The Singapore Family Physician

The College of General Practitioners Singapore
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Growing problems

For parents, this often means 'Does my child get plenty to eat?' when what really matters is not the quantity but the nutritive value—vitamins especially. To ensure that he has an optimal supply of vitamins to compensate seasonal fluctuations and the many other demands made on the organism during the growing years

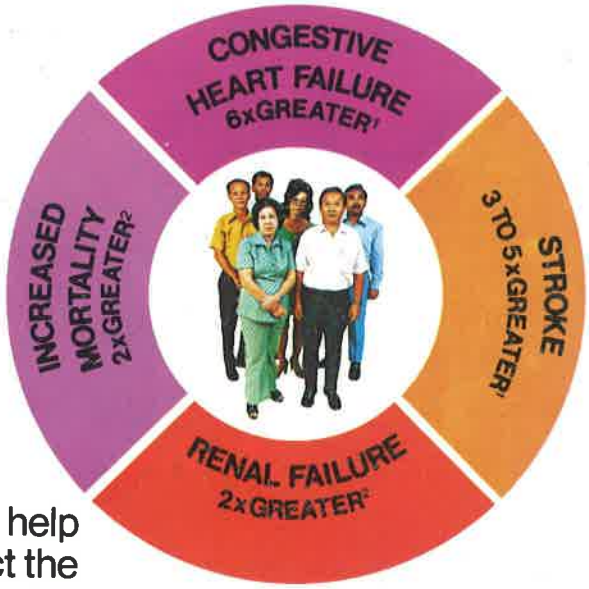
Elevit = Trade Mark

Elevit

Capsules and drops

Even with modest elevations of blood pressure...

the risks are greater



help protect the hypertensive with

Tablets Aldomet Trademark

(methyldopa, MSD)

reduces blood pressure effectively; helps protect vital organ function

- Reduces elevated blood pressure in all body positions
- Acts rapidly and smoothly, usually without hazardous, sudden drops in blood pressure
- Effective in all degrees of hypertension
- Usually does not directly affect heart or kidney function

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1. The Framingham Study, cited by Committee on Hypertension: Drug treatment of ambulatory patients with hypertension, J. Amer. Med. Ass. 225:1647-1653, Sept. 24, 1973.
2. Stamler, J.: Comprehensive treatment of essential hypertensive disease — why, when, how. Monographs on Hypertension, No. 13, October 1970, Merck Sharp & Dohme, Rahway, N.J.

Detailed information is available to physicians on request.

MSD MERCK SHARP & DOHME

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Editorial:
Selection of Medical Students

The selection of a suitable applicant for a position is never an easy task. Prof. Northcote Parkinson of Parkinson's Law fame describes four classical methods by which this is done. The traditional British method is to enquire into an applicant's pedigree and if this is found to be unsuitable, the applicant is then shown the door. The new pattern British method is to ask what school the applicant comes from and what games he plays. If these do not happen to be the correct ones he too is unceremoniously disposed of.

The Chinese method of selection is more sophisticated. The traditional method requires all applicants to sit for an examination. It is quite immaterial whether the subject to be tested on is relevant to the job at hand. Only those with the knack of passing exams are accepted, and those without are got rid of. A newer Chinese method is to completely reject all applicants who apply and invite only those who have not applied. The philosophy behind this is that no real scholar would ever apply for fear of losing face if he were not chosen.

The present method of admitting students into our medical faculty follows closely the traditional Chinese pattern. Only those who do well in the exams are admitted, those who do not are automatically eliminated by the computer. It matters little whether a high degree of proficiency in higher mathematics is of any help in soothing the fevered brow. The important thing is an examination is as good a method as any in sorting out the sheep from the goats.

But alas examinations do not always tell everything we wish to know about the student. It does not even tell us whether he or she is really bright, or whether the student upon graduation is willing to eschew the nice cosy life of the materialistic world and turn his shoulder to the plough in service to the community. How are we then to select our medical students? Will the bright students inevitably be the worst doctors or more important still will the not so bright ones be better doctors?

How much are the students themselves to blame for this lamentable state of affairs, this crass moneytheism? Now that an egalitarian society has made the pursuit of a medical career open to anyone who is willing to work for it, many students have come to look upon taking up medicine as a career like doing any of the other professions. One does not expect lawyers to work for piffling stipends in the service of the community, or accountants to wake up in the early hours of the morning to solve clients' dilemmas, why then is so much more expected of the doctors? The difference, as Prof. Sir Gordon Ransome once said, is because medicine is a profession, a noble profession, all the rest are trades!

This pride in the noble art of healing can only be understood by those who have been exposed to it, by those who see in their lifework the relief of mankind's suffering. You do not get this from the books. It is seen only at the bedside of the sick.

What are we doing in the medical faculty to foster this spirit of service? To quote no less an authority than a 4th year University of Malaya medical student Mr. H.S. Lee writing in the Berita MMA, "the tremendous amount of workload placed on him had forced him to sacrifice part of his social life. It is not unusual that medical students in general are apathetic towards the organization activities of Medical society, student union and other activities . . . In the production of "safe" doctors in service to society, the medical educationist should be aware of the undesirable possibility of a miniculture consisting of highly professional, self-centred academicians **without social awareness."**

Do we still wish to lay the blame solely on the door-step of the students? If we are honest with ourselves we are not entirely without blame. We must not produce doctors without souls.

If we are to have better doctors, doctors who care, doctors who will work for the good of the community then we must seek out students who do care, students who are able to think and not merely learn by rote, students who would be willing to give an undertaking to serve the community for a period of time upon graduation (the bond issue is quite another matter).

From the standpoint of general practice the streets of Singapore are not paved with gold, and the student who wishes to enter this field must be prepared to work long hours for modest recompense. He need not be brilliant but he must be bright. Above all else he must have a heart to help and comfort all those who come to him for relief. He will never be great but he will have satisfaction in his work. He will not be known to all but he will be trusted by many. To those patients who know him well he cannot be replaced, he is their family doctor.

E. K.

(Views expressed in the Editorial are not necessarily the official views of the College).

Use and Abuse of Drugs in Paediatric Practice

by Professor Wong Hock Boon
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DRUGS AND GENETIC EVOLUTION:

GENETIC EVOLUTION has progressed, since life first appeared, by accidental mutational changes and tested by the environment as to whether these new mutational genes have or have not better survival value for the species concerned. This environment was pretty constant in human history till 200 years ago when scientific technology snowballed and changed the environment considerably. This latter environmental iatrogenic changes are the result of SOCIAL EVOLUTION. Medicine as a professional discipline, and one of its tools — DRUGS — is the result of social evolution and not genetic. As such, the genes we have often resist such intrusion of drugs into the body as a genetic protective mechanism.

"Drugs" in the crude sense were incorporated into plants, in a genetic evolutionary manner, to protect itself by predators by the "toxins", such as digitalis, poison ivy, etc. Man initially by empiric means extracted these alkaloids, made them into infusions and found that some were beneficial for certain conditions, e.g. ephedrine as bronchodilators, digitalis as a cardiac decongestant, etc. Hence, arose the practice of drug use.

It is, therefore, obvious that drugs, not being in the scheme of human genetic evolution, will be EXPELLED and MADE NON-TOXIC if introduced into the body. They are all foreign bodies, except for a few natural substances, e.g. vitamins etc. when it is difficult to conceive of them as drugs, unless taken excessively. Therefore, we have evolved genetically a 'drug-destroyer' mechanism to protect ourselves from these foreign bodies. Therefore, when we use drugs purposely to produce a desired effect, very often, we achieve an opposite effect — which should be perfectly understandable.

Therefore, the CRUX of the matter in drug usage lies in the ABILITY of the doctor administrating the drug to recognise:—

1. Whether the desired effect is obtained and for how long?
2. Whether the drug-destroyer apparatus of our body is over-taxed with detriment to it, i.e. we have to weigh the risks. Nothing is for free, we pay for every drug we ingest. Is the payment worth it?
3. Whether the genetic differences in the drug-destroying apparatus are producing more undesired effects than desired effects, i.e. there is **NO** such situation where a CONSTANT effect of a drug on DIFFERENT people is to be expected.

I would like to stress the last point, viz. because there are always genetic differences in any 2 people; control trials with drugs, and analysis for statistical significance to see if any side effects are produced or not, will never be able to guarantee that a PARTICULAR individual will be free of side effects just because such trials showed that the side effects were not statistically significant. That is why, a child may suffer from cardiac arrest after GA for tonsillectomy; a foetus may be malformed because the mother took such an "innocuous" drug as aspirin during the first trimester of pregnancy.

THE DRUG-DESTROYING APPARATUS:

This is done every time for most drugs by 2 organs, chiefly, the LIVER and the KIDNEY.

A) LIVER:

There are 2 main mechanisms, the cytochrome P_{50} oxidase system and glucuronide conjugating system, the latter being classically seen

in biliribin detoxication. There are other mechanisms also. But by these 2 systems water-insoluble substances are made soluble for the next step in getting rid of this foreign body.

B) KIDNEYS:

The urine is the main vehicle whereby the drug is eliminated from the body after detoxification. Thus, the PRICE to be paid is borne chiefly by the liver and the kidney.

A simple example will suffice in regard to the liver. Cortico-steroids are converted in the liver, and their use clinically in pharmacological doses cause liver enlargement in nearly all children. This is due to stimulation of the enzyme activating system in the endoplasmic reticulum of the hepatocytes. Similarly, paracetamol poisoning causes liver failure. All these may be due to:—

1. Stress.
2. Production of intermediate metabolites which may be MORE TOXIC than the original drug.
3. Direct effect of drug on the organ in sufficient dose.
4. Hypersensitive reaction in normal dosage.

Where the liver is concerned, CHOLESTASIS or LIVER FAILURE may occur. Originally, only a handful of drugs such as cinchophen were thought to be able to cause side-effects. The list has now grown so rapidly with increasing use that almost any drug in genetically susceptible persons can cause liver damage, even INAH, tetracycline, salicylates, etc.

The price paid by the kidneys can be equally prohibitive, e.g. salicylate nephropathy, tetracycline tubular damage, ampicillin interstitial nephritis, gentamycin nephropathy and a whole host of drugs, which can potentially cause a nephropathy.

DRUGS AND THE IMMUNOLOGICAL SYSTEM:

Being a foreign body, a drug also encounters another system (the immunological system) besides the drug-destroying apparatus, and this can cause serious upsets. The drug behaves like an antigen or unites with a protein to become antigenic. It may thus provoke antibody formation of either the circulating type or the cell mediated type. An antigen-antibody reaction can occur thus in the circulation as in auto-immune haemolytic anaemia or it can occur in tissues like in the liver, the type of reaction occurring depending on whether the antibody is free in the circulation or fixed to whichever tissue. At any time when the drug is taken again, a severe hypersensitivity reaction may take place as in penicillin anaphylaxis due to the formation of specific circulating IgE to penicillin.

The immunological system, if it is in a healthy state, cannot but do this because it has been genetically evolved to deal just with such foreign body incursions to preserve the species. Of course, under natural conditions, the system has developed to deal specifically with micro-organisms, usually bacteria and viruses. But drugs come within this scheme of things because, unfortunately, they can become antigenic. A good example of how a drug, or an organism may both affect the immunological system in an almost identical manner, is LYMPHADENOPATHY. Histologically, these enlarged glands — usually the TONSILS and CERVICAL GLANDS — demonstrate non-specific hyperplastic changes, i.e. it is termed a non-specific lymphadenitis. Just such a phenomenon occurs in children in the condition termed DIPHENYLHYDANTOIN lymphadenitis and in any number of viral and bacterial lymphadenitis.

In this regard, the doctor dealing with children, must change his attitudes with regard to so-called TONSILLITIS. Normally, a child's tonsils must enlarge because he is at that period of life when he is just coming into contact with the myriad micro-organisms, chiefly viruses, in the air and in the food and water he swallows. This is in the scheme of genetic-protective evolution so that he can gradually develop his RESISTANCE as he grows. Naturally, it is at this period of life when his tonsils are capable of growing at a much more rapid rate compared to other tissues, and this is seen classically in the NORMAL rates of patterns of growth of different tissues:—

The truth of these statements is borne out by your observations and those of observant mothers that occipital glands (and cervical ones) are extremely common and stay palpable for months or years. So IT IS with the TONSILS which are nothing more than a large lymph node. In fact, a child with SMALL tonsils is the abnormal one in that he may be suffering from immunodeficiency disease. More normal enlarged tonsils are removed than normal appendices. You must have observed that many children with tonsillectomy still 'suffer' from whatever he was com-

plaining of prior to tonsillectomy. Even the presence of so-called positive bacteria on culture of a throat swab is not necessarily indicative of infection, if there are no constitutional symptoms. Furthermore, there are children who because of:—

a) Instability of the temperature — regulating mechanism, or
b) Vigorous antibody production

may have fever with the physiologically enlarged tonsils. It is only when the tonsils are destroyed and becomes an ABSCESS (i.e. QUINSY) is it justifiable to remove a tissue which is normally producing antibodies for the benefit of the child in later life.

MISUSE OF ANTIBIOTICS:

Antibiotics are extremely commonly misused in children to the extent that they are often prescribed as ANTIPYRETICS. This should not be so because the commonest cause of fever in a child is a VIRAL INFECTION, and not bacterial. Besides the commoner side-effects such as G-I upsets, etc., the more serious ones include:—

1. HYPERSENSITIVITY REACTIONS
2 ANTIBIOTIC FEVER
3 'ANTIBIOMAS"
4. TISSUE DESTRUCTION
5. SUPERINFECTION BY FUNGI

A) HYPERSENSITIVITY REACTIONS:

These are usually due to reactions working on the immunological system, and they may involve production of IgE, IgG, IgM and cell-mediated antibodies, the latter producing DELAYED HYPERSENSITIVITY REACTIONS.

There are, of course, various clinico-pathological manifestations, some causing severe constitutional symptoms, and hence alarming e.g. anaphylaxis to penicillin, Steven-Johnson syndrome, ampicillin nephropathy, chloramphenicol aplastic anaemia, etc., and the ones with milder manifestations especially SKIN RASH. However, the latter MUST NOT be viewed as benign, because the hidden reactions are not seen, and these may go on quietly and continuously or be exacerbated with every repeated use with presence of just a visible skin rash. After months or years, the serious effects may then manifest itself. Therefore, the mildest reaction should alert the doctor to the FACT that this is an individual who, by virtue of this GENETIC CONSTITUTION, is reacting badly to the antibiotic, and it must be remembered that no two individuals have identical genetic constitutions except identical twins.

It is true that some antibiotics are more likely to produce hypersensitive reactions and this is because of their antigenic properties. However, this must not be taken as a guideline that the others will not produce reactions if used, because one cannot foretell the genetic constitution of any individual to whom we are giving the antibiotic. In fact, there are reports of hypersensitive reactions to **every** antibiotic that has ever been invented and used.

B) ANTIBIOTIC FEVER:

This is not uncommon. It is due to killing off of some commensals and the resistant ones now overgrow and cause a reactionary fever. The latter and the former are normally kept in symbiotic equilibrium and, this again, has been achieved by genetic evolution. Upsetting this causes superinfection by 'normal' organisms. This is most likely to occur with the broad-spectrum antibiotics especially tetracyclines.

Those left behind are resistant to tetracyclines such as E. Coli, proteus, pyocyaneus. The tongue and oral mucosa are red and angry with prominent papillae in tongue — strawberry tongue, and the fauces are red with what is often mistaken for PUS over the tonsils. These are whitish grey exudates caused by the inflammation. The fever plus the angry changes in the pharynx often provokes the use of a more 'powerful' antibiotic with disastrous results. There may be slight enlarged tender cervical glands but there is usually no evidence of hepatosplenomegaly and septicaemia. The superinfection is confined to the pharynx.

Inspite of the fever, the child is relatively well and only when it is very high will he want to lie down and become a little irritable. When the fever which is INTERMITTENT falls, he feels well again and is able to play as usual.

Stoppage of all antibiotics, makes the child afebrile for the first time after 2-3 weeks of fever. The period of time taken to achieve fever defervescence is 1-2 days. The angry fauces becomes less red and there is no more trouble.

C) ANTIBIOMA:

In the genetically-susceptible child, cervical glands may be huge because of antibiotic super-

infection. The fact that it occurs only in some children with antibiotic fever is due to genetic-specific antigen-antibody reaction. They have been mistaken for mycobacterial glands or neoplasms.

D) TISSUE DESTRUCTION:

It must be realised that antibiotics are supposed to kill live cells, viz. bacteria. This they do by interferring with the function and structure of the cell membrane, with the replication of of DNA, with the transcription and translation of RNA and with the metabolism of the cell. In this regard, all the cells of the body are also alive, and it will be too naive to think that antibiotics are so specific that they will only kill bacterial cells but not human cells. Therefore, the destruction of some human cells is the price we have to pay whenever we use antibiotics. The more obvious examples include:—

1. CHLORAMPHENICOL. Its action on bone marrow cells is direct interference with their function and growth in ALL persons. However, in those who are genetically susceptible, this is permanent even after the drug is withdrawn.

2. CYTOTOXICS. Some antibiotics are used as cytotoxics in neoplasm management, e.g. ACTINOMYCIN D in Wilms Tumour, etc.

There will be a whole spectrum of degree of human cell susceptibility, which unfortunately cannot be known beforehand.

E) SUPERINFECTION BY FUNGI:

Although superinfection by fungi is seen chiefly in the mouth in the case of Candida, it manifests itself as candida diarrhoea and systemic candidiasis.

CONCLUSION:

Antibiotics must never be blindly given.

There must be concrete evidence of bacterial infection causing the disease before they are used. The onus is on the doctor.

When they are used, the doctor must be conversant with all the possible complications.

They must not be used as antipyretics.

If used, ALL predisposing and direct causes of bacterial infection must be investigated, and eradicated e.g. obstructive uropathy and pyelonephritis.

USE OF CORTICOSTEROIDS:

One of the drugs which illustrate the maxim aptly: "New medical knowledge has an average ½ life-span of 6 months". Therefore, a doctor who does not keep up will be archaic quite easily within 1-2 years of practice. Steroids were claimed as wonder drugs when first discovered by Hench et al. It is now considered to be one of the most dangerous drugs when misused. Steroids have never cured any disease, but, if intelligently and wisely used, may "buy time" for the patient till disease process burns itself out, and cures itself.

Just as in the use or misuse of antibiotics, steroids may produce the following common complications:—

1.. Lowered resistance to infection.
2. Adrenal crisis.
3. Steroid dependancy leading to a vicious cycle, and cause complications.
4. Cushingoid toxicity.
5. Cataract.
6. Osteoporosis with fractures.
7. Bone marrow depression.

The LEGITIMATE use of steroids, at the moment, include:—

1. MINIMAL LESION in childhood nephrotic syndrome.

2. PUO due to iatrogenic immunological disease, or transient immunological disease secondary to some other primary pathology.

3. Temporary therapy in certain groups of BRONCHIAL ASTHMA, and later convert to prophylactic steroid inhalation to reduce possible complications. STATUS ASTHMATICUS.

4. Rarely, in RHEUMATOID ARTHRITIS, in those patients with life-threatening situations such as uveitis and blindness, pericarditis, severe toxicity not responsive to salicylates.

5. Transplant rejection.

6. Congenital adrenal hyperplasia — this condition is rare anyway.

7. ACUTE LYMPHATIC LEUKAEMIA as an adjunct in INITIATION therapy.

8. FULMINATING RHEUMATIC CARDITIS.

MISUSE OF OTHER DRUGS:

1. PHENOTHIAZINES for vomiting in children, and EXTRAPYRAMIDAL Syndromes.

2. COUGH SUPPRESSANTS in upper respiratory and lower respiratory tract diseases.

3. "APPETITE STIMULANTS" and their effect on the developing hypothalamus.

4. VITAMINS.

5. IMPRESSIONISTIC efficacy of "favourites".

6. CONSTIPATION drugs in GASTRO-ENTERITIS – may have a dangerous 'psychological' effect, KAOLIN/PECTIN etc. ANTIBIOTICS. Misuse of these drugs due to failure to understand basic physiology and pathology of infantile gastro-enteritis.

7. The EXPECTORANTS and POLYPHARMACEUTICAL "Secret remedies". Danger of oral medication in ILL INFANTS especially in those with respiratory, cardiac or neurological disease – ASPIRATION PNEUMONIA.

Antibiotic Misuse in Paediatric Practice

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INTRODUCTION:

Before I discuss antibiotic use in paediatrics, I would like, very briefly, to recapitulate how bacteria live and grow, and how antibiotics are supposed to halt these live processes. With certain exceptions, bacteria consist of an outer rigid WALL made up of peptidoglycan, i.e. a structure consisting of alternating amino sugars of 2 types — N-acetyl-glucosamine and N-acetyl-muramic acid — and joined together by peptide chains linked to the muramic acid residue. Just inside this Wall is the bacterial MEMBRANE, which is made up of proteins and lipids. Both these structures surround the CYTOPLASM consisting of DNA, RNA, proteins and polysaccharides. It is in the cytoplasm that the biochemical life processes take place. These LIVE PROCESSES can be divided up in 3 groups of metabolic reactions. The **first** is GLYCOLYSIS whereby glucose is broken down and thereby energy is produced for the needs of the bacteria. With this energy, certain basic substances are built up, viz. amino-acids, hexosamines and nucleotides. This constitutes the **second** metabolic reaction. The **third** and final reaction is the formation of macromolecules from these small molecules, resulting in the production of peptidoglycans (10-20%), proteins (60%), RNA (10-20%) and DNA (2-4%). The bacterium is now complete, and with this apparatus can metabolise, produce toxins, and reproduce. It can thus be seen that the bacterium is not much different from any cell in the human body except for the rigid cell wall in those which possess it. The genetic metabolic processes are identical with those seen in the human cell.

Chemotherapy is supposed to provide chemicals which are able to disrupt either the structure or the metabolic processes of the bacterium. It is inevitable that since the human cell has the same basic structure and metabolism as the bacterium, that antibiotics may have secondary toxic effects on the human cells. Hence, Chemotherapeutic agents, and hence the antibiotics are selected for their relatively greater toxicity to the bacterium than to the human host. There is no such thing as total host integrity to the action of antibiotics. This secondary side-effect varies not only with the type of antibiotic but also with the genetic make-up of the human taking the antibiotic; for example, in hyper-sensitivity immunological side-effects.

Antibiotics may disrupt the integrity of the bacterium in one of several ways. It can compete with some bacterial substrate needed for bacterial metabolism, e.g. sulphonamides compete with para-amino-benzoic acid which is normally needed by the bacterium to form folic acid, which thus becomes deficient. The antibiotic may interfere with the synthesis of the bacterial cell wall, and the antibiotics with such an action include the penicillins and cephalosporins, bacitracin, vancomycin, ristocetin, novobiocin and cycloserine. The antibiotic may interfere with the function of the bacterial cell membrane, like the polymixins. It may interfere with protein synthesis, and in this regard, chloramphenicol interferes with the amino-acids joining to form peptide chains; streptomycin, neomycin, kanamycin and gentamycin interfere with the mRNA code so that it is misread; tetracyclines interfere with the action of tRNA; while erythromycin and lincomycin compete with amino-acids binding to ribosomes. Finally, antibiotics may interfere with nucleic acid synthesis, these are the antibiotic-cytotoxic drugs such as actinomycin D, mitomycins and idoxuridine. This last group emphasises the potential capability of antibiotics killing human cells besides killing bacteria.

When an antibiotic "kills" a bacterium, it is referred to as bactericidal and when it prevents it from growing and reproducing it is referred to as bacteriostatic. Actually, it is never so clear-cut because the action of a particular antibiotic depends on so many variables in its environment, such as dose, route of administration, pH of surroundings, its inactivation by body cells, its ex-

cretion by the kidneys, etc. and all these also depend on the genetic make-up of the host. Even if the antibiotic achieves its bacteriostatic/bactericidal action, success is not automatic, because the defence organisation of the host must be intact. The phagocytes, with their metabolic processes must function properly. They cannot deal with the "antibiotic-treated" bacteria unless the latter have been "opsonised" by antibodies and complement. Hence, the T and B lymphocytes must be intact, and able to play their part in assisting the antibiotic in its work. Thus, in immuno-deficiency diseases, occasionally, any amount and type of antibiotic, is insufficient to deal with the bacteria which have caused infection in such individuals.

A further consideration which must be borne in mind in antibiotic therapy in children is that the child is developing and growing. He has not completed his full growth. His organs are growing, e.g. the kidney grows till 7 years of age, his intelligence and emotions are all developing. A relevant consequence of this growth process is that the immunological system is also growing, and hence tends to be more active than that of an adult. It will have to produce antibodies to the many viruses in our environment and so the child always gets all sorts of viral infections, and always has enlarged cervical glands and enlarged tonsils. In the former instance, antibiotics are not needed, and in the latter tonsillectomy is not needed. Therefore, the whole spectrum of infection in a child, its consequences, relevant indications for antibiotic therapy, are different from those in the adult.

With this as a background, let us consider the rational use of antibiotics in paediatric practice.

UPPER RESPIRATORY TRACT INFECTION:

Before this can be considered, allergic reactions of the upper respiratory tract must not be construed as infection. The child with allergic rhinitis, the child with minimal bronchial asthma with cough and without wheeze, and the child with wheezy bronchial asthma are not examples of infection but of a genetic disease, and antibiotics have never cured the latter. Use of antibiotics in these situations is unnecessary and may be harmful. The incidence of such allergic conditions in childhood is much commoner than the incidence of upper respiratory tract infections.

With regard to upper respiratory tract infections, the majority are due to viruses. Using the NBT (Nitroblue Tetrazolium) Test, which generally is able to distinguish bacterial from viral infections, the incidence in Singapore is approximately 80% viral and 20% bacterial. In Western countries where culture of viruses is carried out together with serology, the incidence of viral infections is higher – 90%. In Bangkok, a similar study has been carried out and the incidence of upper respiratory tract infections due to viruses is 80-90% with only 10-20% due to bacteria. Hence, throughout the world, infections in children resulting in a clinical diagnosis of PHARYNGITIS, TONSILLITIS, BRONCHITIS and BRONCHIOLITIS, are predominately viral induced, so that antibiotics play a small part in the treatment. Lexombon **et al** (1971) in Bangkok treated 261 children with upper respiratory infection. 88 were given tetracycline, 86 Penicillin and 87 given a placebo. The results were as follows:–

Drug	No.	Mean Duration of Fever	Improved	Complications
Tetracycline	88	4.3 Days	85	1
Penicillin	86	4.3 Days	81	2
Placebo	87	4.6 Days	83	2

There was no significant difference in the outcome whether the patients were given antibiotics or not. Even the complication rate of the infection with or without antibiotics did not differ significantly.

What about the 20% where viruses cannot be cultured? It may be that in some of them, viruses were the cause but a positive culture may be hard to come by. An interesting study was recently carried out in Canada (Steward **et al,** 1972), where throat cultures were carried out in 2588 boys and 2158 girls under 3 years of age, i.e. a total of 4,746. In 2553 of these children, a clinical diagnosis was made by the doctor of an upper respiratory tract infection, while the remainder had no such diagnosis, i.e. without fever and no complaints (the controls). The results were as follows:-

		Cultures		Total
		Positive	Negative	
Clinical Diagnosis Of Infection	Positive	376 (14.7%)	2177 (85.3%)	2553
	Negative	298 (13.2%)	1895 (86.8%)	2193
TOTAL		674 (14.5%)	4072 (85.5%)	4746

Positive cultures mean positive for Group A beta-haemolytic streptococcus, pneumoccus, haemophilus influenzae, staphylococcus aureus or a

mixture of these. Negative cultures mean no growth of organisms or normal commensal flora. What was most revealing was that only 13-14% gave positive cultures, and these were distributed almost equally between those with symptoms and the controls (not significant: $0.3 > p > 0.15$). Hence, the presence of positive cultures did not necessarily mean infection, and 86% of those with infection were due to viruses.

Under these circumstances, it would seem that there is very little valid reason for treating upper respiratory infections in children with antibiotics, especially if the side-effects are more serious than the infection itself. Then, under what circumstances, could antibiotics be logically used? Probably, these would be:—

1. Quinsy where pus is visible in the tonsils.
2. Diphtheria, which is rare anyway in Singapore now.
3. Streptococcal infection, which unfortunately cannot be diagnosed clinically, but needs culture, and even if it is positive, it would be difficult to assign it an infective role because it can be cultured in normal people. Probably, if it is positive in a child complaining of sore throat, then PENICILLIN is all that is necessary in order to prevent rheumatism. However, to be effective in this direction, it has to be used for 10 days.
4. Pyogenic cervical lymphadenitis syndrome. This is a new type of presentation because the child usually has been given antibiotics previously, but usually without adequate dosage or duration of treatment. I call this condition "ANTIBIOMA". The affected glands do not feel as fluctuant abscesses but as firm masses which have been mistaken for viral (infectious mononucleosis syndrome), neoplastic (lymphomas), t.b. and fungal glands.

OTITIS MEDIA:

Acute otitis media, though less common now than before is still occasionally seen. Just as with upper respiratory tract infection, doctors feel that all such cases should be treated with antibiotics, and the earlier the better. This is not necessarily so, as 2 ENT Specialists (Diamant and Diamant, 1974) have recently shown. They studied 2,975 acute otitis ears in 2,145 patients (some unilateral and some bilateral), and assessed the number of ears still suppurating from day 1 to day 20. They found the following:—

	No. Ears	% Suppurating at Day 20
No Antibiotics	1,608	1.6%
Antibiotics	1,367	7.2%

Hence, those ears not treated with antibiotics fared better than those which were antibiotic-treated. They also found that in those ears treated with antibiotics:—

1. Frequency of mastoidectomy is high.
2. Frequency of recurrence in the first month after recovery is higher than in those not antibiotic-treated.

They advocate that no antibiotics be used to treat acute Otitis Media in the first week. If, after the first week, it has not settled, then antibiotics can be given with benefit.

Recurrences	No. Recurrences %		P Value
	Without Antibiotics	With Antibiotics	
Within 1 Month	35/4.7	79/11.7	0.001
Later Than 1 Month	211/28.1	200/29.6	N. S.
TOTAL	246/32.8	279/41.3	0.001

ANTIBIOTIC FEVER:

At this stage, I would like to mention a syndrome which is not uncommonly seen in Singapore children, and which I choose a call "antibiotic fever". The history is that the child starts with a fever and was given antibiotics by a doctor. Almost invariably,this fever had been due to an upper respiratory virus infection. This would upset the ecological balance of the commensal throat flora with excessive growth of those organisms not susceptible to the antibiotic because of reduction of those which were susceptible, i.e. a state of superinfection. The fever, which would have subsided on its viral basis, now continues. The doctor, thinking that the initial antibiotic was not effective, switches to another one with a broader or different spectrum. The superinfection gets worse, and in addition, a fungal superinfection occurs. Another doctor is consulted, and still another, or the same antibiotic is prescribed, and when the patient reaches us in hospital, the child would already be having fever for over 10 days. A PUO of 3-4 weeks is not uncommon. Clinical examination is essentially negative except for the fever which may reach levels of $100^{o} - 120^{o}$F. Occasionally,

the throat is extremely red with prominent follicles on the tongue. White plaques, which have been wrongly construed as pustules, are seen over the tonsils. Swabs from these do not show pus cells but epithelial debris — they are epithelial pearls. The total white count can be low, normal or high, and the erythrocyte sedimentation rate may also be normal or raised. The condition, with such a typical history, is easily recognised. The child is warded and no medicines are given. The temperature falls to normal promptly within 24-48 hours, and the child remains afebrile. Throat swabs yield usually E-Coli, Klebsiella or other Gram negative bacilli. The fever is due to super-infection by these bacilli.

The mechanics of throat superinfection after antibiotics have been studied by Dalton **et al** (1974) in hamsters. Cloxacillin was given to a group of hamsters, and the pharynx cultured before and after the antibiotic. Before antibiotic, the normal flora consisted of a-haemolytic, non-haemolytic and enteric Streptococci, Neisseria species, Corynebacterium, Staphylococcus aureus and S. epiderdimis. E. Coli and proteus were sparse, mainly less than 100 bacteria/ml. of culture medium. After antibiotic, pharnygeal cultures were repeated at 4 hr., 24 hr., 48 hr. and later, and a few were sacrificed, and lung cultures obtained.

The **a**-haemolytic Streptococci count rapidly was reduced even after 4 hours. But the number of gram negative bacilli was increased and all had large numbers of Klebsiella, Proteus, E. Coli and entero-bacter within 48 hours. 28% revealed positive blood cultures within 72 hours. In those animals which were sacrificed, Klebsiella pneumniae were recovered from the lungs in 64% of animals; E. Coli in 56%; Proteus in 36% and enterobacter species in 32%. In these positive cases, histologic evidence of pneumonia was seen.

It is obvious that what I call antibiotic fever in viral upper respiratory tract infection is due to superinfection by Gram negative bacteria released from the constraints placed on their growth normally by the other bacterial commensals which were killed by the antibiotic. This is the "Silent Spring" of Rachel Carson in the ecology of the human body.

DIARRHOEA:

This extremely common malady affecting infants and young children is often misconstrued by parents as a serious illness when it is chronic, and as nothing serious when the infant may die within a few hours in the acute variety. The greatest danger from infantile diarrhoea is fluid and electrolyte failure, and infants so affected can only be treated in a hospital with intravenous fluids.

This severe type aside, most other cases cure themselves, and it is here that antibiotic therapy must be circumspect. The commonest cause is a virus, the ORBIVIRUS, which only in the last 6 months has been shown to be present in the diarrhoeal stools all over the world, including Singapore. The delay in this discovery is because of lack of suitable techniques previously. Antibiotics have no place in these virus diarrhoeas. A small number will be due to bacteria, and in this regard, the vibrio cholera, pathogenic E. Coli, Shigella, Salmonella typhimurium are occasionally the cause. Except for vibrio cholera, the stools usually are blood-stained. The treatment of cholera is of course, fluid and electrolyte therapy. It is legitimate to treat Shigella dysentery with antibiotics, but, there is no real benefit in treating pathogenic E. Coli and Salmonella typhimurium diarrhoea with antibiotics because diarrhoea is often prolonged because of antibiotic therapy, and, of course, resistance strains and the carrier state are produced. Animals and human volunteers given antibiotics first, and then fed with a certain dose of Salmonella typhimurium invariably get diarrhoea while those without prior antibiotics do not get diarrhoea. The role of pathogenic E. Coli as the cause of infantile diarrhoea is still uncertain, as these organisms can be grown in infants without diarrhoea. In conclusion, the use of antibiotics in these 2 types of intestinal infection is only justified in those infants who already are in a bad shape, for fear of Salmonella typhimurium septicaemia. Hence, there are very few indications for the use of antibiotics in infantile diarrhoea.

Just as in antibiotic fever, antibiotic diarrhoea can occur due to superinfection, and stoppage of all antibiotics also stops the diarrhoea. It must be remembered that cessation of all loose stools may take a long time in infants because of mucosal damage, but this type of chronic diarrhoea is never serious, and responds to bland fluid therapy for several days. These babies are well hydrated and look well, except that the stools are loose. The use of antibiotics in these prolonged infantile diarrhoea may convert them into critical acute fluid and electrolyte problems.

THE PARTIALLY TREATED MENINGITIS SYNDROME:

This new syndrome is getting more and more common now in our Department. A child with fever is given antibiotics, usually tetra-cycline be-

cause it is cheap and easily available. If this child was incubating septic meningitis or has early signs of meningitis, this partial therapy will prolong the fever until the child gets a convulsion. He is admitted, and has all the signs of meningitis, and a lumbar puncture shows a cerebrospinal fluid (CSF) with slightly raised cells, usually with lymphocytic predominance, raised protein, but normal sugar. The diagnostic dilemma encompasses:—

1. Tb meningitis
2. Aseptic meningitis due to viruses
3. Viral encephalitis
4. Brain abscess
5. Partially treated meningitis

Actually, they are cases of partially-treated pyogenic meningitis, the antibiotics used being of insufficient dose for meningitis, or incapable of traversing the blood-brain barrier well, or the wrong antibiotic for the type of organism. Failure to recognise this iatrogenic syndrome and treating the patient for the wrong diagnosis will jeopardise his recovery, end in death or survival with serious CNS Sequalae. The only way to prevent such a state is to examine the child carefully at the beginning, and invariably there are signs of early meningitis, and the child sent to hospital immediately.

URINARY TRACT INFECTION:

Infection of the urinary tract in infants and children is different from that seen in adults in 3 main ways:—

1. There are no complaints referable to the renal system because the baby or child cannot say so. Even if the older child complains, it is usually one of central abdominal pain.
2. The majority of renal tract infections finally involve the renal parenchyma, and hence the term PYELONEPHRITIS. This stresses the poor prognosis if undiagnosed, or if diagnosed, but inadequately treated.
3. Some of them have a basis on a pre-existent renal tract congenital malformation, while often the adult, if undetected would have died of chronic renal failure.

It is therefore, understandable why many adult chronic renal failures are due to poor diagnosis and management of urinary tract infection in infancy and childhood.

Unfortunately, this infection is a true PUO, in that clinical signs pointing to the infection are totally lacking except for the fever. Hence, if the doctor does not think of this, and carry out a careful and repeated urinalysis and urine culture, the diagnosis will be missed. Even after diagnosis, the management is not a simple one of giving antibiotics, because the following are needed:—

1. Culture of the responsible organisms and sensitivity tests are needed.
2. If there is pyelonephritis, treatment may have to be prolonged to 6 months, the dosage of the antibiotic being reduced to ¼ of the acute stage dose after the fever had subsided and the urine is clear.
3. An IVP is mandatory after any attack of pyelonephritis in a child, and if the IVP warrants it, a follow-up micturating urethrocystogram is essential.
4. Corrective surgery may be needed for congenital malformations.

It is thus possible that many children with a fever caused by pyelonephritis are treated inadequately with antibiotics without adequate investigations and management. This will lay the seeds for serious trouble in later life in the form of chronic renal failure. To give an idea as to the difficulty in diagnosis, we have found (Tay **et al,** 1974) that a sizeable proportion of 7 year-old girls have infection of the renal tract without any complaints whatsoever.

ANTIBIOTICS & IMMUNOLOGICAL DISEASE:

Finally, I have seen the most peculiar immunological reaction after prolonged antibiotic therapy in children. The obvious hypersensitive reactions are usually dermatological in type, with fever, and even with the severe Steven-Johnson type, recovery is the rule. However, ampillicin interstitial nephritis is increasingly seen by us. Odd collagen diseases which do not fit any pigeon-hole occur, many with fever, high erythrocyte sedimentation rate, with arthropathy, skin lesions, hepato-splenomegaly, etc. It is only one step away from an immunological reaction to neoplasia, and the increased incidence of acute leukaemias seen here may have a certain iatrogenic basis. (Wong, 1972; 1973).

Therefore, antibiotic prescription in paediatric patients needs a wide awareness of the incidence of types of infections and the aetiological agent, their responsiveness or unresponsiveness to antibiotics, and the risks which patients run when they take antibiotics needlessly. No two patients react in the same way to antibiotics, and it is shown that this difference in reaction is as much due to the genetic make-up of the patient as to the type of the drug itself (Lader **et al,** 1974).

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The Significance of Fever in Children

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The presence of fever in a child is often considered to be a serious indicator of a disease state, both by parents and by doctors, who often prescribe antibiotics; the more prolonged the fever, the more powerful the antibiotic. It is very doubtful that the mere presence of fever is always serious, and the wisdom of giving antibiotics to every child with fever is highly questionable. The problem is a practical one — how can one assess the significance of fever in children?

PATHOPHYSIOLOGY OF FEVER

In a general sense, there is an AFFERENT LIMB, A TEMPERATURE CONTROL CENTRE, and an EFFERENT LIMB. **The afferent limb** can be termed the pyrogen, which may be exogenous (such as lipopolysacchacides from bacteria) or endogenous (derived from leucocytes, monocytes or other cells of the reticulo-endothelial system). There is evidence to show that a pyrogen in vivo is produced by the interaction of the bacteria with the leucocyte.

There are two **centres** for temperature regulation:

(a) The ANTERIOR hypothalamus, which acts as a THERMOSTAT, i.e. it tries to keep the level of temperature constant, once it has been set by another centre — the set-point centre.

(b) The POSTERIOR hypothalamus, which is the SET-POINT CENTRE.

The efferent limb is a neurological one, i.e. nerves to blood vessels and muscles. Increased heat will produce vasodilatation and heat loss from the blood while decreased heat will produce shivering with heat production.

NON-PATHOLOGICAL FEVER

In an attempt to assess the significance of fever in children, inconsequential fever must be first excluded: this includes

(1) **Absence of fever** — but mother insists that the child "feels hot". This can be checked with a thermometer.

(2) **Normal variation of temperature** — This is usually due to over-enthusiastic monitoring by doctor or nurse parent. The child is very well despite the rise of temperature. Other causes of fever must be excluded.

(3) **Temporary loss of temperature-regulating tone** — This often occurs after an infection, and fever lingers on, due to continued use of antibiotics in a fervent attempt to find the correct one to reduce the temperature (antibiotics are used as antipyretics!). This usually results in the eradication of normal bacterial flora, causing a metabolic upset with consequent fever and failure of adjustment of temperature control. In this group:
   a. The child is well except for the fever.
   b. The temperature seldom reaches more than 100°F.
   c. The ESR and total white cell count are both normal.

(4) **Environmental causes** — Any baby may develop a rise of temperature if over heated, whether due to a electric lamp for warming, or even associated with excessively hot weather.

(5) Absorption of blood (trauma, surgical procedures) — The rise of temperature under these circumstances is only short-lived, and should not cause confusion in the diagnosis for more than a day or two.

(6) **Dehydration** — The so-called dehydration fever of the newborn consists of a sudden rise of temperature a day or two after birth. It is thought to be due to loss of fluid. The temperature rapidly settles when boiled water or other fluid is given.

(7) **Malingering** — Occasionally, serious diagnostic difficulties can arise from malingering in childhood e.g. by vigorous rubbing of the bulb of the thermometer.

ACUTE FEVERS SEEN WITHIN FIRST WEEK OF ONSET

Generally speaking, the vast majority of fevers lasting 3–5 days are viral in origin. In most viral fevers, the temperature shows signs of settling by the 3rd or 4th day of illness, or even earlier. Usually the child is well apart from the fever. This clinical picture is usually due to a upper respiratory tract infection of viral origin. In such cases, simple conservative measures are given and antibiotics withheld. A temperature of more than 38.5°C or 101°F is not necessarily an indication for antibiotics, but constitutes indication for total body sponging with ice water, especially if the child is between 6 months to 5 years old, when the likelihood of febrile convulsions is increased.

When cases of prolonged fever (PUO) are first seen within the first week of illness, the diagnosis will not be easy. This does not, however, justify the practice of prescribing antibiotics for every febrile illness. The differences between viral and bacterial illnesses and the causes of PUO are discussed below.

CAUSES OF PYREXIA OF UNCERTAIN ORIGIN (PUO)

Pyrexia of uncertain origin is generally taken to mean any unexplained fever lasting for more than 7 days. While the number of possible causes may be legion, they may be conveniently grouped into 5 headings, in order of importance:

I. **INFECTIONS**
1. Pyelonephritis
2. Typhoid
3. Malaria
4. Bacterial endocarditis
5. Septicemia
6. Meningitis
7. Infectious Mononucleosis
8. Hidden pus
9. Osteomyelitis
10. Tuberculosis
11. Others

II. **MALIGNANCY**
1. Leukemia
2. Others

III. **COLLAGEN DISEASE**
1. Rheumatoid arthritis
2. Systemic lupus erythematosus
3. Others

IV. **DRUGS**

V. **MISCELLANEOUS**

I. INFECTIONS

Infections as a cause of PUO may be

a. Viral
b. Bacterial
c. Protozoal (Malaria)

a. **VIRAL** infections generally last for less than 1 week, but it is not uncommon for them to last beyond 7 days. The characteristics are:
1. The patient is generally well in spite of the temperature.
2. Presence of leucopenia.
3. Special virocytes in the peripheral blood film – atypical mononuclear white cells.
4. Prolonged fever more likely to occur in those overdosed with antibiotics.

b. **BACTERIAL** infections may be the cause of PUO despite treatment prior to presentation, such as the causes listed above. Except for two common bacterial infections (viz. typhoid and tuberculosis), the rest generally show the following features on the peripheral blood film:
1. Neutrophilia contributing to leucocytosis.
2. Shift to the left i.e. presence of myelocytes etc.
3. Toxic granulations.
4. Increased platelet count. Bacterial infections may sometimes cause a thrombocythaemia instead of leucocytosis.

The child with a bacterial infection may be more ill or toxic looking as compared to a patient with a viral illness.

c. **MALARIA** is the only common parasite causing PUO. Although malaria is now rare in Singapore (except in those who have been outside Singapore) it must still be thought of in all cases of PUO. In fact, malaria must be considered in any patient with fever and splenomegaly, which is almost invariably present.

NOTES ON SOME OF THE INFECTIVE CAUSES ABOVE

1. PYELONEPHRITIS

The most common cause of fever in a child without abnormal physical signs is a urinary tract infection. They symptomatology is usually non-specific and polymorphous, especially in younger children. PUO is a common mode of presentation of pyelonephritis. It is essential that a clean midstream specimen of urine should be microscoped and cultured (within ½ hour of collection). Appropriate and adequate treatment

and follow up is necessary if progressive damage to the kidney is to be averted.

2. TYPHOID

The diagnosis of typhoid in children is much more difficult than in adults, as the "classical" picture is usually absent. It can present as a "perfect" PUO.

The features of such cases presenting as PUO are:

a. The patient is generally well in spite of fever (though he may be toxic looking).
b. Spleen may be not palpable even in the second week.
c. Absence of rose spots. Even if present, they are difficult to see because the disease is common in Malays and Indians rather than Chinese.
d. Absence of meteorism, diarrhoea, drowsiness, delirium, cough.
e. There is a normal white count or a leucopenia.

In a patient suspected of having typhoid, a leucopenia with a positive NBT test is a useful indicator. Blood cultures and Widal and Weil Felix tests would give the diagnosis.

3. BACTERIAL ENDOCARDITIS

Initially, symptoms are obscure and ill-defined, including pyrexia, malaise, lassitude, pallor, anorexia, weight loss, and arthralgia. The diagnosis of bacterial endocarditis should be entertained in any febrile child with a heart murmur, particularly if signs of pre-existing heart disease are present. **Petechiae** are common and are usually located in oral mucous membranes, conjunctivae and around the ankles and wrists. The clinical picture may be altered by systemic embolization, which may result in infarction, haemorrhage, abscess formation or gangrene.

The older literature stressed other classic signs of subacute bacterial endocarditis such as Osler's nodes (small, tender, palpable, erythematous lesions in the pads of fingers or toes), Janeway's leisons (painless, haemorrhagic nodules in the palms or soles), Roth spots (haemorrhagic areas with a white centre seen in the retina) and clubbing of the fingers. These signs are late manifestations of the disease and are now rarely seen. Splenomegaly may be present but is not constant.

With early diagnosis and adequate treatment, most children recover completely. If therapy is inadequate, recurrences are likely.

4. SEPTICEMIA

Septicemia can cause a P.U.O. Due to the widespread and often unwise use of antibiotics for fever in children,

(a) Many of the other signs of septicemia such as organ involvement (empyema, pneumonia, splenomegaly) may be deficient so that fever may be the only sign.
(b) Organisms such as klebsiella, proteus, pseudomonas pyocyaneus and staphylococci are commoner nowadays, rather than streptococci and pneumococci.

Leucocytosis and thrombocythaemia, toxic granulation of the neutrophils are usually present. Blood culture is the only certain way to make a definite diagnosis.

5. MENINGITIS

Septic meningitis may present as a PUO without any of the other signs of meningitis. This is not an uncommon mode of presentation of septic meningitis, again due to the widespread and indiscriminate use of antibiotics.

This PARTIAL TREATMENT, unknowingly for a septic meningitis, is insufficient to clear the infection totally, so that the fever persists and yet acts sufficiently for a time to suppress the other signs of meningitis.

Two signs are useful pointers: irritability and leucocytosis with thrombocythaemia. A lumbar puncture with microscopic examination and culture of the cerebrospinal fluid is essential for diagnosis.

6. INFECTIOUS MONONUCLEOSIS

The fever in infectious mononucleosis may last more than 1 or even 2 weeks. Signs are usually present, such as a greyish white membrane in the throat (often mistaken for diphtheria), cervical lymphadenopathy and splenomegaly.

The diagnosis is often not considered just because the Paul-Bunnel test (a non-specific test really) is negative. This is well known to be so in children in Singapore.

The peripheral blood film is very useful in diagnosis. There is an increased number of white cells with an unusually large number of atypical mononuclear cells (more than 20% of total white cell count or 1400 per cu.mm.). The neutrophil count is usually less than 50% (average 20%) of the total white cell count.

Evidence of infection with Epstein-Barr (EB) virus has been demonstrated in cases of infectious mononucleosis. It has been found that in Singapore, Malaysia and Africa, nearly

all babies by 1 year of age are already serologically positive to the E-B virus. In the west, it has been found that those in the higher socio-economic group tend to seroconversion in adolescence and young adulthood, while those in the lower socio-economic group tend to show as early a conversion as children in Africa and Singapore. Hence the majority of the population in Singapore are already "immune" to infectious mononucleosis.

7. HIDDEN PUS

Hidden pus somewhere should always be considered in any PUO. The commonest is a missed appendicitis. The child presents with fever and vomiting, and examination reveals nothing specific except for reluctance to allow the doctor to examine, especially the abdomen. It is important to think of the possibility of this diagnosis. Tenderness in the RIF is often a difficult sign to elicit in a child. The child should be well sedated and the abdomen palpated thoroughly. A per rectal examination should be done.

Hidden abscesses in the brain, lung, pleural cavity and the subphrenic and perinephric areas are other possibilities. In all, there is a leucocytosis with toxic granulations in the neutrophils.

8. OSTEOMYELITIS

Osteomyelitis as a cause of PUO is often not thought of. If is important to feel carefully for all bones especially the long bones. Staphylococcus is the commonest organism.

9. TUBERCULOSIS

Tuberculosis seldom remain as a PUO because new signs rapidly appear, such as splenomegaly, positive chest X-ray, or signs of meningitis. Nevertheless, the diagnosis should be thought of, otherwise it can be missed. Contact history and BCG immunisation must be checked for. Fundoscopy for choroidal tubercles, tuberculin test, chest X-ray and gastric lavage for acid-fast-bacilli, are important for confirmation.

10. OTHER INFECTIONS

Dengue haemorrhagic fever seldom presents as a PUO because the fever seldom lasts more than a week.

Typhus and brucellosis are rare in Singapore.

Leptospirosis usually presents as a PUO. Presence of jaundice, tender colons and injected eyes are relatively less frequent.

II. MALIGNANCY

1. LEUKEMIA

Of all the malignancies which may initially present as a problem of PUO, leukemia is by far the most important. Leukemia is often missed in these children where bleeding has not occurred yet, and the spleen may be still not palpable. Again, the child is often investigated for all the other causes of PUO and the possibility of leukemia not thought of. One must be prepared to entertain the diagnosis of leukemia in any child with PUO, particularly if some of the following features are present:

i. History of bone or joint pains
ii. Splenomegaly
iii. Pancytopenia – which may be suspected clinically from the presence of pallor, fever and bleeding tendencies (petechiae or ecchymoses)
iv. The peripheral blood film is very useful – it may confirm the presence of pancytopenia, or in some cases, show the presence of numerous blast cells, which makes the diagnosis of leukemia virtually certain. A study of the buffy coat preparation is particularly useful.

It may be difficult to differentiate leukemia with PUO and pancytopenia from hypoplastic or aplastic anemia with fever. Even bone marrow aspirations in these cases can be inconclusive. Useful pointers are as follows:

i. History: In leukemia, the child is more likely to be more toxic and ill.
ii. Nutrition is generally poorer in leukemia.
iii. Splenomegaly is more likely in leukemia than in aplastic anemia.
iv. The ESR is more likely to be raised in leukemia.
v. X-Ray of bones is of special importance.

In doubtful cases, the presence of a radiolucent metaphysical line is highly diagnostic of acute leukemia. This radiolucent line is about 1–6 mm wide located just beneath the metaphysis. The best sites to demonstrate this line are the upper tibia, lower femur, lower radius and ulnar, and the upper humerus (knees and shoulders especially). These lines differ from those in scurvy in that the lateral cortical margins and the epiphyseal plates are intact.

In addition to these radiolucent lines, Osteolytic lesions are often seen (best seen at wrists), in the form of multiple punctate radiolucencies, decalcification of metaphyses and even evidence of frank destruction. Sometimes,

periosteal reaction may be detected in the bone X-ray in the form of periosteal elevation due to leukemic infiltration.

Various mechanisms for the bone changes in leukemia have been postulated:

i. Areas of rarefaction may be due to actual infiltration with leukemic cells.
ii. Degenerative changes may be due to infarcts.
iii. Radiolucent areas may be due to avascular necrosis and haemorrhages.

2. OTHER MALIGNANCIES

It is rare for children with other malignancies to present with PUO without other accompanying physical signs. The converse is more common, i.e. presence of neoplastic masses without fever. Examples of such malignancies include the following:

a. Solid tissue reticuloses: Lymphosaccoma, Hodgkin's disease, reticulum cell sarcoma.
b. Non-reticulosis: Wilms' tumor, neuroblastoma.
c. Histiocytosis.

III. COLLAGEN DISEASE

1. RHEUMATOID ARTHRITIS

Of all the definite collagen diseases, rheumatoid disease is the most likely one to present as a case of PUO. The fever may precede arthritis for weeks, months or even years. With fever there is high ESR, altered A/G ratio, lymphadenopathy, splenomegaly, presence of the RA factor, transient rashes and so on. Transient rashes of a macular type with episodes of fever are typical and most important. Disseminated lupus erythematosis, polyarteritis nodosa and dermatomyositis usually have sufficient pathognomonic signs not to present as a case of PUO.

2. OTHERS

In children, it is often difficult to pigeon hole collagen disease into definite categories. In this group, the child has a prolonged fever (PUO) with raised ESR and altered A/G ratio, in the absence of an infection.

In both groups above, once infection can be excluded, the diagnosis of a "hypersensitivity state" is confirmed by a therapeutic test with use of corticosteroids. High doses of prednisolone 20–60 mg/day depending on age is given, and for a correct diagnosis, the temperature must come down immediately on the same day or within a day or two. The ESR begins to come down, and steroids gradually reduced.

IV. DRUGS

Indiscriminate and widespread use of antibiotics for fever often prolongs the fever. In such situations, the common tendency is to give more powerful antibiotics, without any effect on the temperature, causing considerable difficulty in diagnosis. The temperature falls by crisis when the drug is withdrawn.

V. MISCELLANEOUS

A subdural hematoma in an infant may be accompanied by fever. The fontanelle may be bulging and there are likely to be retinal hemorrhages.

Hereditary ectodermal dysplasia may be associated with fever from the early days of life. The dry skin and later the dental condition should reveal the diagnosis.

Caffey's disease in the newborn baby may be manifested by unexplained fever for 3 or 4 weeks before the characteristic swelling of the jaw and perhaps tender swellings of the tibial, due to periostitis, become obvious.

In young children with prolonged fever and history of repeated infections, agammaglobulinemia or other immunodeficiency states should be considered.

The Child with Vomiting and Diarrhoea

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INTRODUCTION

Vomiting and diarrhoea are common symptoms in children. The aetiology is legion and it would not be profitable to attempt to list all the possible causes. The more important causes are mentioned below, together with hints on how to detect organic causes and an outline of the principles of management.

VOMITING

1. THE NEWBORN INFANT

1. Irritation of gastric mucosa by material swallowed during delivery.

2. Regurgitation from overfeeding or failure to "burp" infant.

3. Obstructive lesions of the alimentary tract.

   A. **Certain diagnoses** (characteristic clinical features)

      a. Oesophageal atresia (should be diagnosed earlier!)
      b. Imperforate anus
      c. Hirschsprung's disease
      d. Duodenal atresia
      e. Jejunal and ileal atresia

   B. **Uncertain diagnoses** (no pathognomonic picture; obstruction often incomplete or intermittent)
      a. Annular pancreas
      b. Duodenal stenosis
      c. Peritoneal bands
      d. Volvulus
      e. Internal hernias
      f. Intussusception
      g. Meconium ileus
      h. Gut duplications

4. Infections including meningitis, septicemia, peritonitis.

5. Cerebral causes including subdural haematoma.

Clinical features which would make one seriously consider organic disease:

1. Persistent vomiting, as distinct from occasional vomiting.

2. Green vomitus (presence of bile in the vomitus) – should be regarded as being due to intestinal obstruction until proved otherwise.

3. Presence of blood in the vomitus.

4. Abdominal distension – suggests obstruction in lower intestinal tract.

5. Drowsiness, failure to suck well, failure to demand feeds.

6. Visible peristalsis from right to left. suggesting obstruction in the jejunum, ileum or colon.

7. The presence of a bulging fontanelle, suggesting cerebral oedema or an intracranial haemorrhage.

8. The presence of a palpable mass – meconium ileus, enlarged kidneys, reduplication of the intestine or a palpable bladder.

2. INFANCY AFTER THE NEWBORN PERIOD

A. NON-ORGANIC – eg. normal possetting, careless handling after feeds, crying, travel sickness.

B. ORGANIC — 1. Congenital pyloric stenosis
2. Intussusception or other intestinal obstruction
3. Appendicitis
4. Infections including gastroenteritis, urinary tract infection, whooping cough, otitis media, meningitis.
5. Uraemia
6. Increased intracranial pressure
7. Drugs or poisons
8. Hiatus hernia

Clinical features which would make one suspect an organic cause:

1. Sudden onset of vomiting after being previously well.
2. Child is ill or febrile in addition to vomiting.
3. Presence of other symptoms.
4. History of inadequate weight gain or loss in weight.
5. Presence of blood in the vomitus.

3. VOMITING AFTER INFANCY

A. NON-ORGANIC — eg. excitement, fear or anxiety, suggestion and irritation, attention-seeking device, insertion of finger into throat, travel sickness.

B. ORGANIC — 1. Infection e.g. tonsillitis, otitis media, meningitis, gastroenteritis
2. Appendicitis, mesenteric lymphadenitis
3. Intestinal obstruction
4. Poisons and drugs

PRINCIPLES IN MANAGEMENT

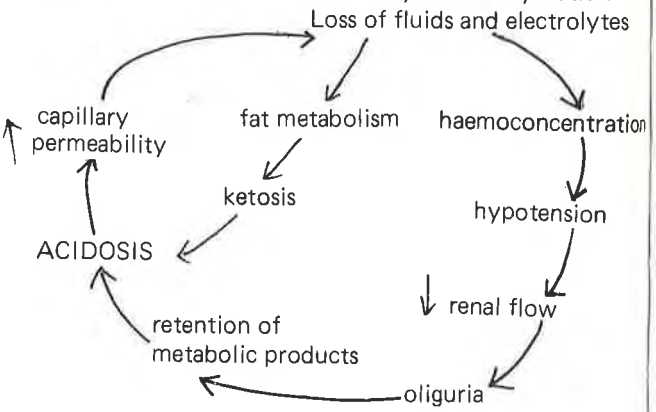
1. Treat the cause.
2. Adequate fluid and electrolyte therapy.
3. Anti-emetics are useless as well as dangerous.

DIARRHOEA

Causes of diarrhoea

1. Gastroenteritis: Bacterial, viral, fungal, protozoal.
2. Diarrhoea in association with parenteral infection: bacterial, viral (sepsis and encephalopathy should always be considered in severe diarrhoea in infants).
3. Cow's milk intolerance.
4. Carbohydrate intolerance and malabsorption.
5. Drugs.
6. Other causes: Hirschsprung's disease and other surgical lesions.
Appendicitis
Adrenal insufficiency
Ganglioneuroma, Neuroblastoma

PATHOPHYSIOLOGY: vicious cycle of dehydration



CLINICAL FEATURES OF DEHYDRATION

NO.	SIGNS	MILD	MODERATE	SEVERE
1	Fever	+	+	+++
2	Oliguria		+	+++
3	Fits	–	–	
4	Coma	–		++
5	Acidotic respiration	–		++
6	Fontanelle	N	N/	
7	Eyes	N	N	sunken
8	Skin elasticity	N	N/	
9	Skin temperature	N	N	cold and clammy
10	Skin colour	N	N	Blue or mottled

N = Normal

CLINICAL FEATURES OF DEHYDRATION

NO.	SIGNS	HYPOTONIC DEHYDRATION	HYPERTONIC DEHYDRATION
1	Temperature	Low grade	Hyperpyrexia common
2	Skin turgor & elasticity	Poor to very poor	Fair to poor. Inelastic.
3	Muscle tone	N or ↓ in presence of hypokalemia	↑
4	Eyes	Sunken and soft	Sunken
5	Fontanelle	Sunken	Sunken
6	Mucous membrane	Slightly moist to dry	Very dry
7	Mental status	Lethargy Convulsions uncommon	Hyperirritability Convulsions common

NB: An obese child may appear to be less dehydrated than he actually is.

COW'S MILK INTOLERANCE

1. Early onset of diarrhoea vomiting, often from birth or from the time of introduction of cow's milk. May present with malignant diarrhoea. (2/3 with onset at age 1 month or less, and 2/3 had onset within the first month of feeding with cow's milk)

2. Often a delay in diagnosis (due to frequent changes in brand of milk used).
(2/3 had symptoms for 2 or more weeks before admission)

3. Usually has failure to thrive on admission (probably due to delay in diagnosis). Weight was less than 2 standard deviation below the mean in 80% cases.

4. May have concomitant allergic reactions e.g. skin lesions (atopic dermatitis, urticaria), bronchial asthma.

5. Usually have family history of some allergic reaction.

6. Symptoms subside after dietary elimination of cow's milk but recur on challenge with cow's milk. Symptoms may also recur when given sobee, isomil or even dextrose saline.

7. Symptoms subside or do not recur when given human breast milk.

8. Excellent results when human milk or rice water is used in therapy.

9. Prevention: Breast feeding.
Human breast milk has a crucial role in (a) diagnosis (b) treatment (c) prevention, of cow's milk intolerance.

MALIGNANT INFANTILE DIARRHOEA

DEFINITION: Infants under the age of 3 months with chronic persistent diarrhoea and acute exacerbations, not responding to usual methods of treatment.

CLINICAL FEATURES:

1. Diarrhoea is so severe that dehydration is extreme.
2. Often has failure to thrive.
3. Minimal vomiting.
4. Stools are watery, but very often it is coloured; not bloody.
5. Stools culture: sterile.
6. Not breast fed. (It is likely that many cases of malignant infantile diarrhoea are due to cow's milk intolerance)
7. Dies of electrolyte imbalance or secondary infection e.g. aspiration pneumonia.

MANAGEMENT OF MALIGNANT DIARRHOEA

Parenteral alimentation is the key to successful treatment. Rice water very useful when starting on oral feeds.

Prevention: encourage breast feeding.

SUGAR INTOLERANCE (eg. Lactose intolerance)

1. Stools: watery
   acidic pH 5.5 with excoriation of buttocks abnormal amounts of sugar (5% reducing substances) gas ++

2. Withdrawal of offending sugar leads to improvement of symptoms.

3. Flat sugar tolerance curve after loading with offending sugar.

4. Abnormal barium studies
   a. distension of small intestine
   b. very active peristalsis with intestinal hurry
   c. very prominent haustral pattern

5. Small intestinal biopsy
   a. abnormal histology
   b. enzyme levels

PRINCIPLES IN MANAGEMENT OF DIARRHOEA

1. Proper fluid and electrolyte therapy together with adequate rest to the gut is the key to successful treatment.

2. Antibiotics are not usually indicated (except in selected cases) and often prolong the diarrhoea.

3. Do **not** give lomotil. Anti-diarrhoeal agents usually do not affect the course of the illness, and can be dangerous. There is no "magic drug" for the treatment of diarrhoea.

4. Rice water is very useful, when starting the child on oral feeds.

5. Breast feeding is a useful preventive measure.

The Child with Cough & Breathlessness

by Dr. K. Vellayappan
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Cough is the commonest symptom of recurrent and chronic respiratory disease in children. As the cough reflex is such an important defence mechanism of the respiratory tract, a thorough knowledge of its physiological basis and of the pathophysiology in respiratory disease is essential in diagnosis and management.

Function of coughing

1. Expulsion of food, particulate and foreign matter which may be accidentally inhaled.
2. Removal of excess secretion or exudate from the airways. Ciliary action is very effective in keeping the airways clean, the mucous sheet being constantly swept up the airways to the glottis and into the pharynx where it is then swallowed. However, if the cilia are injured or destroyed, as frequently occurs in acute and chronic infections of the airways, or if there is excessive secretion as in asthma, then effective coughing becomes very important in its removal. Failure to keep the airways clear of secretion or exudate leads to airway obstruction, pulmonary collapse and subsequent infection, with progressive destruction inflammatory changes in the airways and parenchymatous tissue.

The Cough Reflex

Coughing consists of an explosive blast of gas expelled at high veolocity through the glottis. The normal sequence of events is a deep inspiration followed by a sudden forcible expiration with synchronous closure of glottis and rapid release of gas by sudden opening of the glottis 0.2 seconds later. An effective cough depends on the integration and normal function of the following components which make up the reflex ARC.

Afferent Components

Sensory neurofibrils, which are situated between the ciliated columnar epithelial cells, occur throughout the airways but are concentrated within the larynx, posterior wall of the trachea and carinae of large and medium sized bronchi. They send afferent messages via vagus to brain stem and pons. These receptors are sensitive to mechanical stimulation from touch or foreign substances, to irritation from inflammation, to pressure from tumours or glands either within or without the bronchial tree, and to chemical irritation from noxious gases.

Efferent Components

Efferent impulses travel via the vagus and spinal nerves from C3 to S2 to the larynx, thoracic muscles, diaphragm, abdominal wall and pelvic floor. During coughing sudden FORCIBLE co-ordinated contraction of these muscles results in rapid elevation of intrathoracic pressure. The larynx is initially closed for 0.2 secs. and then suddenly opens as the pressure in the airway rises.

It is important to appreciate that the cough reflex is under voluntary control and may be either inhibited or initiated at will. Voluntary inhibition of coughing may prevent effective cleaning of the bronchial tree of excess secretion and cerebral stimulation may be responsible for nervous coughing.

Inadequacies or Failure of the Cough Mechanism

The sensitive nerve endings in the larynx and airways may become unresponsive to repeated stimuli. Some infants who repeatedly inhale mucus may have minimal or ineffective cough. A child with an inhaled foreign body may have minimal cough after 24–48 hours.

The co-ordinating centre in the brain stem may be depressed due to circulatory toxins or drugs, to mechanical pressure or disturbed circulation from brain lesions so that coughing becomes weak and ineffectual.

The co-ordinating cough centre in the brain

stem may be voluntarily suppressed with resulting retention of secretions in the airways and infection. Often children with suppurating lung disease partially suppress coughing, as they find it embarrassing. The expiratory driving force may become weak and ineffective due to impairment of whole or part of the neuromuscular system. A debilitated infant or sick premature baby, a child with muscular dystrophy or a painful chest or abdomen following an operation cannot cough effectively.

The Child with Cough and Breathlessness

Bronchiolitis

This is the commonest serious acute lower respiratory infection infants. Affected infants are usually between the ages of one and six months but the disease occurs up to the age of 2 years. Respiratory syncytial virus is the cause in approximately 80% of patients but other viruses – parainfluenza, Rhinovirus and influenza A_2 – can cause a similar illness. The inflammation typically affects bronchioles of calibre from 300 um down to 75 um. The bronchiolar epithelium is colonised by the virus with resultant necrosis and destruction of ciliated epithelial cells. Secretions of mucus is enhanced and this together with dense plugs of desquamated epithelial cells blocks the bronchiolar lumen. There is usually impairment of gas exchange with hypoxia and hypercapnia.

The illness typically begins with coryza. Over 1–2 days the infant develops an irritating cough, distressed rapid wheezy breathing and may have difficulty feeding. He is usually not toxic and the temperature is rarely higher than 38.5°C. The chest is barrel-shaped as a result of hyperinflation of the lungs and the liver is displaced as a result of this. On auscultation, widespread fine crepitations are heard towards the end of inspiration reflecting opening of partially obstructed bronchioles. As the disease progresses, gas exchange may be impaired. Respiratory failure develops in 1–2% of patients. A chest X-ray shows marked hyperinflation of the lungs with depression of the diaphragm.

Management primarily consists of good nursing care and avoidance of all unnecessary disturbance and handling.

If the baby is unable to feed orally, fluids should be given by either an intragastric tube or intravenously. Oxygen is administered and the concentration varies from 40% to 70% usually. Approximately 1–2% of patients may need assisted ventilation. Usually antibiotics are not necessary but in very sick infants these may have to be given for fear of secondary bacterial infection.

Acute Pneumonia

It is a common disease in infants but relatively less frequent in older children.

Classification

Viral	–	Respiratory syncytial virus
		Parainfluenza 1, 2 and 3
		Influenza A1, A2 and B
		Mycoplasma pneumonia
Bacterial	–	Pneumococcal
		Staphylococcus aureus
		B haemolytic streptococcus
		Haemophilus Influenza B
		Gram negative organisms

Prior to identification of respiratory viruses and delineation of their importance and role in respiratory disease, the aetiology of pneumonia was considered to be primarily bacterial. Respiratory syncytial virus, parainfluenza virus, and influenza virus are responsible for majority of pneumonias in infants and young children.

General Clinical Features

Common clinical pattern of pneumonia is sudden onset of fever, malaise, rapid breathing and cough in an infant or child who has been off colour for a day or more. There is usually moderate or severe constitutional disturbance while the degrees of respiratory distress depends on the extent of pulmonary involvement. Clinically the physical signs of consolidation may be difficult to detect especially in infants unless the area of lung involved is extensive. A CXR is therefore of considerable value in establishing a diagnosis, especially in the early stages of illness.

Mycoplasma, pneumoniae pneumonia

It is a frequent cause of pneumonia in children aged 5–15 years. The disease often runs in families and the incubation period may be up to three weeks. The onset is usually insidious with constitutional symptoms of malaise, anorexia, severe headache, fever and sore throat. A non-productive paroxysmal cough develops a few days after the onset of symptoms. Later the cough may result in the production of mucoid sputum which later may become blood tinged. Chest pain often occurs. Abnormalities on physical examination of the chest are relatively minor. A chest X-ray reveals patchy consolidation usually unilateral and more frequently

involves the liver than the upper lobes. Erythromycin or tetracycline should be the initial antibiotic therapy.

Bacterial Pneumonias

Pneumococcal pneumonia

Pneumococcus is the commonest cause of bacterial pneumonia. It is frequent in children aged 3–8 years. In infants and very young children, the lesions are usually lobular and give rise to a bronchopneumonic pattern, but in pre-school and school child, lesions are frequently segmented or lobar in distribution. Pleurisy with serious effusion is relatively common in seriously affected children but rarely progresses to empyema. Resolution of the pneumonia lesion is almost always rapid and complete. Even with severe infective destructive changes residual bronchiectasis and fibrosis are rare.

Staphylococcal pneumonia

Staphylococcal pneumonia is of considerable importance as the patients are frequently severely ill and complications especially empyema are common. It usually affects infants under 2 years of age but also occurs in older children. Malnutrition, hospital environments, prematurity and underlying disease are predisposing factors.

Streptococcal pneumonia

This is much less frequent than pneumococcal or staphyloccal pneumonia and is caused by beta-haemolytic streptococci Group A.

Pneumonia due to other Gram Negative Organisms

Pneumonia due to gram negative organisms is seen mainly in neonates and infants with debilitating conditions who have been in hospital for prolonged periods. E. coli, Pseudomonas aeruginosa, Klebsiella and Proteus are important pathogenic organisms. The onset of these infections is usually insidious and constitutional symptoms are often more marked than respiratory ones.

Diagnosis

Three important assessments should be made in all children. The severity of the illness, the degree of physiological disturbance and the probable aetiological diagnosis. The severity of the illness is measured by the degree of prostration, of circulatory disturbance and respiratory embarrassment. A limp semi-conscious child with rapid shallow grunting breathing, who is pale and slightly cyanosed is dangerously ill while a crying flushed infant with a temperature of 40°C and rapid vigorous respiration is not. The state of hydration should be assessed clinically in all patients and base balance and Pa02 measured in those who are seriously ill.

The aetiological diagnosis on clinical and laboratory grounds is extremely difficult except in a few specific instances. A white cell count is usually not helpful in distinguishing between viral and bacterial pneumonias. In some viral infections there can be marked neutrophil leucocytosis. However, the presence of many band forms and toxic granulation is suggestive of bacterial infection.

However, the final determinant of aetiology rests on culture or identification of the virus or bacteria. Culture of the nose and throat for pathogenic bacteria is not very helpful as healthy control children show similar flora. However, in staphylococcal pneumonia there is very good agreement with the type isolated from the nasopharynx and the pleural fluid. Isolation of respiratory virus such as respiratory syncytial, parainfluenza and influenza from the throat swab or nasopharyngeal aspirates almost established the diagnosis.

Management

General measures

Most infants and young children with pneumonia require admission to hospital but the mild cases may be treated at home. Adequate hydration is important and the fluid is usually administered intravenously as this also allows antibiotics to be given. Infants in respiratory distress should be nursed in an oxygen cot. Older children can receive oxygen by face mask. Gentle aspiration of nasopharyngeal secretions is often of considerable value. High fever is best controlled with paracetamol and tepid sponging. Sedatives for restlessness are contraindicated and cough suppressants should not be used.

Antibiotic therapy

Streptococcus, pneumococcus – Penicillin
Staphylococcus aureus – Methicillin
Haemophilus Influenza – Ampicillin
Mycoplasma pneumonia – Erythromycin, tetracycline

Gram negative organism – Gentamycin

In a sick infant, it is best to start with intravenous Gentamycin and Cloxacillin initially. In older children, Penicillin is the drug of choice. However if clinical features suggest mycoplasma pneumonia, Erythromycin or tetracycline should be the initial antibiotic therapy.

Bronchial asthma

A disease characterised by an increased responsiveness of the trachea and bronchi to various stimuli and made manifest by difficulty in breathing due to generalised narrowing of the airways. This narrowing is dynamic and changes in degrees, either spontaneously or as a result of therapy.

The spectrum of asthma (McNicol & Williams 1973)

Grade A – Children with no more than 5 attacks, usually commenced wheezing after 3 years and ceased before 8 years.

Grade B – Mild episodic asthma, usually 3–4 attacks/year with spontaneous remission by 12 years of age.

Grade C – Attacks usually commenced before 2 years of age. Attacks were severe and prolonged and majority of these patients had evidence of airway obstruction in between episodes.

Grade D – Very severe end of the spectrum.

Groups A and B comprised 75% of the asthmatic population. The severity of asthma showed significant correlations with the age of onset, physical growth and airway obstruction as assessed by rhonchi, barrel and pigeon chest deformity, and spirometry (FEV1/Vc ratio).

The Immunological concept of asthma

Allergen + Reagin (IgE) (dust mite) pollens drugs animal furs & danders foods	● Histamine ● SRS – A ● Serotonin ● Kinins	muscle spasm & inflammation in bronchus

However, there are also a number of non-allergenic factors which precipitated asthma. Respiratory viral infection, emotional stress, exercise, coughing and laughing, changes of air temperature, inhaled chemical fumes and other non-allergenic irritants may all be responsible for attacks of asthma.

B adrenergic receptor blockade theory

The tone of the muscle of the bronchial tree is influenced by catecholamines, those affecting alpha receptors induce bronchial constriction, those affecting beta receptors bronchial relaxation. It is postulated that asthmatic subjects have partial B adrenergic receptor blockade due to inherited or acquired deficiency of the enzyme adrenyl cyclase.

But these theories are inadequate to explain the way suggestion or emotional stress can promptly precipitate an attack of asthma. Neither can it explain the prompt relief that can be obtained by suggestion or relief of the emotional stress. Direct nervous control through the central nervous system almost certainly is involved.

Severe attack of asthma

The child will be extremely breathless. He may be too dyspnoeic to speak or can only speak in monosyllabic speech. A pulse rate of 130/min in the absence of fever and pulsus paradoxus are indicative of a severe attack. Cyanosis, if present, indicates a severe attack. But the child is dehydrated and drowsy and if on auscultation there is hardly any air entry, then the child needs intensive care.

Management of asthma

Treatment of acute severe attack:

1. Hospitalisation
2. Hydration I/V fluids 1½–2 x required amount
3. Ventolin nebuliser; to be repeated every 4 hours if necessary
4. I/V aminophylline slowly 3–4 mg/kg/dose to be repeated 6-hourly if necessary
5. If seriously ill, and/or has received prednisolone before I/V hydrocortisone at a dose of 4 mg/kg
6. ±Antibiotics
7. Physiotherapy
8. Oxygen by face mask

Long-term management

1. avoidance of triggers
2. breathing exercises/physiotherapy
3. education of parents
4. games
5. drugs – Becotide, Intal, prednisolone
6. hyposensitisation
7. psychotherapy

Foreign Bodies

80% of patients are under the age of 4 years. Peanuts, other edible nuts, watermelon seeds,

food material, pins and coins are usually the particles inhaled. Most inhaled foreign bodies lodge in a main or stem bronchus, the (R) side being more commonly involved than the (L). A small number of sharp foreign bodies lodge in the larynx and produce symptoms of acute laryngeal obstruction.

Acute presentation

Diagnosis is usually not difficult in children presenting soon after the inhalation episode. In addition to the story of inhalation, the child usually has a wheeze and less commonly an irritating cough. In some children inhalation is not witnessed, a foreign body should be suspected in any young child with sudden onset of wheezing if he has not wheezed previously. On clinical examination there are diminished breath sounds over part or whole of one lung. Obstructive hyperinflation is much commoner than segmental or lobar collapse.

Delayed presentation

Delay in diagnosis could be due to the parents failing to realise the importance of their child coughing and choking when eating and resting. Consultation at a later date or to the doctor being not aware that the child's respiratory symptoms could be due to inhalation of a foreign body.

Clinical patterns

(i) wheezy bronchitis
(ii) failed resolution of acute respiratory infection
(iii) chronic cough and haemoptysis
(iv) chronic cough and lung collapse
(v) respiratory failure

Radiological investigation

A few foreign bodies are radioopaque but they are the exception. In most patients bronchial obstruction is suggested by hyperinflation and collapse. Films taken during full expiration and inspiration as well as screening the chest may be necessary to establish evidence of partial or complete bronchial obstruction.

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Mummy, I have a Tummy-Ache

by Dr. V. P. Nair
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Abdominal pain is one of the most common and yet one of the most difficult problem to evaluate, as about ninety five percent of it is the tell tale of an emotional problem.

"After forty years of extensive experience, I still approach the acutely painful abdomen with apprehension and a great feeling of uncertainty than any other domain of childhood."

These golden words of Joseph Brennemann of Chicago applies to every doctor irrespective of whether he is a General Practitioner, Paediatrician, Abdominal Surgeon or Internist, when dealing with a child who presents with a tummy-ache. Abdominal pain is one of the most common and yet one of the most difficult problem to evaluate correctly, as about 95 percent of it is the tell tale of an underlying emotional distress; whereas only five to ten percent has an organic cause to account for. The matter is further complicated by the difficulty in interpreting young children who cannot help much to provide a relevant history or to co-operate enough for a proper physical examination. To the parent any tummy ache is serious until evaluated and reassured by the doctor after excluding an organic cause by way of physical examination and relevant investigations.

Most of the emotional type of abdominal pain of childhood is vaguely localised around the umbilicus and is often erratic in the presentation and inconsistent in duration or site. The absence of an organic cause and the association of obvious emotional factors such as reluctancy about going to school, reduced peer activities or evidence of hyperactivity of the autonomic nervous system supports a psychosomatic basis for the pain. These children are often over-protected by their parents or grandparents, being the only boy or girl of a large family, the first born of an elderly couple or a delicate darling of the house. The parents themselves may be inadequate, incompetent, immature or nervous.

I FUNCTIONAL CAUSES OF TUMMY-ACHES

1. PERIODIC SYNDROME – Sometimes also known as cyclical vomiting or abdominal migraine – is characterised by acute central abdominal pain associated with vomiting and often headache or fever, the acute illness lasting about one to three days in each cycle.

2. RECURRENT PAINS OF CHILDHOOD – The abdominal pain is often associated with headache and pain in the extremities. The pattern of the symptoms remains constant for each child.

3. EXCESSIVE WIND or aerophagy may cause vomitting, distension and abdominal pain.

4. EVENING COLIC – Found within a week or two of birth with abdominal pain, occurring mainly in the evening causing the babe to be restless and at times screaming for a few minutes is probably due to air being locked up in a loop of bowel.

II ORGANIC CAUSES OF ABDOMINAL PAIN

The important disease processes causing abdominal pain are:

1 Renal – Urinary Tract Infections, pyelonephritis, hydronephrosis.

2 Respiratory – Recurrent Upper Respiratory Tract Infection, lower lobar pneumonia, pleurisy and asthmatic attacks.

3 Alimentary Tract – Pain from vomiting or gastro-enteritis, discomfort of constipation, mesenteric adenitis, intestinal obstruction due to intussuception, volvulus, atresia or incarcerated hernia, acute appendicitis, acute peritonitis, Hirschsprings' disease and worms like ascariasis and giardiasis.

INVESTIGATIONS:

Full blood count, ESR, microscopic examination and culture of the urine, stool for ova, parasite and occult blood, plain x-ray of the chest and abdomen and on special occasions contrast radiography of the renal, gastro-intestinal or biliary tract as well as urine for porphyrins, sickling test, blood lead level, mantoux test and careful exclusion of milk from diet may be needed to boost the morale of the doctor and to satisfy the ego of the concerned parent.

MANAGEMENT:

When organic causes have been excluded or dealt with accordingly and evidence supports an emotional basis, treatment consist of reassurance and exploration to gain access into the underlying problem so as to break the vicious cycle. A few may respond to mild sedation or anticholinergics such as Infacol (dicyclomine). If the pain is interfering with the activities of the child or has become the focus of anxiety in the life of the family, hospitalisation may be considered. The temporary removal of the child from the circle of anxiety at home may be of therapeutic value by itself; but relapses are not infrequent.

FAMILY INTERVIEW, A NEW DIMENSION IN THERAPY –

Recently the value of family interview has come to limelight. The aims of such a planned programme are as follows:

The first aim is to establish a rapport between the child, the entire family and the doctor, to gain mutual trust, to understand the crux of the problem and to chalk out a therapeutic programme, Avoid blaming the child by deliberately keeping away from phrases such as "pain is in the head", "put up" or "psychogenic" as these are hard pills for the concerned parent to swallow.

In the second part of the plan, the doctor should re-define the problem by demonstrating the negative results of the clinical examination and the chemical tests, thereby changing the attention of the family away from the disease orientated thinking. Terms like stress and tension may be used as they are pleasant and more likely to produce desirable results.

The third phase involves the formulation of a therapeutic regime based on the active participation of the child and the parents in a mutually agreeable atmosphere. The child will learn the best way to deal with the underlying stress, become more self-reliant and thus be able to cope with the situation. Now onwards the child will be able to adapt to normal activities without interfering with his normal behaviour like school going, home work or play.

- Establish a rapport between the child, the entire family and the physician.
- Re-define the problem by pointing out the negative results of clinical impressions and laboratory tests.
- Formulate a therapeutic programme based on the active participation of the child and the parents in a mutually understandable way.

The final phase which may not be necessary at all involve the question of, if and when, to refer the child to a child psychiatrist. Such a referral may be needed if delusions, hallucinations or depression suggest a psychotic disorder or when symptoms continue despite repeated family interviews.

CONCLUSION:

Long term follow up of these children over a decade by the Philadelphian family physicians and paediatricians has proved beyond doubt the efficacy of informal psychotherapy by non-psychiatrists in alleviating the hitherto unresolved problem of the grumbling tummy aches. These children were able to cope well with their symptoms and were able to continue activities at home and school in a normal way. Drugs, hospitalisation or formal psychotherapy was unnecessary in the vast majority.

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Preliminary Observation in the use of Beta-Blockers in General Practice

by Moti H. Vaswani
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Synopsis

Although primarily used for treating ischaemic heart disease, the number, types and uses of beta-adrenergic blocking drugs (beta-blockers) have proliferated over the past decade. The experience gained in using beta-blockers in a general practice over an eighteen-month period is reviewed.

Twenty patients receiving beta-blockers for a variety of different clinical conditions were studied. Nine of them were hypertensives, four had ischaemic heart disease, four had thyrotoxicosis, one had ventricular extrasystoles, one suffered from migraine and the last patient had anxiety symptoms.

Significant improvement was noted in all treated patients. A few side effects – notably cold extremities, nightmares and drowsiness were reported but they were not serious nor sufficiently objectionable to require cessation of therapy.

Introduction

With a wealth of beta-blockers commercially available, the General Practitioner is often faced with the difficult task in deciding on the usage of these therapeutic agents in the treatment of a wide variety of clinical conditions, the choice of the appropriate beta-blocker in a particular clinical condition and the cost-factor (See Table I) in their prescription against the background that beta-blockers are relatively "new" drugs and hence have potentially unknown and as yet unrecognised adverse effects with prolonged usage. The hitherto unrecognised serious adverse effects of Practolol came to light only recently. Therefore the decision to prescribe a "newer" but relatively more expensive antihypertensive drug e.g. the beta-blocker instead of the use of an "older" and cheaper as well as better documented antihypertensive agent cannot be made simply on the basis that "beta-blockers are the drugs of choice for most hypertensives who are free from heart failure and asthma."[1]

Clinical Material & Methods

The betablockers employed in this study were propanolol, timolol and acebutalol. The last-named drug, a cardioselective betablocker, was given to patients with a history of bronchospasm.

Twenty patients with six clinical conditions met often in general practice were treated with one of the three betablockers mentioned above. (See Table II). They were seen regularly for eighteen months firstly to ascertain if the use of beta-blockers was beneficial to the conditions for which they were prescribed, secondly whether local patients experienced similar side effects reported with their usage and lastly whether they enjoyed patient-acceptability from the point of view of cost and tolerance.

Observation and Results

Hypertension

Three of the nine cases of hypertension were on beta-blocker alone, one was on propanolol with debrisoquine, while the other five had adjuvant therapy together with the beta-blocker. In 4 cases a thiazide diuretic was given together with the betablocker and in one case a diuretic and a vasodilator were additionally prescribed. A diuretic was usually added to reduce the dosage of beta-blocker and thereby the incidence of side-effects of beta-blockade.

The blood pressure was controlled in one to three weeks after treatment was instituted, and the average daily dosage of beta-blocker used (divided into two daily doses) was 10 mg. for timolol, 80 mg. for propanolol (in one case, only 20 mg. was used together with 20 mg. debrisoquine daily), and 200 mg. for acebutolol.

Ischaemic Heart Disease

The 4 patients with ischaemic heart disease included one who had both ischaemic heart disease and hypertension. Guanethidine was initially used for this patient's hypertension, but substituted with acebutolol when she (a known asthmatic) subsequently developed angina pectoris. Propanolol was used in the other 3 patients.

In 3 of these patients, the subjective clinical improvement was accompanied by improved ECG tracings. The dose of propanolol required was 40–160 mg. three times a day, and that of acebutolol 100 mg. three times a day.

Thyrotoxicosis

In the treatment of thyrotoxicosis, propanolol was used as adjuvant therapy for the control of tachycardia, tremors and sweating in 4 patients. The beta-blocker was gradually withdrawn as the patient's toxic state came under control with neomercazole and these features disappeared. The dose of propanolol required was 30–120 mg. daily, divided into three doses. In one patient with a history of sweaty palms for a few years before he developed the clinical picture of thyrotoxicosis, propanolol failed to relieve this symptom.

Tachy-arrhythmias, migraine and anxiety

Propanolol was also used in the treatment of one patient with ventricular extrasystoles, one with migraine and one with anxiety. The patient with extrasystoles was put on 60 mg. propanolol daily for 3 months, during which the extra beats disappeared altogether. After he had been taken off the beta-blocker, he experienced only occasional and short-lasting attacks. In the patient with migraine, the prescription of propanolol 60 mg. daily cut down drastically the frequency of her severe headaches. The patient with anxiety although presenting with palpitations, tachycardia and excessive sweating had a normal thyroid status. He was completely relieved of his symptoms with 20 mg. propanolol three times a day.

Side-effects reported

The single most common side-effect recorded in these 20 patients was the complaint of cold extremities. One patient complained of having nightmares, and another of drowsiness and 'heaviness in the head'. Cold extremities were recorded in 2 out of 4 patients on acebutolol, in only 1 of the 13 patients on propanolol, and in none of those given timolol.

One patient with no previous history of

Table I: Pharmacological properties, prices and average dosages of the different beta-blockers.

Beta-blocker	Trade Name	Intrinsic sympatho-mimetic activity	Membrane stabilising activity	Tablet/Capsule size and List Price[1]		Average daily maintenance dose in mg.
CARDIO – SELECTIVE AGENTS						
Acebutolol	Sectral	+	+	100mg	28¢	100 – 600
Atenolol	Tenormin*	o	o	–	–	50 – 400
Metoprolol	Betaloc Lopresor*	o	±	100mg	57¢	50 – 400
Practolol**	Eraldin	++	o	–	–	100 – 800
NON – SELECTIVE AGENTS						
Alprenolol	Aptin	++	+	50mg 200mg	20¢ 28¢	50 – 300
Oxprenolol	Trasicor	++	+	20mg 80mg	14¢ 36¢	40 – 320
Prindolol	Visken	+++	+	5mg	27¢	5 – 30
Propanolol	Inderal	o	++	10mg 40mg 80mg	9¢ 23¢ 32¢	40 – 320
Sotalol	Sotacor Betacardone	o	o	40mg 80mg	20¢ 41¢	40 – 320
Timolol	Blocadren	±	o	10mg	37¢	5 – 20

* Not available yet in Singapore

** Practolol (Eraldin) tablets have been withdrawn since 1975 after reports of unacceptable incidence of serious adverse oculo-muco-cutaneous reactions

1 Prices as at July 1977

Table II: Clinical conditions treated with beta-blockers in the 20 patients

Clinical Conditions	Number of cases	Beta-Blocker Used		
		Propanolol	Acebutolol	Timolol
Hypertension	9	3	3	3
Ischaemic Heart Disease	4	3	1	–
Cardiac tachy-arrhythmias	1	1	–	–
Thyrotoxicosis	4	4	–	–
Migraine	1	1	–	–
Anxiety	1	1	–	–

bronchospasm who was put on propanolol for hypertension developed a persistent cough without wheezing or rhonchi. The cough disappeared when propanolol was replaced by acebutolol.

The author has had no experience with the intra-venous use of beta-blockers.

DISCUSSION

Ahlquist first defined in 1948 two types of adrenergic receptors which he termed alpha (α) and beta (β). Those receptors with the highest sensitivity to norepinephrine and the lowest sensitivity to isoproterenol were called α–receptors, and those with the reverse pattern of sensitivity were called β–receptors.

All α–adrenoceptors respond equally to norepinephrine and are blocked equally by ergot and other similar agents. However, the degree of response of β–adrenoceptors to agonists and antagonists varies considerably, so that such receptors have been sub-divided into β_1–receptors in cardiac, intestinal and adipose tissue, and β_2–receptors in bronchial, and vascular smooth muscle and those involved in glycogenolysis.

Beta-blockers antagonise the pharmacological stimulatory effects of catecholamines at these sites by competitive inhibition – i.e., the block can be overcome by increasing the concentration of the agonist.

Dichloroisoproterenol, the first specific β–adrenoceptor–blocking drug, was described in 1957 by Slater and Powell. However, it was later found to be of no clinical value because of its intrinsic sympathomimetic activity (see below).

The hypotensive effect of another beta-blocker, pronethalol, was reported by Prichard in 1964. This was soon followed by the development of propanolol by Black and his team. It soon became apparent that beta-blockers were useful in many other clinical situations besides hypertension and ischaemic heart disease.

1. **Selectivity**

The division of beta-blockers into the cardio-selective ones, inhibiting only the effect of isoprenaline on the β_1–receptors in the heart, and the non-selective ones, which also block the β_2–receptors in lung and vascular smooth muscle, is **not** absolute, and the 'cardio-selective' ones **can** inhibit the vascular and bronchial sites when the concentration of drug is high enough.[1]

The highly selective β_1–blockers have advantages over the other agents for use in subjects prone to hypoglycaemia – in diabetics, during starvation or during anaesthesia.[2,3,4]

2. **Pharmacokinetics**

All the beta-blockers are fairly rapidly absorbed from the gut, with absorption probably less in the elderly and in patients in renal failure. The bioavailability of beta-blockers given orally, however, varies between 10% (with alprenolol and propanolol) and 100% (with practolol and prindolol) depending upon the extent of "first-pass" extraction by the liver.

Most beta-blockers have a plasma half-life of 2 to 6 hours, but acebutolol, sotalol and practolol have plasma lives of up to 14 hours because they are excreted largely unchanged in the urine. Therefore they may be given twice or even once daily. Propanolol is effective longer than its plasma half-life because it has pharmacologically active metabolites with a much longer half-life.[5]

The general practitioner must bear in mind that propanolol, alprenolol and metoprolol are eliminated almost entirely by hepatic metabolism, practolol solely and sotalol mainly by renal mechanisms, while the others are eliminated by both routes. Thus in uraemia, when hepatic metabolism is also decreased, the dose of propanolol may need to be reduced.

3. **Intrinsic Sympathomimetic Activity (partial agonist activity).**
Paradoxically, some beta-blockers, while antagonising the action of catecholamines on β –adrenoceptors, may exhibit a degree of agonist (stimulatory) activity at the receptor site. Such beta-blockers include acebutolol, alprenolol, oxprenolol, prindolol and practolol. Atenolol, metoprolol, propanolol and sotalol have no such activity, and thus slow the pulse rate more, decrease the cardiac output more, and have a greater effect on renin levels, making them most suitable for use in the control of the hyperkinetic and circulatory features of anxiety, migraine and hyperthyroidism. However, the action of propanolol on the peripheral vascular receptors is said to be greater than that of the other agents[6], and there seems to be some literature preference for this drug.

4. **Membrane Stabilising Activity (quinidine-like or local anaesthetic activity)**
Beta-blockers with this property – propanolol, oxprenolol, alprenolol, acebutolol and prindolol – reduce the rate of rise of the cardiac action potential without affecting the resting potential or causing any significant prolongation of the duration of the action potential[7]. However, there is no evidence that this property confers any special advantage in the usual therapeutic doses.

5. **Use of Beta-Blockers in General Practice**
i) **Hypertension**
The therapeutic value of beta-blockade in the treatment of hypertension has been extensively documented, and beta-blockers are often the treatment of first choice. They are especially indicated in patients with associated angina, cardiac dysrhythmias or migraine, and in those in whom the blood pressure has been controlled only at the expense of serious side-effects. Blood pressure reduction is achieved by decrease in heart rate, in force of contraction of the myocardial fibres, and in cardiac output, and probably also by a central effect and by inhibition of the release of renin by the kidneys[8]. There is some evidence to suggest that hypertensive patients with elevated plasma renin respond better to treatment with beta-blockers than those with normal plasma renin levels[9], but this has not been universally accepted.
The anti-hypertensive effectiveness of these agents does not differ with the presence or absence of intrinsic stimulating effects on heart rate; cardio-selectivity likewise does not seem to enhance blood pressure lowering activity[10].
The reduction in blood pressure is directly related to the dose of beta-blocker drug – the higher the dose, the greater the decrease in blood pressure. In patients resistant to one beta-blocker, changing to another usually does not help. However, such change may be worthwhile when a dose-limiting side-effect occurs.
Obviously the beta-blockers possess great therapeutic advantage over other anti-hypertensives. They control both supine and erect blood pressure effectively. Dosage also is relatively simple – twice or even once daily. Side-effects such as postural hypotension and sexual difficulties are relatively absent. The absence of the development of tolerance, unlike other anti-hypertensive drugs, is an added advantage. Beta-blockers also suppress the pressor response to stress and exercise, and protect the myocardium from sympathetic stimulation, thus helping to prevent the cardiac consequences of hypertensive vascular disease. It has also been suggested[11] that treatment of hypertension with beta-blockers may reduce the incidence of sudden deaths and deaths from coronary artery disease.
The dosage of beta-blockers used alone for hypertension may have to be very high (e.g. up to 2–3 gm. of propanolol daily). Because of this, and also due to the high cost involved, they are more often used in combination with other anti-hypertensive agents such as diuretics, vasodilators or sympathetic blocking drugs. The addition of a vasodilator is favoured whenever the patient complains of cold extremities as a side-effect of beta-blockade. The combination of beta-blocker, diuretic and vasodilator seems to be the most widely recommended.
Although the duration of action of beta-blockers has been shown by pharmacological experiments to be only for a few hours, they appear to have a prolonged hypotensive effect with continued medication. Thus a twice-daily dosage regimen

for most beta-blockers has been found satisfactory in the treatment of hypertension, although for atenolol, once-daily dosage has been suggested[12]. However, if ischaemic heart disease or arrhythmias are also present, these regimens will probably not be sufficient. Beta-blockers usually are effective maximally in a week or two, so dosage should be adjusted at weekly or two-weekly intervals.

ii) **Ischaemic Heart Disease**

Beta-blockers have replaced the use of long-acting nitrates in the prevention of attacks of angina pectoris. They reduce relative myocardial ischaemia in patients with ischaemic heart disease by reducing the heart rate and by modifying the circulatory response to exercise, thus reducing myocardial oxygen consumption and greatly improving the exercise tolerance of angina in such patients. It seems that all the available beta-blockers are equally effective in the relief of pain in angina; the absence or presence of properties like intrinsic sympathomimetic activity, membrane stabilising activity or cardio-selectivity does not influence their anti-anginal effect.

Large doses are usually required to control the symptoms (e.g. up to 480 mg. propanolol daily), with the daily dose being divided into 3 or 4 doses. In one case in the present series, a total dose of 480 mg. propanolol daily had to be used for the treatment of intractable angina. Beta-blockers are usually effective when combined with digitalis, when the latter has failed to control the angina induced by paroxysmal tachycardia, flutter or fibrillation.

The use of beta-blockers in angina helps reduce the amounts of other drugs (glyceryl trinitrate or isosorbide) taken to reduce the pain of angina, and are particularly effective in patients with emotionally-induced angina or those with high plasma lipids.

In the treatment of acute myocardial infarction, beta-blockers may be useful in decreasing the final size of the infarct. The usefulness of beta-blockers prophylactically after a myocardial infarction to decrease the incidence of re-infarction[13] and sudden death[14] has also been documented, although the mechanism of this beneficial effect is yet unknown.

iii) **Cardiac arrhythmias**

Propanolol has become the treatment of choice for paroxysmal tachycardia, and is also used in the treatment and prevention of extrasystoles and atrial fibrillation, although the different beta-blockers all probably have similar anti-arrhythmic potencies. Beta-blockers are less useful in the treatment of ventricular arrhythmias. They are especially useful in arrhythmias due to digitalis toxicity, arrhythmias induced by exercise or emotion, and in the Wolff-Parkinson-White Syndrome.

Beta-blockers act by slowing the rate of sinus or ectopic discharge, increasing the functional refractory period of the A-V node, and by retarding conduction in anomalous pathways in the heart[15]. This anti-arrhythmic effect of beta-blockers may be partly due to what is called the 'membrane stabilising effect' of these compounds.

By the reduction of the frequency of ectopic beats, and the suppression of arrhythmias and ventricular fibrillation in patients with coronary artery disease, beta-blockers may be helpful in prolonging life expectancy in such patients.

iv) **Thyrotoxicosis**

Beta-blockers without partial agonist activity, especially propanolol, have proved very helpful in adjuvant therapy, besides anti-thyroid drugs or radio-iodine, in the control of hyperkinetic features of thyrotoxicosis such as tachycardia, tremors, arrhythmias, sweating, diarrhoea, etc.

Although they do not actually help remission and are therefore not very useful in the long-term management[16], they have proved very suitable for short-term management (helping to improve thyrotoxic symptoms before other conventional remedies have had time to act), and especially in the preparation for thyroidectomy, or the protection of a thyrotoxic patient during urgent non-thyroidal surgery, or during thyrotoxic crisis, where beta-blockade improves the prognosis considerably. The use of beta-

blockers in the treatment of hypercalcaemia in hyperthyroidism, in the treatment of neonatal hyperthyroidism and upper motor neurone signs in hyperthyroidism, and in the prevention of periodic paralysis in hyperthyroidism has also been suggested.

v) **Migraine**

It has been proven that propanolol is highly effective in the prophylactic treatment of both classical and common migraine[6]. The beneficial effect of beta-blockers in migraine is probably due to inhibition of peripheral (including extracranial) vasodilatation. However, the effective dose is not known, 40–60 mg. daily being probably effective. The compounds with partial agonist activity show no beneficial effect in migraine.

vi) **Anxiety and Stress**

Beta-blockers do not directly alleviate anxiety, but relief of the somatic manifestations of anxiety and metal stress may be effected[17], thus interrupting a feed-back loop which would otherwise perpetuate the anxiety. However, the possibility of propanolol also having a central action, other than that of sedation, which may or may not contribute to its anxiolytic effects, cannot yet be totally excluded[18]. The lack of sedative effects is an advantage of beta-blockers over the traditional anxiolytics, while the fact that they do not induce physical or psychological dependence is another.

There is probably little to choose between the various agents available[19]. However, the need for peripheral blockade of such widely-distributed sympathetically-mediated symptoms would point to the non-selective compounds, especially propanolol, as the most appropriate for this purpose. The dose of propanolol varies from 60 to 240 mg. daily, and it can be combined with centrally-acting sedatives such as diazepam.

It has also been suggested that beta-blockers be used for the attenuation of the physiological consequences of normal stress, e.g. ski-jumping or motorcar-racing[20], or for the protection of persons at risk (e.g. the coronary artery diseased) from the effects of sympathetic over-activity caused by stress.

There have also been reports of the use of beta-blockers in different psychiatric conditions – in potentiating the anxiolytic effects of anti-depressants, in the management of Parkinsonian tremor, etc. – all on an expirical basis, and with varying degress of success. Thus the therapeutic value of beta-blockers in psychiatry is still debatable.

6. **Side – Effects**

Minor side–effects such as rashes, nausea, vomiting, diarrhoea, malaise and lassitude complained of by some patients on beta-blockers are probably non-pharmacological (idiosyncratic) and are relatively uncommon; most of them disappear with continued use of the drug or when the patient is changed to an alternative beta-blocker.

Side-effects that result from the known pharmacological consequences of beta-blockade include bronchoconstriction, heart failure, bradycardia, hypoglycaemia, claudication and even Raynaud's phenomenon.

i) **Bronchoconstriction**

Although this is probably caused by blockade of β –receptors in bronchial smooth muscle, other factors such as unopposed vagal activity and activation of –receptors which become apparent after β –receptors are blocked probably also play a part.

Asthmatics with **reversible** airways obstruction may get worse with beta-blockade, and this includes some latent asthmatics (as seen in one patient in the above series) who have not experienced wheezing previously. There is no evidence that **irreversible** airways obstruction from obstructive chronic bronchitis or emphysema is made worse by beta-blockade[21].

It has been reported that even the 'cardio-selective' beta-blockers can induce bronchoconstriction in high doses or in susceptible persons; however, these patients seem to respond very well to treatment with β_2–stimulating compounds (e.g. salbutamol) in contrast to those on non-selective beta-blockers.

ii) **Cardiac Failure**

The negative inotropic effect of beta-blockers causes inhibition of cardiac

contractility and can precipitate acute left ventricular failure in patients with impaired myocardial function. The risk is uncommon in normal practice, and is greatest at the beginning of treatment. Beta-blockers with intrinsic sympathomimetic activity appear to be marginally less likely to precipitate cardiac failure.

iii) **Bradycardia**
This is a normal response to treatment with beta-blockers without intrinsic sympathomimetic activity. Therefore, beta-blockers are not used in partial or complete A-V block; however, conduction defects below the A-V node are not affected by beta-blockade.

iv) **Hypoglycaemia**
It is known that beta-blockers can produce hypoglycaemia in diabetics (particularly poorly-controlled diabetics) and in fasted patients, by enhancement of activity of insulin and oral hypoglycaemic agents. However, this effect is much less with the cardio-selective compounds. Beta-blockers may also abolish some of the warning signs of hypoglycaemia such as tachycardia and sweating.

v) **Effects on the peripheral circulation**
Intermittent claudication worsens with beta-blockade. The causative mechanism of cold extremities, which seems to be the commonest side-effect reported by various authors[22,23], is still not clear, although it may be explained by the decreased cardiac output together with the skeletal muscle vasoconstriction resulting from beta-blockade. The mild vasoconstrictor action provides the pharmacological basis for a combination of beta-blockers with vasodilators in the treatment of hypertension.

vi) **C.N.S. Side-Effects**
It has been reported that nightmares, hallucinations, depression and insomnia are especially common with the highly lipid-soluble compounds such as propanolol which presumably penetrate the CNS better, or with those with potent intrinsic sympathomimetic activity.
Although a mild tranquillising effect has been reported with some beta-blockers, these drugs in the usual therapeutic doses produce no impairment of judgement in driving skills.

vii) **Long-term Side-Effects**
Unfortunately, we are still ignorant of the long-term toxicity, if any, of the beta-blockers. However, the potential benefits seem to be greater than the possible risk. The oculo-muco-cutanerus reactions of Practolol must always be kept in mind when a beta-blocker is prescribed. The price to pay for using a "new" drug is continued vigilance. Earlier beta-blockers such as pronethalol and tolamolol were withdrawn from trials because they caused thymic or mammary tumours in rodents when used in high doses. However, the relationship between carcinogenicity in animals and in man is unclear.

7. **Contra-Indications**
While the list of indications for the use of beta-blockers seems to be getting increasingly longer, one must remember that cardiogenic shock is an absolute contra-indication. Brady-arrhythmias, including all degrees of A-V block, are another absolute contra-indication, unless the cardiac rhythm has been controlled by a cardiac pacemaker.
Beta-blockers are also contra-indicated in the presence of uncontrollable cardiac failure. Like all drugs, beta-blockers should not be given in the first trimester of pregnancy unless considered essential.

8. **Precautions in Use of Beta-Blockers**
Patients with impaired myocardial function and potentially at risk of developing cardiac failure should be put on digitalis and diuretics if treatment with a beta-blocker is necessary. The greatest danger of precipitating heart failure seems to be at the beginning of treatment with the first few doses. Thus the dosage used should be low initially, and increased progressively until the optimum effect is achieved.
Since it is known that even the cardio-selective beta-blockers can produce bronchoconstriction in susceptible subjects, they should be used with extreme caution in such patients.
In patients with impaired renal function, dosage reduction may be necessary, especially with beta-blockers excreted mainly by the kidneys. Caution must also be exercised when

using beta-blockers in diabetics – a reduction of dosage of the insulin or oral hypoglycaemic drug may be necessitated.

There are virtually no references in the literature to the use of beta-blockers in the treatment of hypertension and toxaemia of pregnancy, nor is information yet available regarding the presence of beta-blockers in breast milk. Theoretically, beta-blockers could cause increased uterine force and decreased placental blood flow. They cause foetal bradycardia, may increase neonatal hypoglycaemia, and will mask clinical signs of hypoglycaemia. However, they have been used successfully to facilitate labour in uterine dystonia[24].

Conflicting reports have been made regarding the use of beta-blockers during anaesthesia. Some researchers believe that they should be withheld 48 hours prior to elective surgery whenever possible (except in severe angina or dysrhythmias), while others claim that they can be continued during anaesthesia, and may actually reduce the risk of post-anaesthetic dysrhythmias. Whatever the case may be, the medical practitioner must warn the anaesthetist that the patient is on beta-blockers, so that he gives adequate atropine pre-medication to prevent excessive vagal activity during surgery and monitors the patient's cardiovascular function most carefully, being ever-vigilant for the development of metabolic acidosis.

Anaesthesia with agents with cardio-depressant properties (e.g. ether, chloroform, cyclopropane and trichloroethylene) should not be used in patients on beta-blockers because of the increased risk of cardiac failure.

No drug interactions between beta-blockers and any other drugs have so far been reported.

None of the author's patients have developed any tolerance or habituation with the beta-blockers, and withdrawal of the drug in cases of anxiety and paroxysmal tachycardia has produced no alarming reactions. However, it is important that the withdrawal of a beta-blocker should be gradual, especially in patients with ischaemic heart disease; these patients should also have their physical activity restricted during this phase.

The pulse rate of the patient is a very useful index as to the advisability of starting him on or increasing his dose of beta-blockers. The author has made it his rule never to use these compounds in patients with a pulse rate of less than 60 per minute. For the patient who is already on beta-blockers and whose pulse rate is 55 or less, he prefers to add another anti-hypertensive agent, or change to another beta-blocker.

9. **Treatment of Over-dosage**

If overdosage, and resultant severe bradycardia, does occur, atropine sulphate 1–2 mg. should be given intra-venously, followed if necessary by slow (5 mcg./minute) intravenous infusion of isoprenaline (10–60 mcg.).

CONCLUSION

While the beta-adrenergic blocking agents have become the treatment of choice in most cases of angina, hypertension and arrhythmias, the possibility of many other therapeutic uses is always being explored. The general practitioner must keep himself well-versed with any new indications and also the advantages of any further compounds introduced; he must also be on the lookout for reports of side-effects, or the appearance of side-effects in his patients on beta-blockers. He would also do well to confine himself to a few preparations that he can be very familiar with. The successful application of these drugs requires careful selection of patients, individualisation of dosage and regular follow-up.

The advent of these effective beta-blockers also makes it necessary for all general practitioners to re-appraise the management of their patients with hypertension – addition of a beta-blocker or replacement by one if incapacitating side-effects from another drug are present must be carefully considered. Further, all patients whose daily activity is significantly limited by angina pectoris should be given a trial of beta-blockade, provided there are no contra-indications.

In the local context, the most important factor limiting the use of beta-blockers in general practice is their relative expensiveness. The generic form of propanolol is already available in Singapore at a considerably reduced price. We will have to wait for the proprietary rights of the other compounds to expire before we can expect cheaper preparations of these agents too. Choice of beta-blocker for use must depend on comparison of costs and degree of side-effects until one or more of the different beta-blockers is proven particularly superior by further trials.

A gaze into the crystal ball may well show the use of beta-blockers on a prophylactic basis in the prevention of myocardial infarction and sudden death in persons at high risk.

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Annual General Meeting 1978

It is customary to publish a short (if light-hearted) account of the proceedings of the Annual General Meeting of the College each year, mainly for the benefit of those who, for one reason or another (the main one being that they can't be bothered?) are unable to be present — not that it has ever proved to be a very sparkling event. It must again be emphasised, of course, that this is in no sense a "minute" of the meeting, since that is the responsibility of the Honorary Secretary to prepare and present formally for approval next year.

This was the first occasion on which, because of the fact that the Council, serving a two-year sentence (and having completed only half of it) there was no voting for office-bearers of any kind. This took whatever sting there ever is in the meeting out of the proceedings, which never reached the heat and excitement of the coincidental World Cup. Indeed, it was surprising that, for the first time in years, there was no difficulty in getting a quorum, and the meeting was well under way by three o'clock (true, it was billed for two-thirty, but the delay was due to the laissez-faire attitude and the usual minor problems of getting any meeting like this started on time, and not to lack of numbers).

After the Chairman, Dr. Victor Fernandez, had called the meeting to order, it was his regretful task to recall the names of those who had passed away since the last AGBM — a list that included one Honorary Fellow and two Fellows of the College. A one minute's silence was observed as a mark of respect. The Chairman then gave his short address (about five minutes), in which he rightly stressed that academic and teaching aspects of the year that had gone by. He referred to the successful course in Obstetrics and Gynaecology, and to the fifth College Diploma Examination (and called for candidates for the next one), and outlined the new plans for the teaching of family medicine to under-graduates. He mentioned briefly the recent successful Joint Colleges Meeting in Kuala Lumpur, and drew attention to the forthcoming Convocation, at which the College Diplomas would be presented and the First Sreenivasan Oration delivered. Then there was a short summary of the main objects of the future plans of the College, and finally, an expression of appreciation of all the help that had been given during the year by the executive Secretary of the College, Mr. F.B. Vaz.

The minutes of the last AGBM were rapidly despatched after the correction of a few minor errors. The Annual Report of the 1977/1979 Council for 1977/1978 was then dealt with page by page, but expeditiously and without much comment. Explanations were given when necessary, either by the authors of the various reports, or by the Chairman himself. A comment was made from the floor about the apparent high absence attendance rate of some Council members, but the questioner, and the meeting, were satisfied by the explanations given by the Chairman.

In no time the Accounts were being discussed, with the usual laudatory comments (though also with the usual laments about the poor financial state of the College: however, this did not obstruct a short discussion on the best way to obtain the maximum interest on the funds in hand). They were duly accepted without question.

At this point, one of the senior members of the College lamented the continual drain from the members of the Council and Committees, especially the senior and therefore more experienced ones. He pointed out the importance of handing over the responsibilities to the younger generation. In stressing that for ultimate success, the support of the **whole** College was necessary, he hinted that since it was admitted that many of the members simply did not have the time or energy to give to committee work,

their pockets might not feel the strain so much – and the College could put their contents to good use.

One of the members gave a ten minute address on the importance of vocational training, based partly on his recent experience in the United Kingdom. His words of wisdom were noted by all present, and there is little doubt that he will be roped in by the Vocational Training Committee to put his theories into practice.

The Board of Censors proposed that Dr. Rajkumar, should be elected an Honorary Fellow of the College. The Chairman spoke strongly in favour of this, outlining the former's close association with our College over many years and drawing attention to his distinguished career, and pointing out the honour that our College would gain by having him as one of our Honorary Fellows.

There being no "other business", the meeting closed about ten to four (a record for any AGBM anywhere?) with a sincere vote to thanks to the Chairman, the President of the College Dr. Victor Fernandez.

G.H.

PRELIMINARY ANNOUNCEMENT

1ST SOUTH EAST ASIAN & PACIFIC CONGRESS OF CLINICAL BIOCHEMISTRY

14 – 19 OCTOBER, 1979

You are cordially invited to attend and participate in the 1st South East Asian & Pacific Congress of Clinical Biochemistry.

The CONGRESS has been organised specifically to interest delegates from both developed and developing countries and to promote interaction between clinical biochemists from these countries. The PROGRAMME will consist of plenary lectures, symposia & free communications.

The TOPICS to be discussed will include:

- Education & training in clinical biochemistry
- Reference materials & standardisation
- Standardisation of enzyme assays
- Evaluation of the clinical usefulness of laboratory tests
- Evaluation of instruments
- SI units
- Detection of congenital defects
- Diabetes
- Enzymes in disease
- Interpretation of laboratory data
- Clinical aspects of immunoassay
- Recent developments in instrumentation
- Recent advances in endocrinology

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MEDICAL NEWS

Drugs and the Elderly

Based on Adverse Drug Reactions Bulletin Vol. 1 No. 9

The rate of adverse reactions to drugs increases with advancing age. This is largely due to altered responsiveness to drugs in the elderly as a result of deterioration of the organ and enzyme systems with increasing age. The problem is a real one in Singapore as the proportion of the elderly in the community is rising yearly. The burden on the community is great as they made up 15% of all hospital admissions in Singapore.

Factors affecting the drug response in the elderly are many and these include changes in drug absorption, drug distribution, drug elimination, altered tissue sensitivity and defective homeostatic mechanisms. Reduced absorption of drugs is contributed by decreased gastrointestinal motility, rising pH of gastric juice and reduction in the number of absorption cells in the elderly. Changes in the distribution of drugs in the elderly often lead to higher level of drug in the blood as a result of smaller body size and hypoalbuminaemia.

Drug elimination is achieved by hepatic metabolism and renal excretion. Therefore diminished drug metabolising capacity and impaired renal function in the elderly often lead to higher blood level of drugs.

Tissue sensitivity and defective homeostatic mechanisms play as important a part in the altered responsiveness to drugs as altered absorption, distribution and elimination of drugs. The reaction of many elderly patients to barbiturates varies from mild restlessness to frank psychosis instead of sedation. This is due to difference in the sensitivity of the elderly brain to these agents. Therefore barbiturates should be used very sparingly and a benzodiazepine or chloral hydrate is preferred in the elderly. Homeostatic mechanisms are often defective in the elderly and this is well shown by the fact postural hypotension is particularly common in this age group.

Principles of prescribing drugs for the elderly

Perhaps the following questions should be asked first before drugs are prescribed for the elderly.

1. Is the drug necessary? The doctor must realise that some 'diseases' are not causing the elderly patient any immediate harm and therefore no treatment is required. Over the age of 70, systolic pressures of up to 200 mg Hg and/or diastolic pressure of 100 mm Hg as an isolated finding does not require treatment.
2. If the drug is needed, should the dosage be modified? The elderly patient requires smaller doses of drugs than are customarily given to the young adult. For example, the dose of digoxin should be reduced as side-effects of digoxin are particularly common in the elderly.
3. Are too many drugs prescribed at the same time?
4. Is the drug regimen too complex for the elderly patient to follow?
   Medication errors and non-compliance with medication instructions are common in the elderly because of lapses of memory and intellectual impairment. Whenever possible fewer drugs should be given at any one time and when feasible, once daily dosage schedule should be used. As many older people have difficulty in swallowing, large tablets and capsules should be avoided. There is a good case for the use of mixture, syrups and effervescent tablets. Sometimes, the suppository may be the most suitable method of administration.

Drug Scene in Singapore

In "Reach Out", the news bulletin of the Community Probation Service, Dr. John Elliott and Mr. K.V. Veloo discuss the drug experiences of a sample population and the main findings of their study.

"The drug user is himself a source of valuable information concerning the abuse of drugs. He knows something of why drugs are first taken, and why continued. He also knows of the difficulties experienced by those involved in the misuse of drugs."

In rehabilitating drug users or addicts, one of the most important points to note is probably

their reasons for taking drugs. Following are some reasons for taking drugs, as listed by Dr. Elliott and Mr. Veloo in their interviews of drug users:

1. Drugs are first taken as a result of association with friends or associates, but are continued more for pleasure, for 'kicks' than because of social pressure.
2. Although subjects did not mention personal problems as a reason for their own abuse of drugs, some mentioned personal, family or emotional problems as a reason for youth in general taking drugs.
3. Sex was not regarded by respondents as an important factor in creating drug abuse, though they agreed that girls were more susceptible under the influence of drugs.
4. Alcohol and nicotine were widely indulged, but were not regarded as substitute drugs nor a means of avoiding prohibited drugs, except by a very few subjects.
5. There was no substantial evidence of defective upbringing or resentment of family sufficient to warrant its inclusion as a reason for drug abuse, although the extent of subjects' frankness here is unknown.
6. Generally consideration of group influence and socially acceptable habits appeared more important than family and personal background as factors in abuse."

Family Doctor — a rare breed?

In his address at the Opening of the 9th National Medical Convention organised by the Singapore Medical Association, Mr. Kwan Sai Kheong, Vice-Chancellor of the University of Singapore said,

". . . . . The danger in the case of medicine is that, with more intensive specialisation, the provision of comprehensive health care involves an ever increasing number of highly trained doctors, each a specialist in his own field. The patient is carved up, as it were, into small segments, each looked after by a specialist, when in fact the different parts of his body must function as a co-ordinated whole, and it is his total well-being that matters.

"There was a time when the family doctor took care of all the ailments of all the members of the family, the old and the young, from birth unto death. He was the one-man comprehensive medical service. Such family doctors may still be found, but they are becoming extremely rare. With increasing health-consciousness and rising affluence, Singaporeans tend to run to a specialist at the drop of a hat. If baby is sick, his mother brings him to a paediatrician; if mother is expecting an addition to the family, she sees an obstetrician; if father sprains an ankle, he hobbles to an orthopaedic surgeon, and so on. In such a situation, **illnesses are treated on an ad hoc basis, the medical history of the patient becomes fragmentary, and there is no longer a general overseer of his bill of health.** More important, the close relationship between doctor and patient is lost. The doctor is no longer friend and counsellor, but merely a dispenser of pills and mixtures. The extreme case of impersonal health care is seen in the group medical practice to which large firms send their employees. There the patient sees not a particular doctor, but any one of a panel of doctors, depending on who is free at that time."

Depth or Breadth?

"Claims for specialisation arise from the erroneous belief in some quarters that specialisation equates excellence. Nothing can be further from the truth. The specialist is a well-trained doctor in only a narrow field. He does not have and should not claim to have the breadth and depth of experience in the larger field of medicine. He has sacrificed the acquisition of this breadth of experience in a general field, for the depth in a narrow field. The general specialist, like the general physician or surgeon, retains the breadth of experience but sacrifices the depth of a narrow specialty. The general practitioner, on the other hand, retains the entire breadth of the practice of medicine without going into great depths in any field. None is superior to the other. Each has a role to play in a medical service. Where one has technical skills, the other has a perspective denied of his more blinkered specialised colleague."

Dr. Nik Zainal, Cardiologist, Hospital Besar, K.L.
Berita MMA Vol. 9 No. 6.

Singapore Cancer Registry

In his letter to doctors in Singapore, Prof. K. Shanmugaratnam stated that "Comprehensive registration of all cancer cases in Singapore has been maintained since 1968. During this period the Registry has provided valuable information on the nature and extent of cancer in the Singapore population and has collaborated with doctors and scientists engaged in the study of local cancer problems. These studies have included considerations of suspected risk factors

in the environment, host-environment interactions and the results of treatment. These investigations will be extended in future and the Registry will continue to monitor trends and variations in local cancer patterns.

"The registry seeks to obtain information on every case of 'cancer' or 'probable cancer' diagnosed in Singapore regardless of the citizenship or place of domicile of the patient. We would be most grateful if you would notify the Registry of all new cases diagnosed in your hospital, clinic or practice even if the diagnosis is based only on clinical findings (i.e. without histogical, radiological or other methods of confirmation). Please notify a case even if you think that it may have been notified by some other doctor previously."

HYPNOSIS — A special state of conscious awareness

(Milton H. Erickson M.D.
Newsletter of Singapore Society for Clinical Hypnosis Vol. 1 No. 4. May 1978)

"Today, there are still those who think of hypnosis as a healing sleep, a magical force, a kind of demonical power, as has been thought for thousands of years.

But what is hypnosis as we understand it scientifically today? It is certainly not physiological sleep, even though it may seem to resemble it, and may even be used to produce physiological sleep. It is not some special power or magic, nor is it some barbaric force arising from evil sources. It is, in simple terms, nothing more than a special state of conscious awareness in which certain chosen behaviour of everyday life is manifested in a direct manner, usually with the aid of another person. But it is possible to be self-induced. Hypnosis is a special, but normal type of behaviour, encountered when attention and the thinking processes are directed to the body of experiential learnings acquired from or achieved in the experiences of living.

In the special state of awareness called hypnosis, the various forms of behaviour of everyday life may be found — different in relationships and degrees, but always within normal limits. There can be achieved no transcendence of abilities, no implantations of new abilities, but only the potentiation of the expression of abilities which may have gone unrecognized or not fully recognized.

Hypnosis cannot create new abilities within a person, but it can assist in a greater and better utilization of abilities already possessed, even if these abilities were not previously recognized."

Dichotomy of medical studies

". . .misguided enthusiasm and individual interests confined medical students to a pre-clinical period of study divorced from patient contact, and the great dichotomy between the basic medical sciences and patient care was created, the former occupying about half of the traditional five- to six-year medical course."

"During this pre-clinical course, the medical student often cannot see the relevance of his studies vis-a-vis his future vocation. When he reaches the hospital wards, he has to re-orientate himself and very often learn his basic medical science all over again."

". . .the medical doctor trained as an undergraduate in the Western-type of medical school, and nurtured and encouraged as a postgraduate to overspecialise so as to practise in high technology hospitals, or as a private specialist on a fee-for-service basis, perpetuates the vicious cycle of ever-spiralling medical cost, benefiting fewer and fewer people."

from Prof. Wong Hock Boon's lecture to the Association of Southeast Asian Institutes of Higher Learning in Cebu, Philippines.
(the Mirror, July 10, 1978)

Society of Private Practice Circular

The Society of Private Practice published the first Circular to her members on 22-6-78. "This will be a paper with a difference," assured Dr. Adrian Tan and Dr. Winston Lee, the co-editors.

"Basically, this publication will try to promote better understanding and empathy between our many members. We will keep you informed of any news and views which may be of interest to you and your practice as well as any interesting happenings among our colleague."

". . . .we will endeavour to print any comments, articles or views which you may have as long as they are not too slanderous or libellous.

"Also, we will run a small 'classified advertisement' column in every issue for members to announce whatever they may need to buy or sell, be it a car, house, instruments, clinic, pet or even playmate!"

We would like to wish the Society and the editors every success in their endeavour.

The Fifth List of Donors to the College

This is the fifth list of donors to the College, and is as accurate as it is possible for us to make from the records. We apologize in advance for any omissions, which would of course be included in the next list. It does not include the many who have given less tangible donations, but which have nonetheless been equally welcome.

NON-MEMBERS:

The Reuben Meyer Trust Fund	$ 5,000.00
M/s Swee Construction & Transport Co Ltd	5,000.00
M/s Little Pharmaceutical Suppliers Pte Ltd	3,000.00
Mr Tung Kooi Yoon	240.00

MEMBERS :

Dr Si-Hoe Kok Wan	$ 3,000.00
Dr Victor L Fernandez	1,734.00
Dr Wong Heck Sing	450.00
Dr Frederick Samuel	352.00
Mr & Dr (Mrs) J J Murugasu	200.00
Dr Moti Vaswani	164.00
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Dr Gordon O Horne	100.00
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Dr Rajalekshmi Nair	20.00
Dr Rilly Ray	20.00
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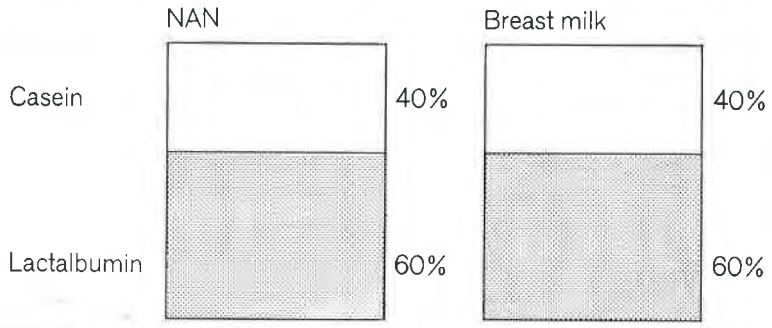

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(P. Royer, Pädiat. Fortbildk., Praxis, 1973, vol. 37, 15-25).

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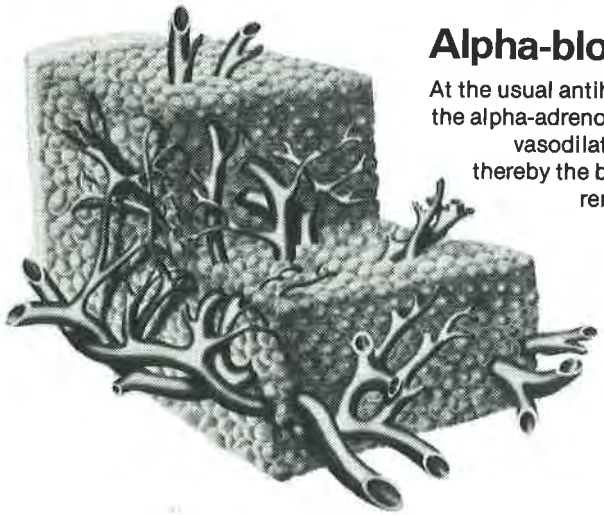
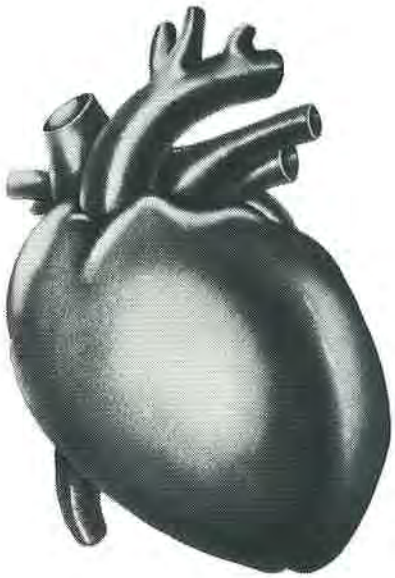


Alpha-blockade

At the usual antihypertensive doses, incomplete blockade of the alpha-adrenoceptors in the arterioles produces adequate vasodilatation to lower the peripheral resistance and thereby the blood pressure, while the barostatic reflexes remain sufficiently active to avoid side effects associated with postural hypotension.



Beta-blockade

The reflex cardiac stimulation normally induced by peripheral vasodilatation is controlled by current blockade of the beta-receptors in the heart, sufficient to prevent undesirable cardiac stimulation but not to reduce cardiac output at rest or during moderate exercise.

An entirely new concept in the treatment of hypertension

- Lowers peripheral resistance
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- Highly effective in all grades of hypertension
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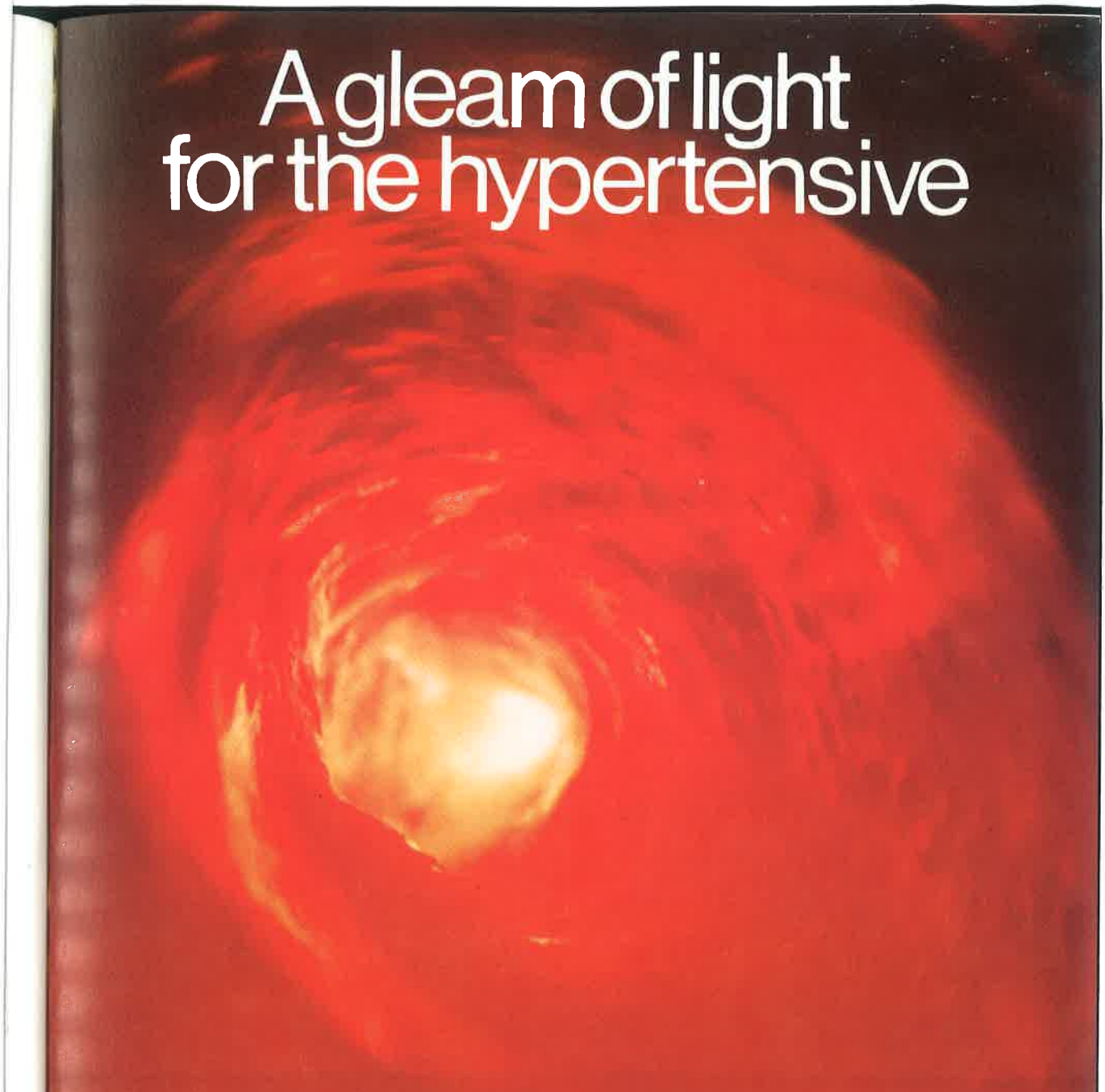
A gleam of light for the hypertensive



Despite treatment many of your hypertensive patients may have a gloomy prognosis, because reducing blood pressure does not prevent myocardial infarction. More patients die from infarction than from any other consequence of hypertension, ***whether or not blood pressure is controlled.***[1,2]

If your patients are treated with 'Inderal,' however, their prospects may be brighter. Although other antihypertensive drugs have failed to reduce the probability of myocardial infarction,[2,3] 'Inderal' has now been shown to reduce it ***fourfold.***[3,4] Only 'Inderal' has been associated with a protective effect against infarction in hypertensive patients who have no signs of heart disease.

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There is now evidence that the use of beta-blockade, in hypertension, reduces the incidence of myocardial infarction[3, 4] and sudden death.[4]

'Sectral'* is unlikely to cause bradycardia and as it does not readily cross the blood/brain barrier, CNS effects are avoided. 'Sectral' is unlikely to interfere with male sexual function.

References

1 *Clin.Med.***82,** 30, 1975

2 1st International Congress of Patient Counselling, Amsterdam, April 21-23 1976

3 Proceedings of the Fourth Meeting of the International Society of Hypertension, Sydney, February 1976 *Clin.Sci.Mol.Med.*, **51,** suppl. 3, 5095, 1976

4 Letter, *Br.Med.J.*, **iii,** 685, 1974

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