE and other electronic literature databases such as EMBASE and CANCERLIT. The Cochrane Controlled Trials Register (CCTR) is one of the best electronic sources for randomized clinical trials (RCTs) (14). The Cochrane Collaboration has an extensive programme of manual searches of medical journals published in English and many other languages, this has helped to identify many published RCTs not listed in Medline. Multiple overlapping search strategies should also be used and must be carefully

planned. It has to be decided whether the search will be extended to include unpublished studies, as their results may differ systematically from published trials. For locating published studies, electronic databases are useful but used alone, they may miss a substantial proportion of relevant studies (14). Searches should extended beyond electronic databases where possible such as manually searching journals and conference proceedings, searching bibliographies of articles, monographs, existing registers of studies, and contacting companies or researchers asking about unpublished work.

2) Selecting and data collection

To plan for study selection, reviewers refer to the focused clinical question and choose selection criteria that are consistent with it. The criteria can be itemized on customized data extraction forms and should at least specify:

1. design of the study
2. patient population
3. disease
4. interventions given
5. measurement of outcomes

The study data to be extracted are usually either binary or continuous measurements. Binary data can be summarized by the incidence risk, odds or rate and treatment effects are estimated by the risk ratio, odds ratio, risk difference or rate ratio. Continuous data can be summarized by the mean response and treatment effect by the difference between the treatment and control group means. It is also important to extract the standard errors or confidence intervals of all the study treatment effect estimates.

3) Appraising Studies

In planning the critical appraisal of included studies, reviewers decide which clinical and methodologic study features are important in order to adequately portray the validity and relevance of each study. Ultimately, primary studies should be appraised and reported in sufficient detail to allow readers to judge the quality of the study and the appropriateness of its inclusion. Blinding evaluators to the names of the authors and their institutions, the names of the journals, sources of funding, and acknowledgments may help reduce reviewer bias and lead to more consistent appraisal scores.

4) Calculating overall effect

Only when the studies are judged combinable because of homogeneity in design should an overall pooled effect be calculated by combining the data. Meta-analysis uses a method that gives the results of larger trials more weight than the smaller ones. There are two statistical techniques to do this, the **fixed-effects model** and the **random-effects model**. The difference between the two models is in the way the variability of the results between the studies is viewed. The fixed-effects model assumes that there is a single true effect to be estimated and considers that study result variability is exclusively due to random variation. The random-effects model assumes a different true effect for each study and takes this into consideration as an additional source of variation. These separate study effects are assumed to be normally distributed, and the mean of this distribution is what we are estimating by the random-effects pooled average. The additional variability measured make the random effects pooled estimates have wider confidence intervals. A substantial difference in the combined effect calculated by the fixed and random effects models will be seen only if studies are markedly heterogeneous. Another quantitative technique for combining data is the **Bayesian method**. This approach incorporates a prior probability distribution based on subjective opinion and objective evidence, such as the results of previous research. Bayesian analysis uses Bayes' theorem to update the prior distribution in light of the results of a study, producing a posterior distribution. This approach has many attractive features, but is controversial because it depends on opinions, and frequently they will vary considerably (15).

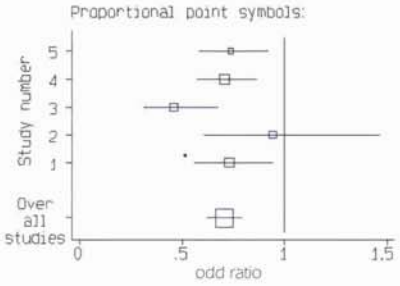

Figure 4. Odds ratios for vitamin A and confidence intervals

5) Presentation

The results of a meta-analysis are presented in a Forest plot (see Figure 4) that shows the point estimates and their confidence intervals (CIs). The presentation shows the extent of heterogeneity, and also the pooled estimate of the individual studies. This display was adopted by the Cochrane Collaboration as its logo. The example of data shown in Table 1 come from a meta-analysis of vitamin A supplementation in infectious disease from five community studies (16). Each study result is represented by a square and a horizontal line, which corresponds to the point estimate and the 95% confidence interval of the odds ratio (Figure 4). The area of the squares reflects the weight of the study. The solid vertical line corresponds to no effect of treatment (odds ratio = 1.0). If the confidence interval in-

Table 1. Vitamin supplementation in infectious disease, odds ratios and confidence interval. Adapted from Glasziou & Mackerras (16)

Study	Dose regime	Vitamin A		Control		Odds	95% CI
		Death	number	Death	number	ratio	
1	200,000 IU six-monthly	101	12,991	130	12,209	0.73	0.56 to 0.95
2	200,000 IU six-monthly	39	7,076	41	7,006	0.94	0.61 to 1.46
3	8333 IU weekly	37	7,764	80	7,755	0.46	0.31 to 0.68
4	2000,000IU four-monthly	153	12,541	210	12,264	0.70	0.57 to 0.87
5	200,000IU once	138	3,786	167	3,411	0.73	0.58 to 0.93

cludes 1, then there is no significant difference in the effect of experimental and control treatment at $P<0.05$. The confidence intervals of all but one study (Study 2) exclude 1, indicating that the effect estimates were significant.

Results of a meta-analysis will vary depending on the overall study quality of the primary trials, on whether certain trials or subgroups of patients have been excluded and on which model for pooling the data is selected (2). Therefore, the robustness of the conclusions to different exclusion decisions and model assumptions should always be examined in a **sensitivity analysis**. The procedure simply involves the re-analysis of different subsets of the data and comparing the results for consistency. To avoid accusations of "data-dredging" there should be logical reasons for the choice of data subsets and models, preferably a priori specification in the protocol. If the sensitivity analyses do not change the results, it strengthens the confidence that can be placed in the original interpretation. If the results change in a way that lead to different conclusions, this indicates a need for great caution in interpreting the results and further investigation as to possible reasons for this.

The Advantages of Meta-Analysis

1) State-of the art literature review

In the past, when seeking advice in controversial topics, clinicians and scientists have relied heavily on narrative reviews. Traditional narrative reviews are often subjective, unsystematic, and inefficient in contrast to systematic reviews. Strategies for identifying and selecting information are also rarely defined. Collected information is often reviewed haphazardly with little attention to systematic assessment of quality. Once a set of studies has been assembled, usually a common way to review the results is to count the number of studies supporting various sides of an issue and to choose the view receiving the most votes. Such procedure ignores sample size, effect size, and research design. There is good evidence to suggest that these traditional methods are often misleading, biased and often reach opposite conclusions (19, 20). Consequently, it has been increasingly recognized that the traditional review article is a subjective method of summarizing research data and prone to bias and error (20,21). By employing pre-planned and specified statistical techniques with systematic qualitative review methodology, meta-analysis injects more objectivity and rigor into the review writing process.

2) Gain in statistical power for average estimates

Meta-analysis also provides a gain in statistical power when estimating average effects. If data from more than one study can be combined, the effective sample size and hence statistical power will increase. This is an advantage when the incidence of events is expected to be rare. However, we should never forget that we are not simply looking for statistical significance but also clinical significance. In order to interpret a pooled average fairly we should have an idea of the result difference that would be clinically significant in our context. It should be remembered that the inevitable gain in precision does not protect a meta-analysis from bias. Thus a large but poorly done meta-analysis could give us a very precise estimate of a very biased treatment effect.

3) Predictive ability

Meta-analyses have been examined for their ability to predict the results of large clinical trials. Villar *et al* examined 30 meta-analyses in perinatal medicine, comparing the results of a meta-analysis of several small trials with a single large trial addressing the same topic (20). Twenty-four of the 30 meta-analyses correctly predict the direction of effect in the largest trial. Cappelleri et al reviewed 79 meta-analyses and also found about 80% agreed with the results from the larger trial (21). The authors suggested that "researchers and funding agencies may use meta-analysis before recommending a clinical practice or to summarize results of three controlled trials before deciding on additional studies of promising interventions". The method of **cumulative meta-analysis** in which a meta-analysis is serially updated with the result of the latest study can help determine when additional studies are no longer needed and highlight the effectiveness of treatments much earlier (22).

Such cumulative analysis can help to determine whether the pooled estimate has been robust over time and can also determine the point in time when statistical and clinical significance were reached. For example, Figure 5 shows a cumulative meta-analysis of mortality results from randomized controlled trials of intravenous streptokinase in acute myocardial infarction. A significant ($P<0.01$) combined difference in total mortality had been achieved by 1973. The result of the subsequent 25 studies, which enrolled a total of 34,542 additional patients, reduced the significance level to 0.001 in 1979, 0.0001 in 1986, and finally to 0.00001. The cumulative method suggested that evidence of the life-saving efficacy of intravenous streptokinase had been in existence almost 20 years ago, long before its submission to and approval by the Food and Drug Administration and its general adoption in practice (22).

4) Explore and explain heterogeneity between studies

Heterogeneity of study results in a meta-analysis can be detected by visual inspection of the Forest plot and by a statistical test for heterogeneity. Result heterogeneity can be due to chance, but more often it is due to systematic differences in the design and execution of the studies. Qualitative appraisal of the studies will help identify these differences. The problem of heterogeneity can be further explored using sub-group analysis and meta-regression methods. The purpose of subgroup analysis is to try and identify a subset of studies that are more homogenous in design and hence combinable. **Meta-regression** uses linear regression as an exploratory tool to measure how specific study characteristic e.g. time of publication, quality of study and follow-up time influence the magnitude of the point estimate of the treatment effect across studies (23). The results are generally reported as slope coefficients with CIs. Once again the conclusions should be treated with caution because a typical meta-regression will involve only a small amount of independent data and would also be based on an unvalidated linear regression model.

5) Other Types of Data and Methods

Meta-analysis of Diagnostic Tests

Meta-analysis is potentially important in the assessment of the accuracy of diagnostic tests for both clinician and policy makers. Meta-analysis may (24) 1) provide an overall summary of diagnostic accuracy; 2) determine whether estimates of diagnostic accuracy depend on the study design characteristics (study validity) of the primary studies 3) determine whether diagnostic accuracy differs in subgroups defined by characteristic of the patients and test; and 4) identify areas for further research.

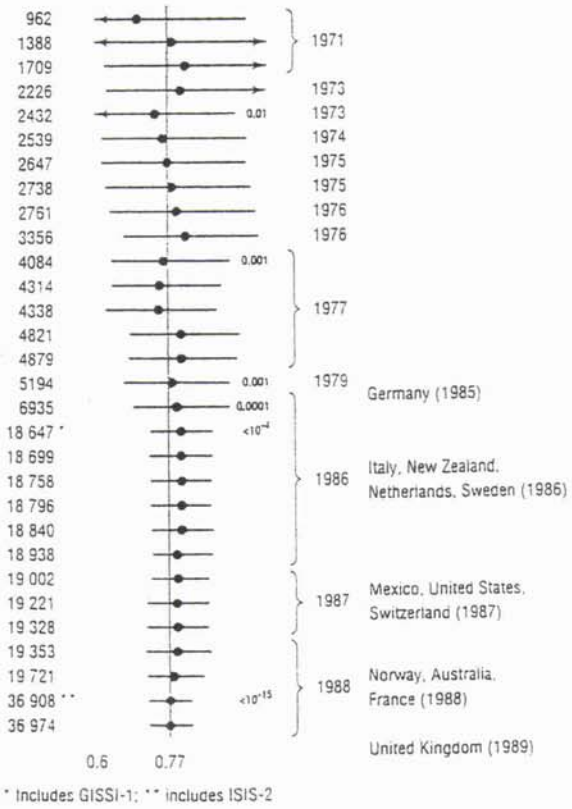

Fig 5. Cumulative meta-analysis of total mortality results from randomized controlled trials of intravenous streptokinase after myocardial infarction. Adapted from Lau *et al* (22)

Meta-analysis of Non-randomized Studies

Data from non-randomized study designs (observational studies) can also be combined in principle by using meta-analytical techniques. Typically such studies would include cohort, case-control and cross-sectional designs. Because of the great vulnerability of such non-randomized comparative studies to bias (15), even greater care must be taken in appraising studies, analysis and interpretation.

Meta-analysis of Individual Patient Data (IPD)

Meta-analysis can be conducted on IPD instead of being based on summary data. Meta-analysis of IPD uses detailed outcome and risk factor data for the individual patients involved in each study rather then relying on published study summaries. However, meta-analysis of IPD is more expensive and time-consuming than meta-analysis of published summary data because it requires the coordination of large teams of investigators (25). Stewart & Parmar (26) investigated the difference between meta-analysis of the literature and meta-analy-

sis of IPD. They concluded that the results of a meta-analysis of the literature alone may be misleading, this was attributed to publication bias, patient exclusion, length of follow-up and method of analysis. Therefore, meta-analysis of individual patient data probably represents the best form of meta-analysis (27). Among the advantages the approach brings are (2): 1) direct computation of survival curves, thus avoiding indirect and biased methods; 2) the ability to check assumption of constancy of treatment effect over time; 3) the ability to identify interactions between treatment effect and patient profiles.

Skepticism

When meta-analysis first appeared, it received a mixed reception. Today, despite its widespread and growing acceptance, meta-analysis continues to be controversial. While some exponents feel that meta-analysis should replace traditional review articles of single topic issues whenever possible (28), others think of it as "a tool that has become a weapon" (29). The common criticism of meta-analyses is that they often inappropriately combine information from multiple trials with different designs, interventions and subject populations into a single estimate of effect (8,30). Thus meta-analyses may generate misleading conclusions by the ignoring obvious heterogeneity among studies. Although we can use a chi-square test to test for heterogeneity of results among studies, this is not a valid way to judge study combinability because, combinable studies must be homogeneous (similar) by design, which is not the same as homogeneous in results. Meta-analyses should therefore state a priori design conditions for combinability in the protocol so that the reader can judge for himself whether they are logical and to what extent the combined studies meet these criteria.

A second problem with many overviews is that they are based entirely on published trials. In some areas of research there has been evidence that journals, perhaps unintentionally exert **publication bias**. This is the phenomena by which significant and positive results are more likely to be reported, than the non-significant and negatives ones. Results which are significant may be emphasized and non-significant results may be ignored by the investigators and editors as uninteresting or uninformative (31,32,33). Often authors and publishers make less effort to publish when the results are not significant. Furthermore, publication of unfavorable results may also be discouraged by the sponsor of research. Consequently, pooling the results of only published trials will perpetuate thisbias and distort the findings of meta-analyses. It is therefore suggested that conclusions based only on a review of published data should be interpreted with caution (33). However, it is usually difficult to locate and get information on the unpublished studies. The Cochrane Collaboration has initiated a scheme to encourage all trialists and drug companies to report all their study results regardless of whether it was a positive or negative finding.

Publication bias is difficult to eliminate, but some statistical procedures may be helpful in detecting its presence. A funnel plot may be used to visually explore the possibility that publication bias is present. It is a simple scatterplots of the trials' effect estimates against their precisions (inverse of the variance, standard error or sample size). Results from small (imprecise) studies will be scattered widely at the bottom of the graph. The spread will narrow as precision increases among larger studies. In the absence of bias, the plot should resemble a symmetrical inverted funnel. If the plot shows an asymmetrical and skewed shape (often a half-funnel), bias is indicated. Figure 6 shows the example of an inverted funnel plot from a meta-analysis of intravenous streptokinase for acute myocardial infarction (18). The risk ratio for the mortality reduction in each study is plotted against the weight of the study, represented by the sample size. The plot shown in the study reveals that there are fewer small studies with risk ratios greater than 0.8 than there are small studies with risk ratios less than 0.8, whereas the number of medium and large studies are fairly symmetrical. These results suggest that some small studies with negative findings were not published. Outlier studies may also be identified by using this plot.

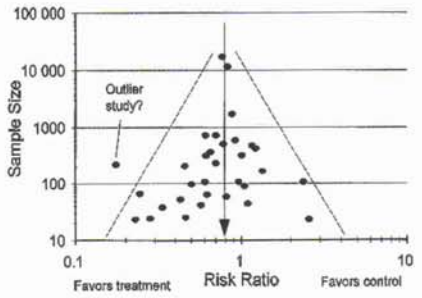

Figure 6. An inverted funnel plot to detect publication bias

In addition, among published studies, those with significant results are also more likely to be published in English, more likely to be cited, and more likely to be published more than once, leading to other biases such **English language bias, database bias, citation bias**, and **multiple publication bias**. Although studies might have been located and data obtained, potential for bias might still arise such as in establishing the inclusion criteria for a meta-analysis (**biased inclusion criteria**) and **bias due to poor study quality**. Any form of bias poses a serious threat to the validity of meta-analysis. While the meta-analyst can minimise the biases in his review methodology, there is little he can do about the biases within each study except to alert the reader to them.

Summary and Conclusions

Meta-analysis has made and continues to make major contributions to both medical research and clinical decision making. However, it is not a panacea and while it remains the most promising approach to reviewing clinical trials, it cannot "clean-up" dirty data. A well-done meta-analysis will in fact reveal the flaws in each study, allowing a more objective appraisal of the evidence than traditional narrative reviews. But it is still only a review of primary studies and therefore cannot be viewed as a substitute for them. In conclusion, for a good meta-analysis, thorough knowledge of the clinical problem, a priori specifications of inclusion criteria, pooling criteria and sub-group analysis, and careful search, appraisal and presentation of data are essential. Meta-analyses will often not give a final solution to a problem, rather it will reveal the progress that has been made and the flaws in present studies so that future ones can be better designed, conducted, analyzed and reported.

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SMOKING AMONG STUDENTS IN A RURAL SECONDARY SCHOOL

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ABSTRACT: A cross-sectional study on the prevalence of smoking among Form 3, 4 and 5 students of a rural national co-educational school was carried out using a self-administered questionnaire. By the age of 18 years old, three quarters of boys had tried smoking compared with 12% of girls. About a third of boys were still smokers while only 0.7% of girls were still smokers. There was a higher prevalence of smokers among students who stayed with their parents and those who were working part-time. Most smokers knew about the dangerous and addictive effect of cigarette smoking but smoked because of "influence by school peers", "curiosity" and "to increase concentration and decrease tension". *(JUMMEC 2000; 2:85-88)*

KEYWORDS: Cigarette, smoking, prevalence, students.

Introduction

Although there were many articles published in foreign journals about the prevalence of smoking and its associated factors in different age groups, especially teenagers, few studies were carried out in this country (1,2,3). The objective of this study is to examine the factors that have been found to be associated with smoking in the local context.

Unlike Canada and the United States, the prevalence of smoking among Malaysian females was low (1,2,3,4,5). However, when compared with our neighbour, Singapore, the prevalence of smoking in Malaysia was high (6).

According to Mohamed Ismail (3), 40% of Form 3 and Form 5 students in Sabak Bernam started to smoke at the age of 14 years old. Thambypillai(1) had found that the mean age at initiation of cigarette smoking among the Form 4 students of urban schools was 13.3 years old. However, in Singapore, the median age at experimentation was even younger i.e. 12 years old (7).

Studies in Singapore and Canada had linked cigarette smoking among teenagers to a parent (usually the father) who smokes (4,7). Although there is no such study in Malaysia, it was postulated by Hussain Habil (8) that the role of a smoking parent on the development of cigarette smoking among teenagers is very important.

Both foreign (5,9,10) and local researchers (2) have found that most of the students knew about the dangerous and/or addictive effect of cigarette smoking. But Kessler (9) had postulated that young people smoked because they did not believe that these dangers applied to them.

Compared to non-smokers, smokers had higher monthly family income and daily pocket money (2).

Nyi Nyi Naing (2) and Mohamed Ismail (3) have found that most students started smoking due to influence by friends. Other reasons included "eagerness to try", to forget problems, to be like an adult and "following father". However, in Singapore, most students smoked "to relax" and "out of sheer curiosity" (7).

Emmanuel (7) has found that most students obtained their first cigarettes from their friends. Nyi Nyi Naing (2) found that most students smoked between 1– 5 cigarettes in a day.

Thambypillai (1) found that 42% of smokers wished to stop smoking while Mohamed Ismail (3) found that as many as 84% of smokers wished to stop. Emmanuel (7) also found that most smokers wished to stop.

Materials and Methods

The study population included all Form 3, 4 and 5 students of a rural secondary school with age between 15

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and 18. The study by Thambypillai (1) showed that the mean age at initiation of smoking was 13.3 years old. However, in Emmanuel's study (7), it was found that it took about 2 years for the experimental smokers to become regular smokers. Hence, the target age group was 15 years old and above.

Data was obtained through a self-administered questionaire written in the Malay language. To obtain maximal responses from the students, the questionnaires were completed under the guidance of trained medical students, in the absence of their teachers. They were also assured that the information gathered would be treated confidentially. As students may deliberately absent themselves to avoid participating in the questionnaire, the students were not informed of the date of the administration of the questionnaire.

Errors and Limitations

The students may not attempt the questions honestly for fear of being victimized. Some of the students, especially those in poorer academic classes, were not able to understand the questions. Although assisted by our interviewer, some of the answers received were not valid. These answers have been omitted from the analysis.

Definitions

Definitions pertaining to the smoking status of students are as follows:-

a) Smoker: a person who at the time of the survey, was still smoking

b) Ex-smoker: a person who had stopped smoking

c) Experimental smoker: a person who had tried smoking in the past but did not continue smoking

d) Non-smoker: a person who had never tried smoking before

Results

Of the 636 targeted students, 564 (88.7%) responded. The rest (47 boys and 25 girls) were absent from school. The number of respondents to different questions in the questionnaire differed slightly due to incompleteness of the answers given by the students.

The respondents comprised of Malay and Indian ethnic groups only, as there were no Chinese students in Form 3, 4 and 5 in the school. The Indians made up only 6.9% of the studied population. Overall, 41.0% of students had tried smoking in the past. This comprised 34.5% smokers, 27.9% ex-smokers and 37.6% experimental smokers.

More boys than girls smoked (or tried smoking). Among the boys, an overall 74.6% had tried smoking in the past. This included 29.7% who were still smoking. On the other hand, among the girls, only 12% had tried smoking where only 0.7% were active smokers.

Among those who had tried smoking, the percentages increased with the experience of smoking among the boys (28.5% experimental smokers, 31.6% ex-smokers and 39.9% smokers). This trend was reversed among the girls (86.1% experimental smokers, 8.3% ex-smokers and 5.6% smokers).

An unexpected result was that the percentage of smokers among those who stayed with their parents (16.2%) was two times the percentage of smokers among those who stayed in the school hostel (8.1%). The percentages were also lower for other positive smoking categories - 10.4% of students who stayed in the school hostel compared with 12.7% of students who stayed with their parents were ex-smokers; 9.6% compared with 17.3% were experimental smokers.

Smoking status also changed with working status. As many as 48.8% of those who were working part-time were smokers, compared with 26.6% of those who had worked in the past and 5.3% of those who had never worked before.

Our survey results did not show any significant difference in the prevalence of smoking parents among students with different categories of smoking status.

Knowledge about the danger and the addictive effect of smoking was well established among the student population as evidenced by the fact that as many as 91.1% of the students knew about these. Only 0.9% of the students did not know that smoking is dangerous and can lead to addiction.

Survey results showed that overall, majority of students (51.1%) had smoked without the knowledge of both their parents and school teachers compared with 16.3% of students who had smoked with the knowledge of both their parents and school teachers. However, among the smokers, the number of students who had managed to smoke secretively (32.4%) and those whose activities are known to both their parents and teachers (35.3%) was almost equal. (Table 1)

The three most important reasons given by smokers and ex-smokers for their initiation of smoking were "influenced by school peers" (65.4% of smokers and 76.2% of ex-smokers), curiosity (60.3% of smokers and 52.4% of ex-smokers) and "to reduce tension and increase concentration" (39.7% smokers and 38.1% ex-smokers). However, for the experimental smokers, curiosity (69.1%) topped the list followed by "influenced by school peers (37.0%) and "to reduce tension and increase concentration" (12.3%). (Figure 1)

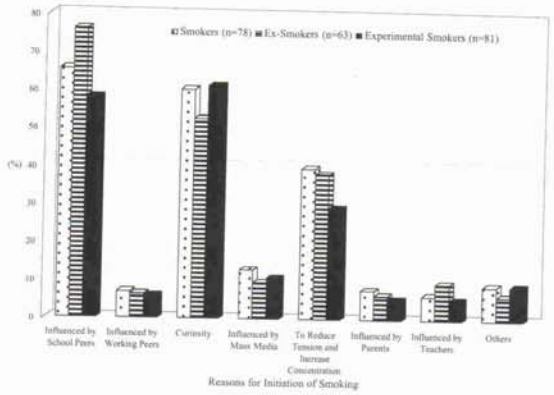

Figure 1. Reasons for Initiation of Cigarette Smoking

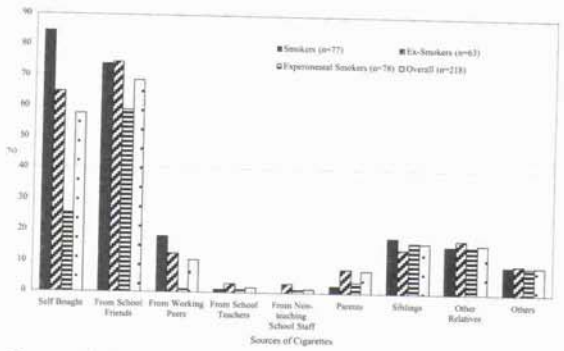

Figure 2. Sources of Cigarettes for Students Who Had Tried Smoking

Table 1. Parents' and Teachers' Knowledge about the Smoking Status of Students

Parents' and Teachers' Knowledge	Smoking Status			
	Smokers (%)	Ex-smokers (%)	Experimental Smokers (%)	Total (%)
Parents and Teachers Know	24 (35.3)	11 (17.5)	1 (1.3)	36 (17.1)
Parents Know and Teachers Don't Know	10 (14.7)	10 (15.9)	16 (20.0)	36 (17.1)
Parents Don't Know and Teachers Know	12 (17.6)	10 (15.9)	4 (5.0)	26 (12.3)
Parents and Teachers Don't Know	22 (32.4)	32 (50.8)	59 (73.8)	113 (53.6)
Total	68 (30.8)	63 (28.5)	80 (36.2)	211 (100.0)

More than three quarter of students who had smoked, had easy accessibility to cigarettes. Among the 22.6% with difficult accessibility, 50.0% were experimental smokers and 38.0% were ex-smokers. Most of the students perceived the price of cigarettes as expensive (78.5%) but not many faced financial difficulties in purchasing them (50.0%). This was especially obvious among the smokers (57.7% had no financial difficulties). The percentage of smokers who perceived cigarette as expensive and at the same time faced financial difficulties in purchasing them (34.6%) was almost the same as the percentage of smokers who perceived cigarette as expensive but did not have any financial difficulties in purchasing them (33.3%).

Data showed that overall, most of the students had obtained their cigarettes from their school friends (68.8%), followed very closely by purchasing them themselves (57.8%). However, for smokers, 84.4% managed to buy the cigarettes themselves whereas 74.0% obtained them from their school friends. (Figure 2)

The mode and median for the amount of cigarettes used per day is 3. However, the range of cigarettes used per day range from 1 cigarette per day to 31 cigarettes per day.

Only 16.0% of the smokers had thought of trying something stronger than cigarette smoking. Among this, 4 students said they would like to try glue sniffing, 7 students wanted to try ganja while a student would like to try both. Among the smokers, 61.3% had the intention to stop smoking and had even tried, but have obviously failed. However, 18.6% had no intention to quit at all.

Discussion and Conclusion

The survey had shown that by 18 years old, 74.6% of boys had tried smoking compared with 12% of girls. Among the boys who had been initiated to smoking, 39.9% were current smokers compared to 5.6% of girls.

The survey also showed that among the boys, the percentage of non-smokers is highest in the 16 years old age group. The authors postulate that this could have been due to the fact that a large number of smokers have stopped schooling after Form 3 (there are only 75 boys in Form 4 compared with 117 boys in Form 3). However, further studies will be needed to confirm this hypothesis.

About 8.1% of students who stayed in the school hostel were smokers compared with 16.2% of students who stayed with their parents. However, as expected, a higher prevalence of smokers was seen among those who had started working. The authors suggest the need for further studies to look into the reasons for these discrepancies.

Consistent with the findings of Califano (5), 91.1% of students knew about the danger and addictive effect of cigarette smoking. However, knowledge of someone

who had contracted an illness or who had died due to cigarette smoking was low among these students. It is probable that although these students knew about the danger and addictive effect of cigarette smoking, they had little sense of their own vulnerability (5).

The three most important reasons for initiation of smoking were "influenced by school peers", curiosity and "to increase concentration and decrease tension". These results are similar to the ones found in Singapore (7) although in Singapore, "to relax" hit the top list and only 13.6% of smokers "follow friends".

More than three quarter of students who had tried smoking had easy accessibility to cigarettes. However, among those with difficult accessibility, half of them are experimental smokers. Their difficulty in getting cigarettes could have deterred them from continuing the habit. These results should prompt the authority to implement the already-approved national policy not to sell cigarettes to minors. According to Kessler (9), 3 of the ways to reduce cigarette smoking in young adults is to reduce access to cigarettes, to convince danger to self and not to others, and to reduce the number of advertisements.

Again, more than three quarter of students perceived the price of cigarettes as expensive but only half of the students had financial difficulties in purchasing them. Most of the ex-smokers and experimental smokers perceived the price of cigarettes as expensive and faced financial difficulties in purchasing them too. This could have deterred them from continuing to smoke. The act of increasing cigarette taxes every year should decrease the consumption of cigarettes among students (10) as well.

About 70% of students obtained their cigarettes from their friends while less than 60% of students purchased these cigarettes themselves. This showed that school friends played a major role in contributing the cigarettes for the students' consumption. As both the students and their friends are minor, implementing the national policy of not selling cigarettes to minor may help in reducing the number of students who smoke.

More than four-fifths of students had intention to quit in the future. This suggests that smoking cessation campaigns should be carried out more vigorously.

Acknowledgements

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SPECTRUM OF OPPORTUNISTIC INFECTIONS RELATED TO THE CENTRAL NERVOUS SYSTEM AMONG AIDS PATIENTS IN HOSPITAL KUALA LUMPUR

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ABSTRACT: A retrospective study was conducted in Hospital Kuala Lumpur, May, 2001. 49 (12.1%) of 406 AIDS patients were diagnosed as opportunistic infections related to the central nervous system. The sex ratio (M:F) was 7.2. The median age was 34 years. The predominant age group for male as same as female was 25-34 years.The majority of the study subjects were Chinese (79.6%), married (49%), unemployed (42.9%) and heterosexuals (95.9%) as the risk behavior related to HIV infection. The most frequent clinical manifestations was headache (71.4%). At the time of diagnosis, the greater number of patients 39 (79.6%) had CD4 count < 200 cell/cumm. Outcome of acute therapy the patients had a complete (85.7%), treatment continued (10.3%), and transfer to other hospital (2.0%). Toxoplasmic encephalitis (7.6%) and cryptococcosis (3.9%) were the frequent cause of focal intracerebral lesions and meningitis in these patients respectively. Oral candidiasis (32.7%) was the most common among other opportunistic infections in this study. *(JUMMEC 2000; 2:89-92)*

KEYWORDS: AIDS, Opportunistic infections, central nervous system, clinical manifestations, outcome.

Introduction

With the incidence of patients infected with human immunodeficiency virus (HIV) increasing in many developing countries, each with its own characteristics in terms of the trends in HIV prevalence, those affected, and the HIV-related opportunistic diseases observed (1). Central nervous system infections are among the most frequent and serious causes of morbidity and mortality in HIV/AIDS patients. In previous study, neurological disease occurred in 63% of patients with AIDS and heralded the disorder in 20% of these patients (2) Disease due to a coinfecting pathogen may be due to primary infection, recurrent infection, or the reactivation of latent infection (3). Certainly, the central nervous system (CNS) manifestations of the disease will be seen more frequently. This study was conducted to determine the prevalence of opportunistic infections related to the central nervous system among AIDS patients in Hospital Kuala Lumpur (HKL), Kuala Lumpur, in order to accumulate information which lead to better understanding and management toward HIV/AIDS patients in the future.

Materials and Methods

406 patients and age more than 14 years with anti-HIV antibodies positive by any serological tests (ELISA (I,II), CLIA, or LA) were recruited in this retrospective study, who attended the OPD clinic or admitted to the ward in HKL. All patients' data (demographic characteristics, risk factors related to HIV infection, clinical manifestations, investigations and outcome of opportunistic infections related to the central nervous system) were recorded in the data collection sheet.

Statistical analysis

The results were analyzed by using the statistical software SPSS. The data with quantitative variable were expressed as mean and range, qualitative variable were expressed as frequency and percentage.

Results

Table 1 and 2 summarise the patients' baseline demographic profiles at the time of this study. The age range of patients was 20-62 years with a median of 34 years. The ratio of M:F was 6.8:1. The predominant age group for male as same as female was 25-34

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years. The various ethnic groups were Chinese 39 (79.6%), Malays 7 (14.3%) and Indians 3 (6.1%). The majority of patients were married 25 (51%), unemployed 21 (42.9%), and heterosexuals 47 (95.9%) as the risk behaviors.

We found that the spectrum of opportunistic infections related central nervous system (49) among AIDS patients (406) was 12.1% included toxoplasmic encephalitis 31 (7.6%), cryptococcal meningitis 16 (3.9%), neurosyphilis 1 (0.3%), and tuberculous meningitis 1 (0.3%) as shown in table 3.

Table 4 and 5 show headache (71.4%), fever (53.1%) were the common clinical manifestations in this study. The greater number of patients had CD4+T cell count < 200 cell/cumm. (79.6%).

Table 6 shows the outcome following the acute therapy the patients had a complete (85.7%), treatment continued (10.3%), loss follow up (2.0%) and transfer to other hospitals (2.0%). Relapsing toxoplasmic encephalitis (6.1%) and cryptococcal meningitis (2.0%) were detected in this study

Oral candidiasis (32.7%) and tuberculosis (20.5%) were among other common opportunistic infections coinfected with AIDS-related to the central nervous system infections in this study as shown in table 7.

Discussion

The prevalence of toxoplasmic encephalitis in this study was 7.6%. It is not surprising even though it was much lower than other studies e.g. 25-50% from Europe and Africa (4,5), 47% from Austria (6), or 30-50% from USA (7). Most cases of clinical toxoplasmosis in AIDS result from reactivation of a chronic infections (8). Brain toxoplasmosis is one of the more frequent opportunistic infections and the most common of brain focal lesions complicating the course of AIDS (9,10). Furthermore, toxoplasmic encephalitis is a life-threatening condition and early diagnosis is highly desirable for initiation of specific therapy and to avoid misdiagnosis, especially with primary brain lymphoma (11).

In this study, we found that 4% of patients were diagnosed as cryptococcal meningitis. Cryptococcal meningitis is the most common life-threatening fungal pathogen among patients with acquired immunodeficiency syndrome (AIDS) (12). However, this result was considered similar with other studies that showed the prevalence in smaller series has ranged from 2% to 4% (13,14), or 6% in New York (15), but much higher (24.10%) in Thailand (16).

It is interesting to note that the prevalence of syphilis in this study was 4.9% and 0.3% of patients developed neurosyphilis later. Syphilis has been recognized as one

Table 1. Demographic and baseline characteristics of the study subjects

Characteristics	No. of patients	Percentage
Sex		
Male	43	87.80
Female	6	12.20
Race		
Chinese	39	79.60
Malay	7	14.30
Indian	3	6.10
Marital status		
Single	23	47.00
Married	25	51.00
Divorced	1	2.00
Occupation		
Labourer	12	24.50
Nonlabourer	16	32.60
Unemployed	21	42.90
Risk behaviors		
Heterosexual	47	95.90
Injecting drug user (IDU)	2	4.10

Range of age = 20-62 years Median = 34 years

Table 2. Age distribution of the study subjects

Age group	No. of patients	Percentage
Male		
15-24	2	4.10
25-34	21	42.90
35-44	15	30.60
45-54	3	6.10
55-64	2	4.10
Female		
15-24	2	4.10
25-34	3	6.10
55-64	1	2.00

M:F = 7.2:1

Table 3. The spectrum of opportunistic infections related to the central nervous system among 49 AIDS patients in this study

	No of patients	Percentage
Toxoplasmic encephalitis	31	7.6
Crytococcal meningitis	16	3.9
Neurosyphilis	1	0.3
Tuberculous meningitis	1	0.3
Total	49	12.1

Total No. of AIDS patients = 406

of the infectious complications of HIV-1 infection (17). Reports from few different studies in the past showed varying prevalence e.g. 16.6% in Germany (18) 44% in AIDS patients with neurosyphilis but only 1.5% under hospitalization in USA (2). Previously the neurosyphilis was very rare, but the incidence of neurosyphilis has been increasing since AIDS has appeared. The reason for development of this stage of syphilis, may be an inadequate treatment as well as a weakening of the immunological responses (19). In light of its diverse manifestations, syphilis should be considered in the differential diagnosis of any HIV-1 infected individual presenting with an unexplained neurological disease.

We found that the prevalence of tuberculous meningitis in this study was 0.3% out of 30% of AIDS-related tuberculosis (TB) patients. Although meningitis due to *M. tuberculosis* has been described in HIV-1-infected patients, it is an unusual complication of systemic tuberculosis although it may pursue an atypically indolent clinical course compared with non-HIV-1-infected populations (20). Tuberculous meningitis has been the most life-threatening form of extrapulmonary TB and was uniformly fatal before the advent of antituberculous chemotherapy (21).

Unexpectedly, 6.1% of TE patients had relapsed. Lifelong pyrimethamine plus sulfadiazine is the treatment of choice but this therapy has had to be discontinued due to adverse reactions in up to 40% of patients. Atovaquone appears to be an effective therapeutic agent in this situation, and is generally well excepted (22).

Last but not least, 2.0% of patients had relapsing cryptococcal meningitis in this study. Although life-long therapy has been widely advocated, the true efficacy of maintainance therapy remains unproved. Prognostic factors associated with a higher risk of relapse or worse, early death remain largely unknown (23).

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Table 4. Clinical manifestations of the study subjects

Clinical manifestations	No. of patients	Percentage
Headache	35	71.40
Fever	26	53.10
Neurological deficit	14	28.60
Seizure	2	4.10

Table 5. The relationship between CD4 +T cell count and the study subjects

CD4+T cell count (cell/cumm.)	No. of patients	Percentage
≥ 500	2	4.1
200- 499	8	16.3
< 200	39	79.6

Table 6. Outcome of the study subjects

Outcome of treatment	No. of patients	Percentage
Complete	42	85.70
Treatment continued	5	10.30
Loss follow up	1	2.00
Transfer to other hospitals	1	2.00
Relapsed		
Toxoplasmic encephalitis	3	6.10
Cryptococcal meningitis	1	2.00

Table 7. The spectrum of other opportunistic infections in this study

Opportunistic infections	No. of patients	Percentage
Oral candidiasis	16	32.70
Tuberculosis	10	20.50
Pneumocystis carinii pneumonia	5	10.20
Herpes zoster infection	5	10.20
Sexually transmitted diseases	4	8.20
Cytomegalovirus infection	2	4.10
Bacteraemia	2	4.10
Scabies	1	2.00
Mycobacterium avium complex infection	1	2.00

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IMPROVING INTERNET ACCESS IN THE UNIVERSITY OF MALAYA MEDICAL CENTRE: A NADI IT INNOVATION

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ABSTRACT: In early 2001, Nadi IT (the IT department of the UMMC) migrated the UMMC leased line from its old 64 kbps line to the 34 Mbps University of Malaya leased line. The migration was a new learning experience for Nadi IT and many lessons were learnt along the way. This paper describes the idea behind the migration process, the reason for the migration, problems and solutions to all these problems as well as the benefits derived from the migration. The experience of this process may be useful to others wishing to improve IT facilities without resorting to expensive solutions. *(JUMMEC 2000; 2:93-97)*

KEYWORDS: Internet, leased line, migration

Introduction

The Internet (also known as the Net), is a worldwide network of computers[1]. It connects thousands of inter-connected computer networks. In other words, the Internet is a network of networks. Though it started out as a means of communication, today the Internet provides several services such as information retrieval, as a forum for discussion and as medium for which to conduct commerce. The Internet is no stranger to many of us, having experienced the World Wide Web at one time or another. So many of us depend on the Internet now as a means of communication and as a source of quick reference. Some of us access the Internet from the office while others do so from home. We normally do not bother to take notice of how we access the Internet but as long as it serves our needs.

The means of access can broadly be divided into two main categories namely dial-up and always-on connections[2]. Examples of dial-up connections are the PSTN (public-switched telephone networks) and ISDN (integrated services digital networks), which in Malaysia, charge according to the time used. Always-on connections on the other hand, charge according to flat rates (per month or year) regardless of the amount of time the connection is used[3]. The cost of maintaining a leased line in Malaysia depends on the bandwidth of the line and up until now is quite prohibitive, typically ranging from RM 38,000 per year for a 64 kbps line to RM 200,000 per year for a 2 Mbps line (inclusive of access fee and line rental). Because of the high costs involved, always-on connections are usually used by large organisations or businesses. Examples of always-on connections are leased line connections, DSL (digital subscriber line) and cable modems. Since DSL is still in its infancy in Malaysia in 2001, it is not widely available and thus most always-on connections are leased lines.

The Internet is really a very large network. As with any type of network, it must conform to a set of rules called a protocol. A protocol defines how the software running on one computer will communicate with another software running on another computer[4]. The Internet is based on a suite of network protocols commonly referred to as Transmission Control Protocol/ Internet Protocol or TCP/IP. Computers on the Internet are identified by something called an IP or Internet Protocol address. This consists of a number which is unique e.g. 161.142.2.17. There are basically two types of IP addresses: public and private. Public IP addresses are strictly governed as no two computers on the Internet may use the same IP address. Users accessing the Internet using dial-up accounts via an Internet Service Provider (ISP) are usually assigned a temporary public IP address, which is taken back by the ISP after the dial-up session is over[5]. Thus their IP addresses will differ each time they log onto the Internet. Permanent public IP addresses, on the other hand, have to be applied for by a person or organisation and are applicable for always-on connections such as leased line or DSL. These have to be strictly governed to prevent chaos and to make sure that whatever Internet traffic arrives safely at its destination. The organisation controlling these addresses on the worldwide level is INTERNIC while in Malaysia, MYNIC has been entrusted with this function[2].

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Private IP addresses are used for internal networks of an organisation[6]. An organisation can decide to have its own internal IP address without applying for permission. As long as it can organise its IP addresses properly and makes sure that no two computers have the same IP address, this will work fine within its internal local area network (LAN). It thus does not have to depend on a finite number of IP addresses that has to be applied for. It also improves security, as none of its computers are visible to others on the Internet. However, this means that the IP address of such a computer is no longer unique once it gets connected to the Internet as it is possible that some other computer in the world has the same IP address. It does not mean however, a computer on a private network cannot get connected to the Internet. It can use a dial-up connection to get connected (whereby it temporarily borrows a real public IP address from an ISP) or it can share a public IP address with another device to get connected. The former approach is familiar to us as it is what many of us use to get onto the Internet (via phone connections). The latter is what is used in many organisations with a leased line connection but does not have many public IP addresses.

As any Internet-savvy person can tell you, if your computer is connected to 100 million computers on the Internet, then 100 million computers are connected to your computer. That means anyone with the right tools could theoretically try to break into your computer. While this is less likely with dial-up connections (owing to the short time the computer is connected to the Internet), it is a real and distinct possibility for computers with permanent Internet connections. There are a few ways to minimise these and thwart these efforts. One way is to install and manage a good firewall[7]. A firewall is basically a hardware device or software, which sits between the user's computer and the rest of the world. The firewall acts as a guard and watches over Internet traffic coming into and going out to the Internet. It thus filters that traffic and ensures that only certain types of traffic are allowed past based on certain predetermined conditions. The firewall also can act as a proxy for computers using private IP addresses and thus shares its public IP address with those computers, thus enabling those computers to access the Internet. Firewalls (as with many other things) are only as good as how it is configured. As a matter of fact, a supposedly good firewall, which is badly configured, is worse than having no firewall as it just provides a false sense of security.

The UMMC network

The University of Malaya Medical Centre (UMMC) is a new entity made up of the amalgamation of the Faculty of Medicine and the University Hospital. Gazetted on 25th May 2000, the UMMC is a fully government-owned corporatised entity. In addition, the University of Malaya Specialist Centre also provides services to private patients within the UMMC complex.

The UMMC has a unique computer network. It is divided into two parts that are physically connected to each other but use different configurations. The hospital side (UHNet) uses private IP addresses while the faculty side (FOMNet) uses public IP. There are seven Virtual Local Networks (VLANs) used for operations in UHNet while one VLAN is used for academic staff who have offices in the hospital complex. Private IP makes it easier to manage and control the network as well as access to the Internet. Public IP on the other hand makes it easier to gain access to the Internet but at the same time limits the size of the network as well as the control over Internet access. Mixing the two makes a network more difficult to manage so it is usually easier to keep private and public IP networks separate.

Because of the nature of the configurations of the two networks, access to the Internet is achieved differently for both networks. Users in the seven VLANS of the hospital use a 64 kbps leased line to get to the Internet. Every year, the UMMC pays rental of RM 20,000 to the telecommunications provider and RM 18,000 to the ISP for Internet access. Thus the annual payment for this Internet access totals RM 38,000. On the other hand, academic staff use the University of Malaya (UM) leased line (via the faculty) which has a much higher bandwidth of 34 Mbps (upgraded from 2 Mbps to 34 Mbps in October 2000). Rental of the UM leased line is borne by the university and the faculty does not need to contribute anything to this regardless of the number of users utilising the line. This rather strange state of affairs may have started because of the different times the networks were developed in the hospital and the faculty. Because of this, there are obvious differences in the speed of Internet access by the two groups of staff. To enable staff in the hospital to gain access to the mail server (in order to check mail), a limited trust relationship exists between the two networks.

For UHNet, a firewall sits between the network and the Internet. This firewall acts to translate the private IP addresses of the hospital to a public IP address when a user surfs the Internet. The firewall of course on the other hand acts to prevent access from Internet to the UHNet network. Academic staff on the other hand access the Internet directly as their computers utilise a public IP address.

E-mail addresses for the hospital and academic staff also differ even though the e-mail server used is the same. Hospital staff use addresses ending with "uhkl.edu.my" while faculty staff use addresses ending with "medicine.med.um.edu.my". This unique situation can happen because of the use of a domain name server (DNS) in the hospital that would redirect incoming

external mail to the mail server located in faculty. Figure 2 shows how this is achieved.

Reasons for migration

Many problems were faced before the migration of this leased line was carried out. Among these were:

1. E-mail access

The mail server is located within the faculty premises while there are two possible routes for incoming mail. This complicates maintenance and problems with the hospital route may even go unnoticed for some time until someone complains. Simplifying the route makes the maintenance and troubleshooting less difficult.

2. Speed of Internet access

The old leased line used by the hospital utilised a bandwidth of only 64 kbps which makes it rather difficult to add more users. The UM leased line, on the other hand has a bandwidth of 34 Mbps which is some 500 times the bandwidth of the hospital leased line and runs on fibre-optic cables as compared to the copper line used by the hospital (fibre-optics are less susceptible to lightning strikes and are generally viewed as being more stable than copper). It was deemed rather incongruous that hospital staff could not enjoy the same sort of Internet experience as academic staff even though both work in the same complex.

3. Security

The different ways of accessing the Internet also exposed the network to a potential security loophole. A hacker could theoretically seize control one of the academic staff computers (which utilises a public IP address) and use it to launch attacks on servers within the hospital complex. This is because academic staff computers are not protected by any firewall and are accessible to anyone on the Internet with the right tools and determination. Figure 3 illustrates the loophole in the network.

Methodology

The migration of the Internet access was achieved in three phases.

Phase I

The aim was to ensure that all e-mail meant for the uhkl.edu.my address need not go through the hospital leased line. Two things were done in this phase.

a) We applied to MYNIC (organisation responsible for registering all Internet domain names in Malaysia) for a change in the Internet traffic bound for "uhkl.edu.my"

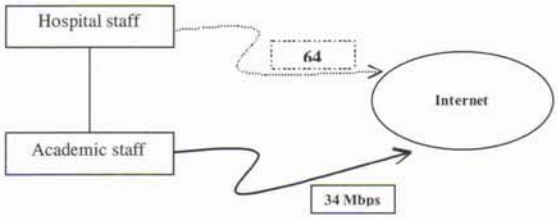

Figure 1. Different Internet access speeds for hospital and academic staff

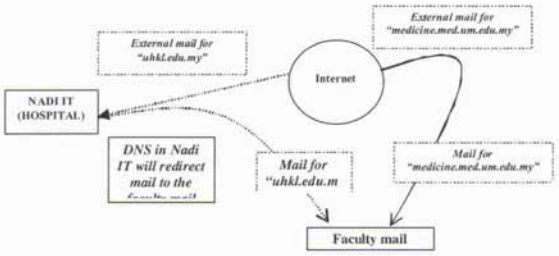

Figure 2. How the mail service functions for the two different domains

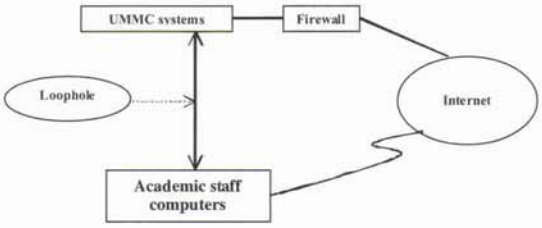

Figure 3. Loophole in the UMMC network before migration

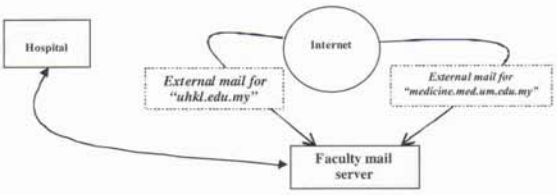

Figure 4. E-mail system after Phase I

to be directed to the faculty's DNS (domain name server). During that time we shut down the external DNS in Nadi IT to allow MYNIC to refresh its database and avoid confusion. This resulted in users in the uhkl domain not being able to receive mail from external sources for several days but could not be avoided as it had to happen sooner or later.

b) We moved Nadi IT's external DNS to the faculty and reconfigured it as well as the faculty's DNS.

c) We made changes to the DNS record in the University of Malaya's DNS.

Work on this started on 31 January 2001 and it was completed on 15 February 2001.

Phase 2.

The aim was to ensure that all traffic to the Internet from the UMMC went through the University of Malaya (UM) leased line. It would also close the loophole illustrated in Figure 3. This was accomplished in three steps:

a) We applied for and obtained permission from the Centre of Information Technology in UM to use the university's leased line.

b) We upgraded our firewall software and changed the direction of Internet-bound traffic from the original leased line to the UM leased line.

c) We revamped our network gateways and reconfigured our network switches to reroute the traffic and close the loophole in Figure 3. This took a lot of doing and many unexpected problems occurred along the way, which necessitated the reconfiguration of the VLANS in the network.

As a result of this work, the network configuration was changed and this can be seen in Figure 5.

Phase 3

The aim was to ensure that all UMMC staff had the same domain name i.e. ummc.edu.my

The steps involved were:

a) We registered a new domain name for the UMMC i.e. ummc.edu.my.

b) We changed the UM DNS records to reflect the change.

c) We applied to the UMMC management to change all e-mail addresses to the new domain name.

d) We changed all e-mail addresses from uhkl.edu.my and medicine.med.um.edu.my to ummc.edu.my.

The change was authorised by the UMMC management on 23 March 2001 and work to change the e-mail addresses were completed on 31 March 2001.

Benefits of the migration

Many benefits can be realised from the migration of Internet access from the UMMC leased line to the UM leased line. Among them are:

Cost reduction

The previous rental cost of RM 38,000 is no longer necessary as the UMMC now rides on the UM leased line. This is based on the premise of continued use of the 64 kbps line. Had the UMMC decided to upgrade its leased line to 2 Mbps, it would incur a recurring yearly expense of at least RM 166,000. In other words, we saved the hospital at least RM 38,000 per year or potentially RM 166,000 per year by avoiding the need to upgrade the leased line.

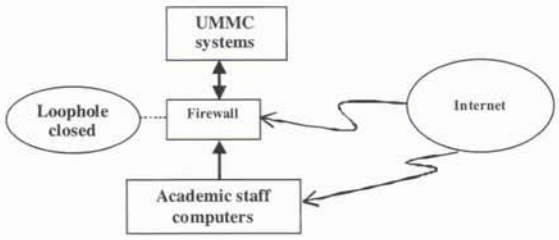

Figure 5. UMMC network after Phase 2

Increased productivity

The migration has resulted in better throughput access. Measurement of throughput before and after the migration was carried out showed tremendous increase in the throughput speed. We measured the throughput before and after migration using a standard Pentium-class PC with 64 MB RAM at similar times. Before the migration, average throughput for file transfer was around 2 KB/sec. This improved to 200 KB/sec for the same file transfer, indicating an improvement of 100 times. Improved throughput results in reduction in time spent on the Internet which is expected to translate into increased productivity as less time would be needed to surf the Web and download files.

Preparation for future increase in Internet usage

It was very difficult to increase the number of Internet users with the old leased line with a bandwidth of 64 kbps. The new arrangement makes it possible to double or triple the number of Internet users without affecting the speed of access.

Preparation for Telemedicine

The UMMC is preparing for Telemedicine in a big way. Telemedicine will certainly require a much bigger bandwidth than was presently available. The old leased line with a bandwidth of 64 kbps would not be able to support Telemedicine. Video-conferencing for example might require at least a bandwidth of 384 kbps to appear acceptable with a refresh rate of 15 fps (frames per second). The new arrangement makes bandwidth of up to 2 Mbps available to a single computer thus enabling real-time video at 30 fps possible.

Better network security

With the closure of the loophole in the network, it is expected that network security will be enhanced and this will make it more difficult for hackers to penetrate

the network (see Figure 5). This has been worrying system administrators in the UMMC for some time and the migration provided the opportunity to close this loophole.

Reduction in complaints

With the use of a bigger pipeline to the Internet, it is expected to result in fewer complaints regarding the Internet service. Most complaints from users regarding the Internet service are related to speed of Internet access. Thus we hope to reduce these complaints to a minimum. More stable access is expected with the use of the fibre-optic leased line used by UM as fibre-optic lines are less susceptible to lightning strikes compared to copper cabling.

Conclusion

Information technology (IT) is here to stay. It is touted to bring countless benefits to all of us and will radically change the way we work. Physical borders will be reduced with the use of IT and Internet technology. Unfortunately, many people associate the use of IT to increased cost, which in reality is only partly true. While it is true it costs money to implement IT solutions, there are ways to save money and innovation is the key. There may be trade-offs in some areas but generally, when the benefits outweigh the trade-offs, one can accept these.

Our efforts in migrating the leased line access was motivated by the need to improve service while saving money. In Malaysia, affordable broadband access is still some way off so we have to make maximum use of our resources. Where possible, Nadi IT believes in saving money, which can then be used to serve other needs. This exercise was an eye-opener for many of its staff and it augurs well for the future of the UMMC efforts that its staff was very enthusiastic about the project. We believe that Nadi IT's efforts in improving Internet access in the UMMC can be emulated by other organisations wishing to improve Internet access at minimum cost. Because of the cost-saving nature as well as its benefits in improving services to the UMMC, this project was nominated for the Civil Service Award for Innovation for the year 2001.

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OCULAR PRESENTATIONS AND TOXOPLASMA SEROLOGY

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ABSTRACT: During the period 1996-1998, 134 patients suspected of having ocular toxoplasmosis were seen in the Ophthalmology Clinic of the University Hospital, Kuala Lumpur. Clinical presentations in these patients ranged from poor vision to severe retinal detachment. Of these patients, 72% were confirmed positive for *Toxoplasma gondii* infection by serological methods. Chorioretinitis and vitritis were found to be the most apparent symptoms, both having 100% correlation with serological positivity. This was followed by uveitis, floaters, and retinal detachment with correlation at 78%, 75% and 75%, respectively. However, there was no correlation between level of serotitre and ocular presentations. *(JUMMEC 2000; 2:98-102)*

KEYWORDS: Toxoplasmosis, serology, chorioretinitis, uveitis

Introduction

Toxoplasmosis, the most common parasitic infection is also the most frequent cause of focal retinochoroiditis. Current therapy includes the synergistic combination of pyrimethamine, a dihydrofolate reductase inhibitor and sulphadiazine which is a competitive inhibitor of dihydrofolate. Other drugs that can be used include clindamycin, azithromycin, clarithromycin, dapsone and doxycycline.

Diagnosis of ocular involvement of the disease relies on characteristic ophthalmoscopic appearances while the laboratory method is by serological assessment. Although Toxoplasma serology plays an important role in the assessment for prophylatic treatment against encephalitis in HIV-seropositive patients, the diagnostic value in ocular toxoplasmosis however remains controversial (Grant *et al.*, 1990; Aarons *et al.*, 1996;). Some authors believe that a positive titre indicates nothing more than previous exposure to *Toxoplasma gondii* and rely more on clinical judgement. Other methods (antibody calculation, PCR, determination of specific IgA and antibody avidity) do not appear to provide conclusive results (Garweg *et al.*, 1998). Although other workers (Norose et al., 1996) demonstrated the usefulness of quantitative PCR, it was found to have restricted applicability when applied for routine diagnosis (Garweg *et al.*, 1996).

The typical ocular lesion associated with toxoplasmosis is that of necrotizing retinitis or satellite retinitis or inflammation at the edge of an existing scar. However, it can also present in other forms such as anterior uveitis, pars-planitis, periarteritis, retinal vessel occlusion, scleritis and papillitis which can be confused with other diseases such as cytomegalovirus (Rose, 1991; Elkins *et al.*, 1994; Schnyder, 1995).

With more visual impairments believed to be related to toxoplasma infection, clinical examination should always be supported by laboratory tests for establishing diagnosis. It would be impractical however to send every sample from all visual impairment cases for laboratory diagnosis. Therefore, in deciding whether or not sample should be sent for laboratory test, it would be convenient for the clinicians if some guidelines existed. This study was carried out in the attempt to look for the possibility of establishing a correlation between ocular presentations and toxoplasma serology in hope that such correlation can be used to guide physicians to the need of a laboratory test to confirm the diagnosis of ocular toxoplasmosis.

Materials and Methods

Patients

One hundred and thirty four patients with ocular toxoplasmosis were examined over a 3-year period by the

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ophthalmologists at Ophthalmology Clinic of the University Hospital, Kuala Lumpur, and their findings recorded. Five ml of blood sample was taken from each patient and sent for serological testing.

Antigen preparation for in-house direct ELISA

Frozen *T. gondii* tachyzoites harvested from infected BALB/c mice were thawed and washed in PBS. The parasites were then homogenised (on ice) for half an hour and left undisturbed for another half an hour. The homogenate was then transferred into a fresh 3 ml tube and sonicated for 4 pulses (30 secs/pulse). The material was then centrifuged at 10,000 rpm for 15 mins in a Spinwin microcentrifuge. The supernatant was collected and stored at -20° C until use.

Serological tests

a) 'In-house' direct ELISA

Flat bottom microtitre plates (Nunc, USA) were coated with 50 ml/well at 10 mg/ml of prepared antigen (optimal concentration of antigen used was pre-determined using chequerboard titration). The plates were left overnight at 4° C and washed 3 times with PBS-0.05% Tween 20 (PBS-T) to remove excess antigen. The plates were then tap-dried and 100 ml of 1% BSA-PBS (blocking solution) was added to the wells and left at room temperature for 2 hours. The plates were then washed as described earlier, before 50 ml of test serum (diluted in PBS) was added into each well. After 1 hour of incubation at room temperature, the contents were discarded and the plates washed as before. Alkaline phosphatase conjugated IgG or IgM immunoglobulin (Sigma, USA) was added and the plates were incubated at room temperature for 1 hour. The wash procedure was repeated. After the final wash substrate solution was added (100 ml per well) and the plates were incubated in the dark for 30 minutes at room temperature. The enzymatic reaction was stopped by the addition of 50 ml of 3 M sodium hydroxide to each well. The absorbance was measured at 405 nm using an ELISA reader (Microplate Autoreader EL311SX).

b) Toxo-ISAGA

Human IgM antibodies in serum were detected using Toxo-ISAGA commercial kit (BioMerieux Vitek, Inc). Strips pre-sensitised with anti-human IgM monoclonal antibody were reacted with serum samples (diluted in PBS) at 1:100. The strips were covered with adhesive sheet and incubated at 37° C for 2 hours. The strips were then emptied by inverting the plate and washed once in PBS-T. The strips were immediately emptied and washed twice in PBS-T, followed by a 5-minute wash in PBS. After each wash, the strips were thoroughly cleaned on filter paper without allowing to dry. Antigen diluted at 1:20 in BABS buffer was added to the first well (100 ml) and second well (150 ml). The strips were covered as before and incubated at 37°C overnight in a moist chamber. The result was read by placing the strip at approximately 50 cm above a suitably lit white background.

c) Toxo IgG and IgM ELISA

The kits for these tests were obtained from Veda Lab, France. Microwell plates pre-coated with Toxoplasma antigen were used to detect the presence of human IgG and IgM antibodies in serum. Diluted patient sera were added to the wells and incubated. After washing, horseradish peroxidase-labelled antibodies to human IgG/IgM were added. Substrate tetramethylbenzene (TMB) was then added to the well and incubated. The intensity of the colour was measured at 450 nm (A_{450}) using the ELISA reader (Microplate Autoreader EL311SX). The A_{450} value was proportional to the amount of antibodies present in the sample.

Results

In the three-year (1996-1998) period of study, 134 patients suspected of having ocular toxoplasmosis were examined. Malays were the highest number seen, closely followed by the Chinese. Out of 134 patients, 60% of them were male (Figure 1). Examination performed on the patients showed that there were 57 descriptions of ocular presentations, with blur vision/poor vision being the most frequently encountered. The first ten major ocular presentations are shown in Figure 2. Almost half of these patients presented with more than one ocular presentation; combination from these 57 types (Figure 3). One of the patients showed up to five ocular presentations.

Attempt to look for correlation between the ocular presentation and toxoplasma seropositivity was done in the hope that with such correlation, certain ocular presentation shown by the patient, can be used as an 'indicator' that ocular toxoplasmosis need to be included as one of the differential diagnosis. Based on ocular presentations and toxoplasma seropositivity (detection of immunoglobulin subclass IgG in patients' sera), we found that, out of the ten major presentations listed, five of these presentations showed high degree of correlation with toxoplasma seropositivity. Chorioretinitis and vitritis were found to have 100% correlation, followed by uveitis at 78%, while floaters and retinal detachment were at 75% (Table 1).

Discussion

In practice, the diagnosis of ocular toxoplasmosis is most often based on clinical findings. As the clinical signs can be diverse, the criteria for clinical diagnosis may vary

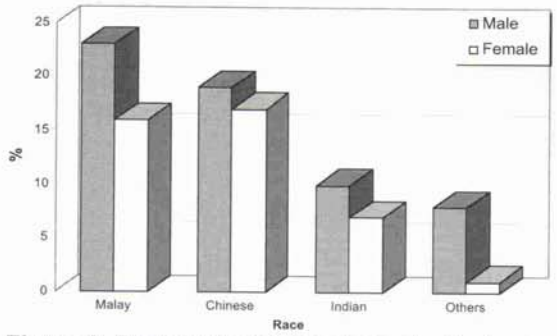

Figure 1. Breakdown of race and sex of patients seen at the Ophthalmology Clinic, University of Malaya Medical Centre, Kuala Lumpur

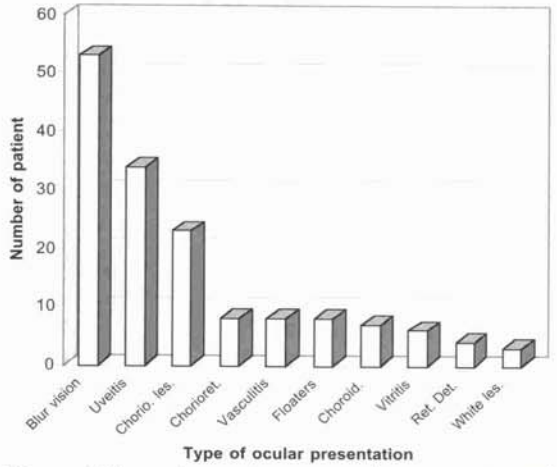

Figure 2. Ten major ocular presentations encountered among patients at the Ophthalmology Clinic, University of Malaya Medical Centre, Kuala Lumpur

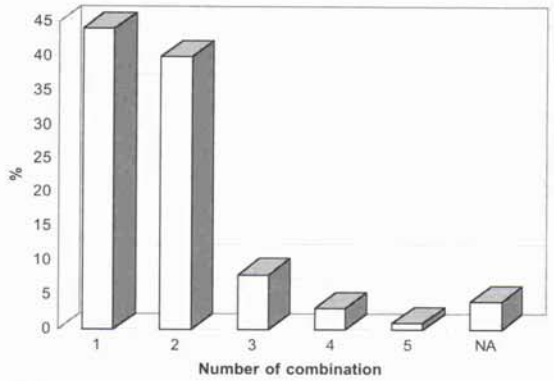

Figure 3. Ocular presentation combinations in patients

from one ophthalmologist to another. The presence of specific antibodies in the serum can therefore be used as supportive evidence of ocular toxoplasmosis in a patient. In this study, we present our findings on the various presentations seen in 134 patients suspected of having ocular toxoplasmosis, and we also tried to establish possible relationship between these presentations and the results of toxoplasma serology.

Fifty-seven different types of presentations (in different combinations) were noted in our study with the more commonly encountered conditions being blurred or poor vision, uveitis and chorioretinal scar/lesion. The number of patients with conditions involving one of these three presentations (single or in combination with other presentations) made up more than half the total number of patients in our study (Table 1). We observed that in certain instances, high frequency of occurrence did not correlate with toxoplasma seropositivity. This is

Table 1. Relationship between ocular presentation and toxoplasmosis

Ocular presentation	Number of patients				
	+ve/+ve	+ve/-ve[a]	-ve/+ve	-ve/-ve	BL
Blur/poor vision	23	44 (67)	1	25	7
Uveitis	13	65 (78)	0	22	0
Chorioretinal scar	13	35 (48)	4	35	13
Chorioretinitis	25	75 (100)	0	0	0
Choroiditis	17	33 (50)	0	50	0
Floaters	25	50 (75)	0	25	0
Vasculitis	0	14 (14)	43	14	29
Vitritis	29	71(100)	0	0	0
White fluffy lesion	0	33 (33)	0	0	67
Retinal detachment	25	50 (75)	0	25	0

[a]Figures in brackets indicate total percentage of patients with positive IgG serotitres
+ve/+ve: positive for IgG andIgM
+ve/-ve: positive for IgG only
-ve/+ve: positive for IgM only
-ve/-ve: negative for IgG and IgM
BL: borderline positive

Table 2. Relationship between ocular presentations and with IgG titre.

Ocular presentation	Percentage (%) of patients having IgG titres stated below						
	1:64	1:128	1:256	1:512	1:1024	1:2048	1:4096
Blur/poor vision	0	11	6	14	8	3	17
Uveitis	0	13	0	17	13	5	13
Chorioretinal scar	0	25	12	0	7	12	0
Chorioretinitis	0	33	0	0	67	0	0
Choroiditis	25	0	0	0	0	0	0
Floaters	0	0	0	20	0	20	20
Vasculitis	33	0	0	33	0	0	0
Vitritis	50	50	0	0	0	0	0
White fluffy lesion	0	0	0	67	0	33	0
Retinal detachment	0	0	50	0	0	0	0

seen in the case of poor vision and chorioretinal scar, in which only 59% and 56%, respectively, of the patients had positive IgG serotitres. On the other hand, all (100%) patients who presented with chorioretinitis or vitritis were positive for toxoplasma serology. It was also observed that positive serotitres were found in 61% of the patients with uveitis. This is significantly higher than that obtained by Phaik *et al.* (1991), whose survey in Singapore found only 28.7% of patients with uveitis had positive serotitres for toxoplasmosis.

It is generally believed that ocular toxoplasmosis patients have low positive serotitres because the disease is commonly a localised inflammation and is less likely to result in significant rise in serum antibody levels (Scott, 1974; Rothova *et al.*, 1986). Analysis of our data, however, revealed a wide distribution of serotitres, ranging from 1:64 to 1:4096 (Table 2). The high serotitres obtained might possibly be due to proliferation of toxoplasma trophozoites in the retina (Desmont, 1966). Furthermore, there was no clear link between severity of disease and serotitre levels. This finding is thus in agreement with the study of Damms *et al.* (1991).

Although there are doubts to the diagnostic value of serology in ocular toxoplasmosis, there is still a great body of evidence which advocates the use of serology in the diagnosis ocular toxoplasmosis. Damms *et al.* (1991) showed that the incidence of positive titers and antibody levels were significantly higher in patients with ocular toxoplasmosis while Phaik *et al.* (1991) reported that 89.6% of their clinically positive ocular toxoplasmosis cases had raised serotitres, ranging from 1:64 to 1:4096. Payeur *et al.* (1988) found high correlation between clinical indicators and ELISA test results. The sensitivities of such commercial ELISA kits have been evaluated in the past and the results were in close agreement with those of reference laboratories (Joynson 1989).

In conclusion, our study shows that there was relationship between toxoplasma seropositivity and the incidence of clinical ocular toxoplasmosis. There was, however, no correlation between the various presentations with serotitre levels, suggesting that it may not be useful as a guide during treatment. Nonetheless, the titres can help the physician where the diagnosis may be equivocal.

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A CASE OF CHRONIC FATIGUE SYNDROME IN MALAYSIA

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ABSTRACT: **A case of chronic fatigue syndrome (CFS) like illness was identified recently. Diagnosis CFS is commonly used in the western countries but not in Malaysia or other parts of Asia. It is probably because the diagnosis of neurasthenia has gradually disappeared especially in the United States and United Kingdom. Neurasthenia is dropped in the DSM-111 and DSM-1V but is still retained in the 10th International Classification of Disease. This paper is reporting the case and discussing the definition of chronic fatigue syndrome.** *(JUMMEC 2000; 2:103-104)*

KEYWORDS: **fatigue, chronic fatigue syndrome, neurasthenia**

Introduction

Chronic fatigue syndrome (CFS) is an unexplained clinical condition characterized by severe and disabling fatigue that affects both physical and mental functioning. In the medical world the concept of CFS has existed for a long time- only the label has changed. It was quoted that CFS is the 'disease of the fast paced 21st century' (1). In Malaysia, the diagnosis of CFS was not commonly used. This is probably the diagnosis of neurasthenia is still being accepted in this part of the world. Some authors viewed the diagnosis of chronic fatigue syndrome as a new wine in the old bottle (2). However, the definition of chronic fatigue syndrome has been reviewed in the United States (3), Australia (4) and United Kingdom (5). The prevalence estimates for chronic fatigue syndrome vary between 0.07% and 1.8% (6) and this probably reflects differences in case definition and sampling techniques between studies.

Case report

A 43 years old married gentleman, who was a director in a private company, reported feeling of fatigue for the past one a half year. It was a sudden in onset and severe enough to cause him to be unable to function at work place as well as socially. The fatigue was not as a result of ongoing exertion and rest could not relieve it. He also reported poor concentration, his mind was easily gone blank, and he felt sleepy all the time but had disturbed sleep at night. In the morning he felt unrefreshed and suffered from headache. He would feel tired for a long time if he exerted himself like hovering the house or driving outstation. There was recurrent sore throat within the one and a half year episode together with muscle pain.

He attributed his fatigue as due to the multiple stresses he faced within 6 months prior to the onset of the illness. First the mother had stroke and later followed by his younger brother. His mother in law committed suicide that had affected his wife mostly. He also had some misunderstanding with his brother regarding the company. The patient did not report feeling depressed but admitted that feeling of frustration for not being able to function as before. He had no lost of interest or hopelessness but had many plans in his mind to do many things. His appetite was normal. He went for investigations but the results were all normal. He had no family history of mental illness and he described his premorbid personality as a perfectionist and orderliness. His mental status examination was normal except having difficulty in concentration. He was diagnosed as chronic fatigue syndrome and was started for cognitive behaviour therapy.

Discussion

From the history, it was reported in 1750, Sir Richard Maningham published a treatise on febricule, describing its feature as including, "little low, continued fever, little transient chilliness, lassitude and weariness all over the body, little flying pains and sometimes the patient is a little delirious and forgetful. Subsequently in the first

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half of the 19th century, George Beard coined the term 'neurasthenia' to signify the lack of strength of the nerves that he believed to underlie cases of chronic fatigue (7). However, further studies could not find the evidence that peripheral nerves weakness or cerebral exhaustions as the origin of neurasthenia. Hence, the diagnosis of neurasthenia gradually disappeared, especially in the United States and United Kingdom and it was dropped from the DSM-111 (8), the American diagnostic criteria for mental illness. The term is still being used in other part of the world, and is retained in the International Classification of Disease (ICD-9 and ICD-10).

In 1956, an article in Lancet (9) coined the term 'myalgic encephalitis' after a series of epidemic outbreaks of a contagious condition, which presented with neurological signs and symptoms, accompanied by myalgia and signs of emotional distress. Up to now the term is still being accepted in the United Kingdom to signify chronic fatigue. During the 1980's many doctors used the term Post-viral Fatigue Syndrome, as it frequently followed an apparent viral infection (10). However, the realization that viruses were unlikely to underlie all cases of chronic fatigue, the label needed to be changed.

Table 1. The Oxford Definition of Chronic Fatigue Syndrome

1. Principal symptom is a fatigue with definite onset and not life long
2. Fatigue is severe, disabling, and affects physical and mental functioning
3. Fatigue for at least 6 months, during which it is present at least 50% of the time
4. Other symptoms may be included, such as: Myalgia, Mood disturbance, Sleep irregularity
5. Medical and psychiatric exclusions:

   Established medical condition known to produce chronic fatigue

   - Schizophrenia
   - Manic depressive illness
   - Substance abuse
   - Eating disorder
   - Organic brain disease

The center for Disease Control and Prevention (CDC) convened a working group to establish a case definition as chronic fatigue syndrome to highlight what was felt to be the most consistent and significant manifestation of the illness and to avoid the use of aetiologically biased modifiers that were not applicable to all cases (3). A further definition of CFS was proposed by Lloyd and colleagues in Australia and retained the name "chronic fatigue syndrome" (4). In 1991 the British doctors proposed a new set of criteria that became known as the 'Oxford' criteria (Table 1)(5).

Therefore the case reported did fulfill the criteria for chronic fatigue syndrome. This may be evidence that CFS exists in Malaysia. The diagnosis of CFS should be recommended even though it is not in the mental disorder classifications.

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MALIGNANT TRANSFORMATION OF RECURENT JUVENILE LARYNGEAL PAPILOMATOSIS

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Introduction

Recurrent juvenile laryngeal papilloma, although usually confined to the larynx canoccasionally progress into nasopharynx, trachea and even into extensive bronchopulmunary disease. Most cases of recurrent laryngeal papilomatosis withbronchopulmunary involvement are cytologically benign and do not undergomalignant transformation. However, very rarely squamous cell carcinoma can arise in recurrent juvenile laryngeal papiloma in the absence of known risk factors such as radiation and smoking.

Case report

The patient was a 22-year-old lady with a history of symptomatic laryngeal papilomatosis since early childhood. Her first presentation to the Otorhinolaryngologist was at the age of 2 with history of stridor. A diagnosis of juvenile laryngeal papilomatosis was made then. A tracheostomy was perfonned in 1977 (at the age of 4 years) to maintain an open airway in view of her airway obstruction. Her condition necessitated multiple endoscopic removal of laryngeal papilomas and thus was referred to UMMC in 1986 for laser excision of the papilomas. Results of multiple biopsies were consistent with recurrent laryngeal papiloma and failed to demonstrate any evidence of malignancies. The patient was a nonsmoker, did not consume alcoholic beverages and did not receive any radiation. In 1993 (20 years of age), a routine chest x-ray revealed an opacity in the right upper zone. Biopsy of the lesion was concluded as benign and thus she was referred to the cardio thoracic unit where she underwent right upper lobectomy. During the operation, seedlings of the papilomas were noted in lower right lobe.

In view of the extensive and recurrent nature of the lesion with tracheobronchial involvement, the decision to start interferon was made. She was given an induction dose 3 miu daily (I.M.) for 28 days. This was followed by a maintenance dose of 3 miu (I.M) three times per week. Her progress was carefully monitored and serial CT scans were done to evaluate her progress. Despite the interferon therapy, the papilomas were noted to rapidly increase in size. The decision to use 5 cycles of 5-Fluro Uracil was then made. However in mid 1995 (22 years of age), she was noted to have changes in her routine CT scan compatible with malignant change and enlargement of right pre hilar lymph nodes was noted (Figure 1). Biopsy of the lung lesion was reported as Squamous cell Carcinoma. Patient was again referred to the Cardio thoracic unit and right pnuemonectomy was done. Intraoperatively, tissues were removed from chest wall and these were also noted to be invaded by carcinoma. The decision was made for chemotherapy followed by radiotherapy. She underwent one cycle of Mitramycin, Ifosomide and Cisplatin, however she expired after the first month of chemotherapy.

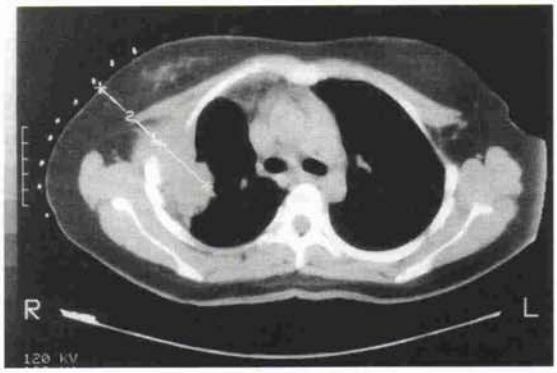

Figure 1. CT scan of lung showing carcinoma and rib erosion

Discussion

Juvenile laryngeal papilomatosis are the most commonest benign neoplasms of the respiratory tract of children. The exact etiology still remains unknown although viral cause is widely believed. These lesions are multiple, recurrent and often involve bronchi and bronchioles, even extending into alveolar region. These lesions rarely undergo malignant transformation unless previously radiated. Adult laryngeal papilomas on the other hand are less frequently seen and are usually solitary. They also have a much higher incidence of

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malignant transformation.

Juvenile laryngeal papilomatosis often starts in the upper airway and progresses to involve distally. Several hypotheses have been suggested for this behavior, including posttraumatic transplantation following intubation, multiple biopsies, tracheostomy and also viral dissemination. Such recurrence and spread is not seen in the adult variety. It has been suggested that multiple lesions, deeply attached lesions, severe basal cell hyperplasia, high nuclear cytoplasm ratio and large nuclei are more prone to recurrence (I). Distal spread to bronchiole tree and alveoli is also associated with higher risk of neoplasm than papilomas confined to the laryngeal region. This is also associated with higher morbidity with higher incidence of pneumonia, brochiectasis and abscesses.

There have been several reports of malignant transformation in juvenile laryngeal papiloma in the western world. Toso reported a patient who was a heavy smoker with a late age of onsef (2); Shapiro *et al* described a patient who was a heavy smoker and an alcoholic (3). In situ and invasive malignant neoplasm was noted in the laryngeal papilomas. Brach *et al* and Russel and Kessler reported young patients who were non-smokers with lung involvement and malignant transformation was noted in the lung lesions. 2 cases were reported in the German literature; Kaiser and Justus each described malignant change in long-standing, recurrent juvenile papilomas without radiotherapy (4). Chandra Bewtra described a similar case in 1982. The first 2 reports suggested that heavy smoking and alcohol consumption might have contributed to the malignant change. The other reports have many similarities to our patient. In all of these cases, including ours, extensive papilomatosis involving pulmonary airways with malignant transformation involving pulmonary regions, for which, no demonstrable cause is found.

Use of radiotherapy is contraindicated in the treatment of recurrent juvenile laryngeal papilomatosis, as is it associated with an increased incidence in malignant change (1). The incidence of stricture, cartilage necrosis and abnormal maturation of larynx has also been noted. Laser has been effectively used in many centers as the main modality of treatment of surgical excision of papilomas and till date, there has been no evidence to link it to any malignant transformation. 5 Floro Uracil was used in this patient due to the rapid involvement of the pulmonary tree and has not been shown to cause any malignant change either. Rady in 1998 showed that malignant transformation of recurrent laryngeal papilomatosis is associated with integrated human papillomavirus type 11 DNA and mutation of P53(5). In conclusion, incidence of malignant change is higher in long standing, severe, diffuse papilomatosis of the tracheo bronchial tree and this may arise as a result of radiotherapy, smoking and alcohol consumption and very rarely spontaneously.

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DEVELOPMENT AND APPLICATION OF GASTROINTESTINAL ENDOSCOPY

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The early beginings

Man's innate curiosity to study the internal organs of the human body dates back to the time of Hippocrates where basic speculums were invented to peer into the buccal cavity and vagina. The first instruments used to intubate the esophagus and stomach in the 16th and 17th centuries, were designed for the purpose of extracting foreign bodies stuck in the esophagus (or pushing them down into the stomach).

The first scopes invented used candle light for illumination (Bozzini, 1806) and subsequently gasogen which is a mixture of alcohol and turpentine (Desormeux, 1853). These scopes were however, mainly designed as urethro-cysto scopes. Desormeux was the first to call such instruments, "endoscopes".

Development of rigid scopes

Adolf Kussmaul in 1868 is credited with inventing the first gastroscope. Taking the cue from sword swallowers who were popular entertainers at that time, Kussmaul attempted to insert a long rigid hollow tube into a professional sword swallower at a meeting of the Society of Naturalists in Freiburg, Germany. Illumination was provided by a gasogen lamp but was poor and as a result the examination was unsatisfactory. Water cooled electrically heated wire platinum loops were then used by Nietze for providing light but these were found to be cumbersome and impractical. The "enlightenment" of endoscopy followed Edison's invention of the incandescent lamp in 1879. A miniaturized or "mignon" light bulb was used with oesophagoscopes by Leiter and Mickulicz (1887). Despite much effort at developing a gastroscope by many workers, the first really usable rigid gastroscope was produced by Elsner in 1911. Rudolf Schindler, who more than anyone else popularized upper gastrointestinal endoscopy at that time, called the Elsner instrument "the mother of all instruments". He himself modified this rigid scope in 1922 by adding an air-channel into the scope to clean the lens. Through numerous examinations and assiduous recording by color drawings he published his classic book, "Lehrbuch und Atlas der Gastroskopie" in 1923.

Schindler and the semiflexible gastroscope

But the rigid scope had serious drawbacks. Instrumental perforations were not uncommon and as a result, the initial enthusiasm for the procedure waned. Schindler set about to invent a semiflexible gastroscope with the collaboration of a Berlin instrument maker, Georg Wolf. Working on the optical principle proposed by Hoffmann in 1911 that lenses attached to a flexible wire at short focal intervals from one another would bend light, Wolf and Schindler produced such a scope in 1932. It had a flexible distal 30cm tip which was made of a bronze wire spiral and which incorporated a number of short convex lenses. This instrument was a major advance at that time, as not only was it much safer, it also provided significantly more information about the stomach. Despite the temporary setback of World War II and the incarceration of Schindler himself in a Nazi concentration camp, the semiflexible scope gained many ardent followers. This was in no small measure due to Schindler who was an enthusiastic and indefatigable teacher. Following his release from prison in 1934, Schindler and his family emigrated to the United States, where he was given an academic position at the University of Chicago. He continued his good work and Chicago soon became a "Mecca" for gastroenterologists and endoscopists. In 1941 Schindler, started, at a meeting in his own house, the American Gastroscopic Club, the forerunner of the American Society of Gastrointestinal Endoscopy (ASGE). The ASGE chose to recognize his tremendous contributions in 1962, as a Schindler Award Recipient, the society's highest tribute for contributions to the endoscopic field.

Dawn of a new era - Fiberoptic endoscopy

The Schindler-Wolf semiflexible gastroscope was the standard bearer for gastroscopes until 1957 when a further dramatic innovation, that of fiber optics was introduced into endoscopes. The inspiration for the making of a fiber scope was a 1954 paper appearing in Nature entitled "A flexible fiberscope using static scanning" co-authored by HH Hopkins and NS Kapany. In this paper Hopkins and Kapany showed that light could be transmitted through a single glass fiber based on the principle of total internal reflection. Basil Hirschowitz who was then a GI fellow at Ann Arbor, University of Michigan was fascinated about the possibility of using

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fiberoptics in endoscopes and with the encouragement of his former mentor, Sir Francis Avery Jones paid a visit to Hopkins and Kapany at the Imperial College, London. On his return, Hirschowitz enlisted the help of Wilbur Peters, a physicist and Larry Curtis, a sophomore student at the University of Michigan. Working feverishly with his co-workers, Hirschowitz was able to develop the first fiber optic gastroscope, which he presented to the American Gastroscopic Society in Colorado Springs in May 1957. Before the year was out, the American Cystoscopic Makers Inc (ACMI) contracted to manufacture fiberscopes under license and in October 1960 the ACMI 4990 Hirschowitz gastroduodenal fiberscope was available for sale and use. Hirschowitz reported his initial experience with the fiberoptic scope in the Lancet in 1961. By the late 1960s, fiber optics had almost completely displaced lens-optic gastroscopes. The Olympus Optical Company's (Tokyo, Japan) first fiber gastroscope was introduced in 1968. ACMI produced the panendoscope in 1970. Japanese and American manufacturers rapidly and competitively improved fiber-optic instruments. In the words of Hirschowitz, "There seemed to be no end to the ingenuity of endoscopists and instrument makers and the application of fiber-optic instruments to diagnosis and therapy".

While developments were taking place in the United States, Dr Tatsuno Uji and engineers from the Olympus Optical Company, Japan, had developed a gastrocamera in 1952. In essence it consisted of a miniaturized intragastric camera which could take high quality pictures. It was presented to Western endoscopists at the World Congress in Washington DC in 1958. Olympus Optical Company subsequently developed a model incorporating fiberscope and a gastrocamera in 1963 but the gastrocamera had been quickly rendered obsolete by fibreoptic scopes.

Fiberoptics was soon introduced for examination of organs other than in the upper gastrointestinal tract. Bergein Overholt presented his experience with the first fiberoptic sigmoidoscopy in 1967 at the ASGE meeting and subsequently in 1969 fiber optic colonoscopy and shortly thereafter, endoscopic polypectomy was performed by Wolff and Shinya in New York. Colonoscopy opened up a whole unexplored field of endoscopy and was particularly significant in the face of widespread skepticism at that time. Comments included: "it requires a tricky skill that few will be able to acquire", "it will tell you nothing a good radiologist couldn't show" etc.. Time has however, proven otherwise.

Further innovations

One of the most exciting and elegant innovations of fiber optic endoscopy was the canulation of the ampulla of Vater. WC Watson of Glasgow in 1966 reported in the Lancet, his observations of the ampulla of Vater with a flexible duodenoscope and concluded that " endoscopic examination of the ampulla of Vater could be helpful in the diagnosis of biliary and pancreatic disorders". McCune and colleagues from George Washington University reported in 1968 the first successful canulation of the pancreatic duct using an Eder duodenoscope with a makeshift housing for a canula. But the Japanese were responsible for developing endoscopic retrograde cholangiopancreatography (ERCP) as a standard diagnostic procedure. Itaru Oi and Kunio Takagi and colleagues together with engineers from the Machida Manufacturing Company and Olympus Optical Company developed specially designed "ERCP" scopes: the FDS and JF and JFB-2 models respectively. In 1973, Keichi Kawai from Japan and Meinhard Classen and Ludwig Demling from Germany simultaneously reported endoscopic electrosurgical sphincterotomy of the papilla for the non-operative extraction of common bile duct stones. In 1980, Nib Soehendra from Hamburg, Germany introduced stenting of the biliary system with plastic tubes. The range of innovations that have come out in this field from pioneer ERCP-dedicated endoscopists such as Peter Cotton and Kees Huibregtse have been truly amazing.

Endoscopic ultrasonography, a more recently developed specialty in the 1980s combines the diagnostic capability of an ultrasound probe and that of a fiber optic scope. Lutz and Rosch from Germany was the first to report on a transgastroscopic ultrasonography and subsequently Strohm and colleagues and Eugene DiMagno from Mayo Clinic, improved on the applicability of these instruments. The first mechanical sector scanning instruments for endoscopic ultrasound displayed 180 ^{0} images. The subsequent introduction of a full 360 ^{0} image endoscope, the Olympus GF-UM3, provided the first commercially available echoendoscope.

Videoendoscopy provided perhaps the latest innovation in GI endoscopy. It is certainly not a new technique of performing endoscopy but a new way of viewing, acquiring and storing images in the digital form. The mechanical control and internal lumen subsystems remained essentially unchanged. The first videoendoscope system was developed by Welch Allyn Incorporated (Skaneatales, USA) and exhibited at the ASGE meeting in 1983. It drew little interest the as the prevailing attitude was " why replace something that is perfectly good with one that provided an image of lesser definition and at greater cost?". Again time has been the best judge. With further development and refinement of the system predominantly by the Japanese companies, Olympus Optical Company,

Pentax and Fujinon, videoendoscopy has achieved not only "maximum" quality imaging, the ease of storage and transfer of images makes it the standard system in all forms of endoscopy today.

What of the future?

Videoendoscope instruments with even better imaging reaching a million pixels have been produced. Magnifying endoscopes and chromoendoscopy have enhanced the details of the GI mucosa and fluorescence and infra red spectroscopy have been able to demonstrate submucosal details. Endosonography and more recently optical coherence tomography (OCT) have enabled endoscopists to examine beyond the lumen of the GIT and OCT has allowed us to start thinking of an "optical biopsy" diagnosis. Miniaturization of electronic components may allow construction of new types of endoscopes that no longer require external wires, cables, or optical fibers. A "video pill" would allow the operator to perform a "drive through" endoscopy.

The development and the subsequent widespread use and application of GI endoscopy ranks as one of the landmarks in annals of medicine and gastroenterology. GI endoscopy is indispensable to the field of gastroenterology and gastrointestinal surgery. The "endoscope" has evolved from a candlelit instrument in the early 19th century to its current state of sophistication. Procedures are now performed in well-planned dedicated endoscopy units with dedicated staffing. Training, credentialling, audit, re-training and maintenance of standards of practice are important issues. The field of GI endoscopy has developed into a distinct and separate field on its own, with journals, workshops and international meetings and a global fraternity of its own. With continuing advances and technical sophistication, GI endoscopy will remain an exciting field stimulating further research and spearheading advances in the diagnosis and treatment of gastrointestinal diseases.

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