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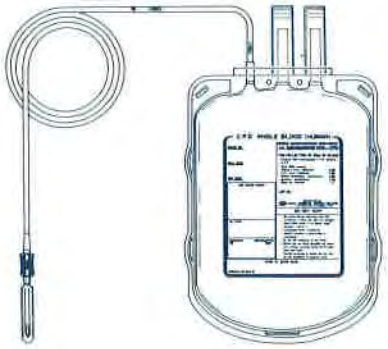

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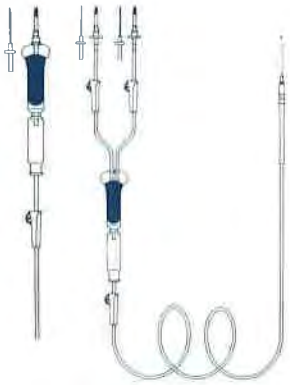

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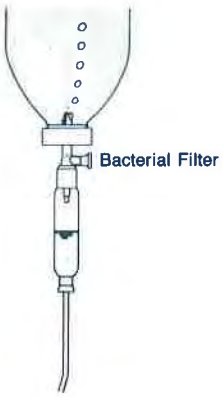

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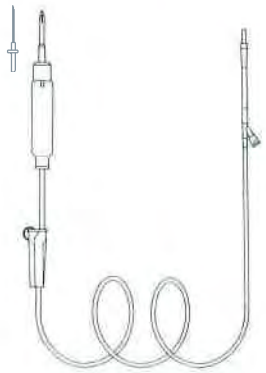

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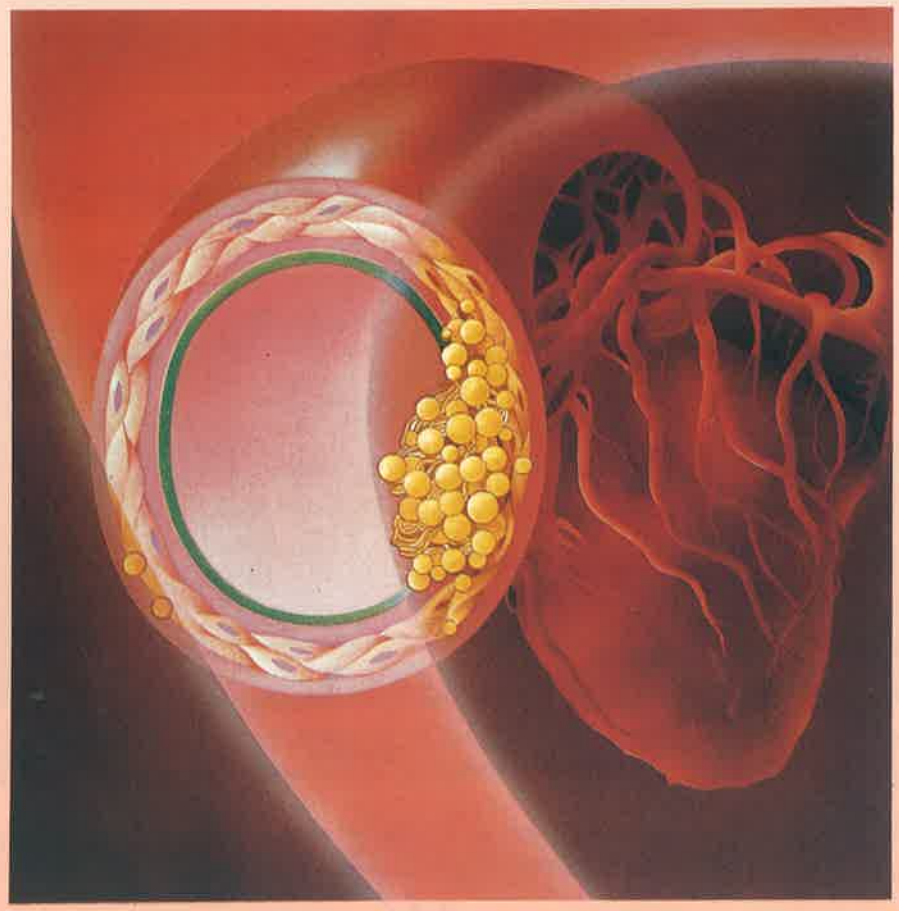

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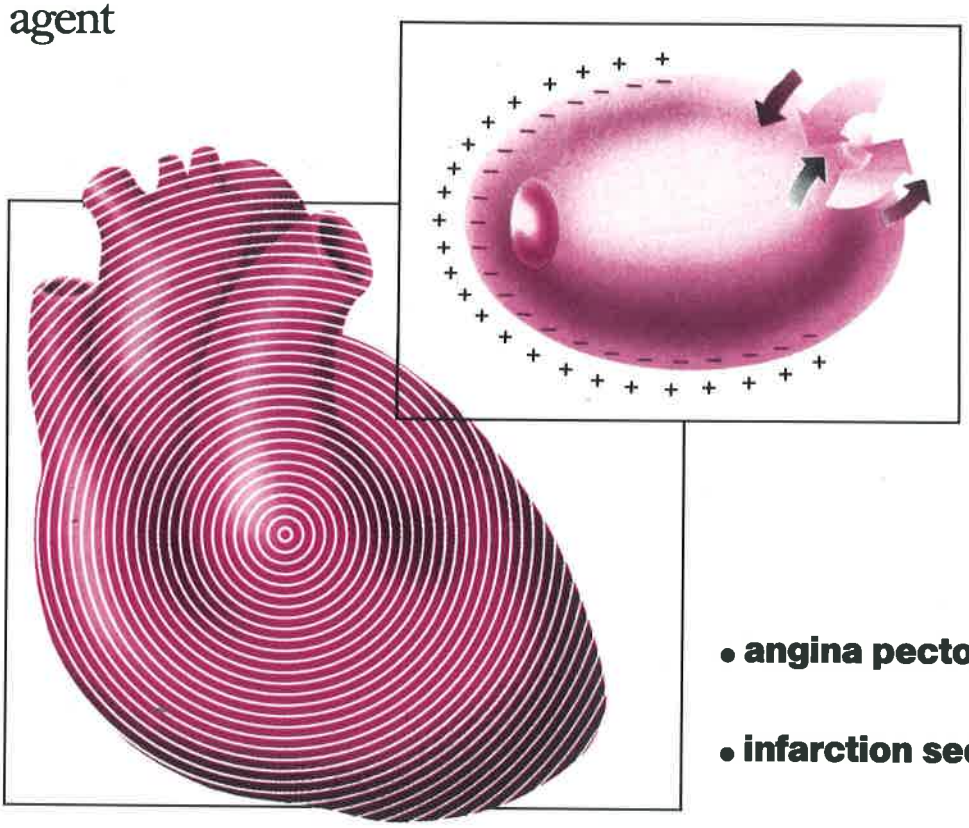

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EDITORIAL

OUR TASKS IN MEDICAL EDUCATION

General practice is the "Cinderella" of medicine. Many specialists see general practitioners as "cough and cold" doctors with nothing to contribute to the progress in medical care or in the education of medical students. At best, some of our medical teachers see the "GP posting" as an "exposure" of medical students to general practice — and many medical students come for their general practice posting with this different attitude — not expecting to learn anything except to get some idea of the kind of cases we see as general practitioners.

Such attitudes infect even some of us as general practitioners. Consequently, we feel uneasy and inadequate when our hospital colleagues ask us: "What are you doing to teach that I can't?"

Many GPs are not aware of the wealth of knowlege and experience in general practice which they can impart to medical students. There is a vital gap in medical education which I believe can best be filled by general practitioners.

THE CRISIS IN MEDICAL EDUCATION

Current medical education has been described as being in a crisis by Professor Prawase Wasi. In his view, our present methods of medical education are outdated and reform is needed if future physicians are to have the knowledge and dynamism necessary to address the issues that are beginning to confront the medical profession and society today.[1]

Professor Wasi identified the teaching of the use of technology without adequate emphasis on the ethical issues spawned by technology as a major defect of today's medical education. The subsequent indiscriminate use of technology has made the practice of medicine more mechanical and less holistic. Another deficiency is that our medical education is content-oriented and content-congested.

What modern society urgently need are wise doctors. In order to produce new physicians who are wise men and not merely medical mechanics, Professor Wasi recommends a restructuring of the medical education that will change the emphasis from mastery of content to mastery of process. Medical teachers must be trained not only to teach content but also to teach the process of learning and of thinking critically as well.

At a medical conference organised by the World Federation for Medical Education in August 1988, the problem of younger doctors being more insensitive with poor bedside manners was discussed. It was suggested that a cause of this problem was that medical schools took a "too academic" approach when selecting students. The conference reiterated that Medicine needs doctors who are warm, caring and humane and that good bedside manners help to speed a patient's recovery.[2]

THE ART OF LISTENING

However, the fundamental deficiency in medical education is not so much the poor selection of students as the failure to teach our medical students the art of listening. It is the disease-oriented approach to medical care that has produced insensitive doctors with poor bedside manners.

One medical student shared how he felt frustrated when a patient who was being

readmitted again and again for obstructive airways disease kept telling him about his family problems — of how he was rejected by the wife and children. He failed to see that the family rejection is the main reason for the constant readmissions!

Unless this gap is filled, it will not be possible to achieve the objective of the medical faculty to produce balanced, scientific and humanitarian doctors. It has been said that "when we listen with the heart, we tell someone they are important and we show them we care."

The art of listening is not only a skill that can be taught and learnt but one that needs constant practice. Teaching the art of listening is therefore an important area of medical training in which general practitioners can play a very important role.

It is a challenge to general practitioners whom I believed are well suited for such a task as they are well versed in the art of listening since they have to deal with undifferentiated problems. The ability to listen to what is not said as well as to observe the nonverbal cues is essential for the first phase of problem definition which is discovering why the patient came.

THE HIDDEN AGENDA

Discovering why the patient came is not the same as making a physical diagnosis. We tend to assume that all patients see a doctor because they want to be healed. But many general practitioners will have encountered patients who do not want to be healed and who, in fact, are out to prove that they cannot be healed.

Many patients have a hidden agenda when they see a doctor and it is necessary to go beyond the presenting complaint and physical diagnosis to see this agenda. For example, patients may be anxious about the meaning of a symptom.

It is a common experience in general practice to have a patient requesting for a check-up because a friend just died suddenly. A girl may present with giddiness and epigastric discomfort when she is actually worried about pregnancy.

Other patients may have problems of living like the office worker who presented with chest pain because she was divorced and having a problem with her youngest son.

There are also the patients who need to legitimatise a sick role. An example is a teacher with SLE complaining of arthritic pain because she was unable to finish an assignment on time.

As general practitioners we can open the eyes of the medical students to these hidden agenda of patients. This is important because our medical training is only orientated towards making diagnoses and prescribing the right treatment and this has a blinding effect on the psychosocial problems of the patients.

THE DIAGNOSIS OF PSYCHOSOCIAL PROBLEMS

Medical advances have given us a fantastic amount of knowledge about the physiology, pathophysiology and aetiology of diseases. This has led to the tendency to view man like a motor car and to think that all that is needed is to do a few tests, make the diagnosis, apply the appropriate treatment, and all will be well.

But man is more than the engine of a motor car for he is the driver as well who can be affected by many other social factors such as the family, work, friends. Unfortunately, the specialists know more and more about the car but but less and less about the driver. It is the general practitioner who can see the damage that the driver inflicts on the car and also how the car can give the driver a headache.

With a specialist and hospital-based medical education there is a tendency to focus only on those aspects of the patient's problem which are the easiest for the doctor to handle. Consequently, many doctors fail to recognise underlying psychosocial problems as they are too busy chasing a physical diagnosis and asking the patient a barrage of questions. For example, many medical students have the habit of asking patients a list of questions in-

stead of allowing them to describe their symptoms.

THE HOLISTIC APPROACH

General practitioners are in the best position to observe the close and intricate relationship between physical illness and the inner disharmony of the mind and the emotions. With an awareness of such a relationship the management of minor illnesses will be seen from a different perspective. It is then not simply a matter of coughs and colds but as Dr Bernard Lau, a psychiatrist in Hong Kong pointed out:

"A family physician then becomes well placed to observe and influence family interactions by virtue of his ongoing contact with families. Handling a trivial complaint of a member of the family may ultimately turn into management of the psychopathology of the family in trouble, which is even more challenging, rewarding and satisfying than routine dispensing of trivial complaints."[3]

General practitioners therefore have the important task of teaching medical students to see the patient as a human being who has a body, mind and soul rather than a broken down motor car in need of repair and spare parts.

THE BEDSIDE MANNER

Another important teaching point in general practice is the so called bedside manner. Dr David Mendel noted that an essential ingredient of proper doctoring is the much aligned bedside manner and made the following observation:

"The best doctors acquire one over the years, but many never do. I think this is due to the usual overswing of the pendulum. Around the turn of the century, medical remedies were not very effective; in the circumstances the bedside manner was all there was.

Now that we can cure many disease, both doctors and public have replaced the wise avuncular physician of the past with the 'intensive care whizz kid image.' We don't need all that mumbo-jumbo when we have proper scientific methods, they say."[4]

Dr Bernie Siegel has written on the need for our modern doctors to apply the insights of psychology and religion to medicine as such an expanded outlook will help them inspire hope and to share major decisions with the patient. He suggested that such an approach rewards both the physician and the patient, for the doctor who acts out of love will not burn out.[5]

It is sad that the bedside manner is dismissed as simply a personality trait or common sense or "mumbo-jumbo". The patient-centred model has been described by McCracken et al as a powerful teaching tool as they have seen students change their styles dramatically after even only a day's of concentrated exposure to the precepts of patient-oriented medicine.[6]

A good bedside manner is more than good manners — it is the therapeutic doctor-relationship. It is the adoption of a patient-centred attitude towards medical care and the formation of a healing partnership with the patient.

To quote Dr Francis Peabody, described as a pioneering medical researcher by Dr Siegel:

"The treatment of a disease may be entirely impersonal; the care of a patient must be completely personal... the secret of the care of the patient is in the caring for the patient."[5]

Conclusion

General practice is the last bastion against the dehumanising effects of modern technology. Professor Wasi has expressed his concern that physicians are seen increasingly as medical mechanics or even commercialised medical mechanics — a perception, which in his opinion, is too often true. In general practice, we hold the key to help our future doctors understand the true meaning of health and of the mechanisms by which health is maintained and preserved as well as the recovery from ill health. As general practitioners, we have the challenge and the critical task of training tomorrow's doctors to be wise and caring physicians instead of mercenary medical mechanics.

PK

REFERENCES

1. Prawase W: A Historical Challenge to Medical Education. JAMA SEA, 1988; May: 4-5.
2. Straits Times, August 20, 1988.
3. Lau WKB: Management of Trivial Complaints In Family Practice. The Family Practitioners 1988, 11: 48-51.
4. Mendel D: Proper Doctoring. Great Britain, Springer-Verlag, 1984.
5. Siegel BS: Love, Medicine and Miracles. London, Rider & Co. Ltd.
6. McCracken EC, Stewart MA, Brown JB, McWhinney IR: Patient-Centred Care: The Family Practice Model. Can Fam Physician 1983, 29: 2313-2316.

ORIGINAL ARTICLES

THE ROLE OF COLONOSCOPY TODAY

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Mr S S Ngoi, *MBBS (S'pore), FRCS (Edin), FRCS (Glas), M Med (Surgery) (S'pore)***
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INTRODUCTION

The era of fiberoptic endoscopy began in May 1957 when Hirschwity et al[1] presented a paper describing the fiberoptic gastroscope. Over the next decade, the development of new instrumentation enabled doctors to perform endoscopic procedures to visualise the upper gastrointestinal tract with an ease not possible previously. By 1969, the fiberoptic colonoscope was introduced as a means of directly visualising the large bowel.

Presently the colonoscope has opened new areas both in the diagnosis and treatment of diseases of the large bowel.[2] Local surgeons have widely adopted the colonoscope as an integral first line investigation modality in large bowel disorders and are increasingly exploiting the therapeutic potential of the instrument.

INDICATIONS

During the early stages of development of colonoscopy, a set of indications have evolved (Table 1), to which new indications have been added as the field developed with time (Table 1B).

TABLE 1: INDICATIONS FOR COLONOSCOPY

Confirmation/refutation of suspected radiological abnormality
Evaluation/follow up of inflammatory bowel diseases
Differential diagnosis of diverticular disease/ malignancy
Follow up evaluation of patients with prior colonic surgery
Evaluation of lower GI bleeding
Endoscopic polypectomy
Reduction of sigmoid volvulus
Investigation of GI symptom eg vague abdominal pain

TABLE 1B: NEW INDICATIONS FOR COLONOSCOPY

Decompression of megacolon.
Treatment of lower bleeding GIT by Laser, electrocoagulation heat probe etc.
Percutaneous endoscopic caecostomy
Evaluation of terminal ileal disease eg. Crohin's disease
Resection of polyps or tumours from the terminal ileum

In the 1970's, it was generally accepted that colonoscopy supplements but does not replace the barium enema in the evaluation of large bowel disorders. In most instances, the procedure is employed either because the barium enema study has demonstrated a probable abnormality or because the barium enema has failed to identify the lesion when symptoms suggest colonic disease.

However today colonoscopy by an expert has become less time-consuming or uncomfortable than barium enema. It also offers a considerable improvement in diagnostic accuracy over the radiological procedure as in most series, up to 30% of lesions may not show up during the barium enema, as shown in Table 2.

**Resident*
***Lecturer*
Department of Surgery
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TABLE 2: COLONOSCOPY vs BARIUM ENEMA

Study	Total number of patients	% of total patients with positive colonoscopic findings after "normal barium enema"			
		Adenoma	Cancer	Other	Total
Wolff et al (3)	500	23%	2%	8%	33%
Swarbrick et al (4)	239	17%	10%	10%	37%
Tedesco et al (5)	258	18%	11%	7%	36%
Hunt (6)	561	14%	11%	10%	35%

In addition, the radiologist cannot determine whether the lesion is benign or malignant, a distinction which requires histological examination. For these reasons when an adequate level of technical expertise exists, more gastroenterologists and surgeons believe that colonscopy should be used as the first line colonic investigation leaving the Barium enema for those patients where colonoscopy has failed to visualize the bowel adequately.

However, some possible situations where colonscopy may be unsatisfactory are:

(1) Patients with obstructive lesions which cannot be negotiated endoscopically.

(2) Patients who cannot tolerate an adequate bowel preparation.

(3) Patients with tortuous sigmoid or transverse colon segments. (This problem is relative and dependant on the colonoscopist's skill).

THERAPEUTIC COLONOSCOPY

In 1973, Wolff et al[7] demonstrated that by using a wire loop snare and electrocautery, polyps could be removed through the colonoscope. Henceforth, colotomy and polypectomy at open surgery has nearly become obsolete as nearly all colonic polyps can be removed or at least biopsied with the colonoscope.

In experienced hands, even sessile lesions can be removed through the scope and the mortality and morbidity of colonoscopic polypectomy should be below 0.2% and 2% respectively.[8] In addition, the colonoscope could be used for a complete evaluation of the entire large bowel as the presence of a polyp is often associated with polyps elsewhere (up to 10%).[9]

Recently, ingested foreign bodies have been reported to be removed by the colonoscope. Also it has been used successfully in the treatment of sigmoid volvulus. Most recently, with the use of Nd-Yag laser, the scope can be used as a palliative procedure in advanced colorectal cancer especially for relieving obstruction, persistant PR bleed or discharge. In addition, bleeding due to angiodysplasia can often be stopped by either diathermy or laser coagulation.

Ogilvie's syndrome, a condition where there is acute dilatation of the large bowel without mechanical obstruction can be treated by colonscopic decompression. Wide bore plastic tubing is then threaded over the scope and left to decompress the bowel for a few days after which the condition usually resolves.

COMPLICATIONS

In 1976, Smith[10] surveyed members of the American Society of Colon and Rectal Surgeons and found that from 162 respondants and 20,000 colonoscopic procedures, the overall complication rate was 0.4% for diagnostic colonoscopy and 2% for polypectomy. The list of complication of colonoscopy is shown in (Table 3).

TABLE 3: COMPLICATIONS OF COLONOSCOPY
Haemorrhage
Perforation
Retro peritoneal emphysema
Post colonoscopy distension
Explosion
Volvulus
Bacteraemia
Infections
Medical problems (CVs, Resp, Renal)

It becomes apparent that the incidence of complications decreases considerably as the endoscopist becomes more experienced. Also as polypectomy carries a 4-5 fold increased risk, therapeutic endoscopy should not be performed by anyone until he has achieved 50 diagnostic scopes safely. If complications do occur, early recognition and proper treatment will eliminate extensive morbidity and mortality.

CONCLUSION

Although colonoscopy was slow to become an established procedure, increasing experience world wide has dispelled widely held views that colonoscopy is a difficult technical procedure. Successful and safe colonoscopy requires basic endoscopic expertise and sound clinical judgement. In experienced hands in a well organised unit, the procedure seldom take more than 30 minutes and provide an extremely accurate means of surveying the large bowel. In addition, both proper training and improved instrumentation have greatly decreased the complication rate. By the late 1980's the colonoscopy has been increasingly used as the initial investigative procedure for large bowel disorder and will continue to be so through the 1990's as more doctors become familiar with its use, both for diagnostic and therapeutic procedures.

REFERENCES

1. Hirschowitz BI, Curtiss LE, Peters CW, Polland HM: Demonstration of a new gastroscope, the fiberscope. Gastroenterology 35: 50, 1958.
2. Overholt BF: Colonoscopy: A review. Gastroenterology 68: 1308, 1975.
3. Wolff WI, Shinya H, Geffen A, Ozoktays, De Beer R: Comparison of colonoscopy and the contrast enema in five hundred patients with colorectal disease. Am J Surg 129: 181-186, 1975.
4. Swarbrick ET: Colonoscopy for unexplained rectal bleeding. Br Med J 2: 1685, 1978.
5. Tedesco FJ et al: Colonoscopy evaluation of rectal bleeding: A Study of 304 patients. Ann Intern Med 89: 907, 1978.
6. Hurt RH: Rectal Bleeding, Clin Gastro 7: 79, 1978.
7. Wolff WI, Shinya H: Polypectomy via the fiberoptic colonoscopy: Removal of neoplasms beyond the reach of the sigmoidoscope. N Eng J Med 288: 371, 1983.
8. Hunt RH: Towards safer colonoscopy. Gut 24: 371, 1983.
9. Coller JA, Corman ML, Veidenheimer MC: Colonic polypoid disease: Need for total colonoscopy. Am J Surg 131: 490, 1976.
10. Smith LE: Fiberoptic colonoscopy: Complications of colonoscopy and polypectomy. Dis Col & Rect 19: 407, 1976.

IS THERE NO HOPE FOR PATIENTS WITH COLORECTAL CARCINOMA AFTER SPREAD TO THE LIVER?

Mr C Seow, *FRCS (Edin)*

INTRODUCTION

Colorectal carcinoma is rapidly growing as the prime cause of cancer mortality all over the world. It is widely stated that early lesions eg. Duke's A have an extremely good prognosis. That is, more than 90% of these cases live to 5 years. Advanced cases, so called Duke's D have an extremely poor prognosis. Perhaps less than 5% live to see 5 years. It is also significant that up to 35% of all patients with colorectal carcinoma have apparent or occult metastases at the time of initial laparotomy.

All these add up to a generally dismal picture for the patient, his general practitioner, his surgeon and his oncologists.

"I'm sorry, this man has a secondary liver nodule!" "There is nothing I can do!" This reflects the general pessimism of most doctors when confronted with a patient with liver secondaries.

Patients with colorectal liver secondaries were often left to languish away. Chemotherapy and radiotherapy were not believed to be effective. Major hepatic resections were thought to have extremely high mortality and morbidity. And anyway, these patients only have a short time to live.

BUT THERE IS HOPE!

However, contrary to the popular belief, there is hope yet for some patients with hepatic colorectal secondaries. Hepatic resection does offer a glimmer of hope as the only currently curative treatment for this problem. And major hepatectomies have an acceptable low morbidity and mortality of less than 5 per cent. Even hepatic re-resection appears beneficial in select cases.

Cure is possible in well selected cases and long term survival definitely obtainable. But obviously, hepatic resection cannot be offered for all cases with colorectal liver metastases.

WHEN THEN IS LIVER RESECTION FOR HEPATIC SECONDARIES FROM COLORECTAL CARCINOMA BENEFICIAL?

Much work had gone into answering this question. Although some of the data are still conflicting, it is generally agreed that up to 33% of patients with liver involvement will benefit from hepatic resections.

Patients with a localized primary tumour i.e. Duke's A and Duke's B are in a favourable position to benefit from hepatic resection when the liver secondaries are discovered. Well differentiated tumours are also thought to be a plus factor. Solitary liver nodules or patients with up to 3 liver secondaries are more favourable than those with 4 or more nodules. They have a definite survival advantage after resection. Bilateral nodules are less favourable than unilobar secondaries but some surgeons will still resect them if there are less than 4 nodules.

Tumour nodule less than 8cm in diameter have also been noted to have a better post resectional prognosis compared to secondaries more than 8cm in diameter.

Registrar
Department of Colorectal Surgery
Singapore General Hospital Pte Ltd

Extrahepatic secondaries whether nodal or visceral (eg. peritoneum, lung, brain etc) have been proven to have the gravest significance. And the presence of extra-hepatic visceral or lymph node spread is a major contraindication to major hepatic resection.

The ideal patient for hepatic resection then appears to be a fit patient with a resected Duke's A or B primary colorectal tumour, with well differentiated histology, 3 or less secondaries in 1 lobe of the liver, each less than 8cm in diameter, with no evidence of extra hepatic secondaries.

Up to 75% 5 year survivals have been obtained in very favourable cases.

CAN POTENTIAL CANDIDATES BE ACCURATELY STAGED THEN?

Every surgeon operating on colorectal carcinoma should be able to examine the liver thoroughly during the first laparotomy for colorectal tumours. It had been widely proven that intraoperative ultrasound is far superior to bimanual palpation intraoperatively or even to pre-operative C.T. scanning in picking up small hepatic secondaries. It picks up nodules up to 0.4 cm in size and Machi et al picked up 15% missed by intraoperative bimanual palpation.

If no liver nodules are proven, these patients are followed up closely with frequent colonoscopy, pelvic and liver ultrasound, and C.E.A. levels. Any suspicious areas that then arises will indicate a need for a more thorough investigation including C.T. and arteriography.

If nodules are found at initial laparotomy, these are assessed on its own merit. They can be resected synchronously if surgeon and patient are well prepared.

Most surgeons however, do not resect the liver synchronously as the colorectal carcinoma. They would rather wait 3 months, so as to reinvestigate the patient and ascertain if other secondaries are present. This also allows micrometastases to appear which may then alter the surgical management. A disease free interval of more than 1-2 years between initial laparotomy and subsequent liver involvement had been proposed by some to be related to better survival. Others claim that it is of no prognotic significance.

Careful follow-up and staging is then of utmost importance. Firstly to save lives and prolong survival. Secondly to prevent unhelpful laparotomy on poor risk patients. Infact, poorly selected patients usually die from post operative complications as a result of meddlesome surgery or waste away rapidly due to an upset in tumour-host factor after needless surgery.

HOW MUCH LIVER NEEDS TO BE RESECTED FOR A REASONABLE CHANCE OF SURVIVAL OR CURE?

The extent of liver resection is related to operative mortality amd morbidity but does not appear to be related to prognosis. Rather it is associated with the extent and volume of liver secondaries. Wedge resection does not confer any disadvantage over major hepatectomies as long as all gross diseases are removed with a tumour free margin of about 10mm.

CONCLUSION

Aggressive hepatic resections for colorectal secondaries have given new hope to patients, and fresh enthusiasm to general practitioners and surgeons in an otherwise gloomy situation. "The patient has advanced colorectal carcinoma! There is a liver nodule present" "But there is hope yet....."

REFERENCES

1. Taylor I. Colorectal liver metastases — to treat or not to treat? Br J Surg 1985 (72): 511-516.
2. Little JM, Hollands M. Hepatic resection for colorectal metastases selection of cases and determinants of success. Aust NZ J Surg 1987 (57): 355-359.
3. Gray BN. Resecting liver metastases: Controversy. Aust NZ J Surg 1987 (57): 497-499.
4. Adson MA. Resection of liver metastases — when is it worthwhile. W J Surgery 1987 (11): 511-520.
5. Greenway B. Hepatic metastases from colorectal cancer: resection or not. BJS 1988 (75): 513-519.
6. Hughes KS, Simon R, Songhorabodi S, et al. Resection of the liver for colorectal carcinoma metastases: A multi-institutional study of indications for resection. Surgery 1988 103(93): 278-288.

7. Augelli NV, Lucas RJ, Howells GA. Hepatic resections: An eight year experience at a Community Hospital. The American Surgeon 1988 (54): 373-375.

8. Hughes KS, Rosenstein RB, Songhorabodi S, et al. Resection of the liver for colorectal carcinoma metastases: A multi-institutional study of long term survivors: Dis Col Rectum 1988 (31): 1-4.

9. Fortner Joseph G. Recurrence of colorectal cancer after hepatic resectioin. The American J Surgery 1988 (155): 378-382.

10. Finlay IG, Meek D, Brunton, et al. Growth rate of hepatic metastases in colorectal carcinoma. BJS 1988 (75): 641-644.

11. Lefor AT, Hughes KS, Shiloni E, et al. Intra abdominal extrahepatic disease in patients with coloretal hepatic metastases. Dis Col & Rectum 1988 (31)(2): 100-103.

12. Ekberg H, Tranberg KG, Anderson R, et al. Pattern of recurrence in liver resection for colorectal secondaries. World J Surg 1987 (11): 541-547 Glenn Steele. Invited commentary.

13. Boldrini G, de Gaetano AM, Giovannini I, et al. The systematic use of operative ultrasound for detection of liver metastases during colorectal surgery. W J Surg (11): 622-627.

14. Cobourn CS, Makowka L, Langer B, Taylor BR et al. Examination of patient selection and outcome for hepatic resection for metastatic disease. SGO 1987 165(3): 239-246.

15. Machi J, Isonoto H, Yamashita Y, Korochiji T, et al. Intraoperative ultrasonography is screening for liver metastasis for colorectal cancer: Comparative accuracy with traditional procedures. Surgery 1987 101(6): 678-684.

16. Bradpiece HA, Benjamin IS, Halevy A, Blumgart LH. Major hepatic resection for colorectal liver metastasis. BJS 1987, 74(4): 324-326.

AN UPDATE ON CANCER CACHEXIA

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INTRODUCTION

Cancer cachexia is a syndrome characterised by a progressive loss of fat and lean body mass with major visceral malfunction, poor treatment tolerance and decreased survival. It affects a sizeable proportion of cancer patients we see. 50% of cancer patients undergoing treatment and nearly 100% of cancer patients at death suffer from cancer cachexia. It is a major contributor to the morbidity and mortality of the cancer patient. This review aims to update the practising physician on some recent advances in the research into and treatment of cancer cachexia.

WHAT CAUSES THE CACHEXIA?

Theories of the aetiology of cancer cachexia have included the following:

1) The tumour preferentially competes for nutrients at the expense of the host. However, some occult tumours have been associated with severe cachexia and yet in some large sarcomas, the patient exhibits no wasting at all.
2) Hormones or peptides produced by the tumour causes inefficient energy utilisation. However, no such peptides has been isolated to date.
3) The cachexia is caused by a product of the patient's response to the tumour. This is the theory that is presently favoured. The clue lies in that cachexia cancer patients exhibit clinical and biochemical features similar in many ways to that of patients with weight loss after multiple trauma or severe sepsis. As such, it is postulated that products of the patient's inflammatory response is the cause of the wasting.

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Cachectin

A polypeptide has been isolated in cancer patients that is produced by monocytes ("monokine") in response to the presence of the tumour.[1] Appropriately called "cachectin", it inhibits the enzyme lipoprotein lipase in vitro. It has been recently synthesised by recombinant DNA techniques. Experimental studies have shown that cachectin injected into rats caused anorexia and cachexia.[2] In a study with human volunteers, injection of cachectin caused changes in protein metabolism similar to that seen in cancer cachexia patients.[3]

Receptors to the monokine cachectin is found in most peripheral tissues of the body. The exact mechanism of action leading to the wasting process is not known. The exciting possibility is that with better understanding of the mechanism of action of cachectin, a receptor blocker can be found and its administration can then prevent or reverse the wasting. Now that cachectin is more readily available through recombinant DNA synthesis, a breakthrough in research into the management of this distressing condition may be possible.

WHAT CAUSES THE ANOREXIA?

Again, the exact causative mechanism is unknown. One study has suggested increased hypothalamic serotonin levels to be the cause.[4] Some drugs have been tested aimed at reversing the anorexia by interfering with the neurotransmitter receptors

at CNS level. Learned food aversions may be another factor.[5] Studies indicate that food aversions result from subconscious association of foods with unpleasant symptoms induced by chemotherapy or tumour growth. Cachectin itself can cause anorexia.

DOES NUTRITIONAL SUPPORT MAKE A DIFFERENCE TO OUTCOME?

Without doubt, cachexia leads to poor treatment tolerance, increased infection rates and significantly higher operative mortality and morbidity. Clearly the best way to resolve the nutritional deterioration is through removal of the tumour. However, often the tumour has spread beyond the organ of origin and surgery no longer effects a cure.

Reversing the cachexia as shown by improvements in body weight, serum albumin levels and skin anergy tests etc is possible through nutritional support either enterally or parenterally.

However, whether it makes a difference to the outcome is controversial. As studies on cancer cachexia usually involve small numbers of patients and in different stages of the disease, the results are difficult to interpret. Klein in a statistical analysis of 28 collected randomised prospective studies on total parenteral nutrition (TPN) in cancer patients found that TPN benefited surgical patients (improved operative mortality and morbidity) but not patients on chemotherapy or radiotherapy with regards to survival, treatment tolerance and treatment response results.[6]

There has always been worries that nutritional support to the cancer patient may accelerate tumour growth. Animal studies have demonstrated this but to date, no human study has objectively shown stimulation of tumour growth by nutritional support.

OTHER NEW MODALITIES IN CACHEXIA TREATMENT?

At present, studies are conducted with new drugs. One such drug that has shown promise is Hydrazine Sulphate.[7] This is an enzyme inhibitor that interrupts gluconeogenesis, hence reducing the peripheral mobilisation of amino acids. In trials with cancer patients, it has produced significant improvement in caloric intake, weight gain and protein kinetics.

Another interesting concept was to use high fat and ketogenic diets to selectively feed the host and starve the tumour.[8] This is based on the premise that malignant tumours are usually poorly vascularised and hence do not metabolise fatty acids as well as normal tissues. By supplying the calorie content in the diet through mostly fats, the tumour can be starved.

Recently human recombinant growth hormone has been tried in a small number of patients in conjection with TPN to promote protein synthesis and the results have been promising.[9] This may be yet another way to reverse the cachexia.

However all these modalities must be assessed based on the final outcome of the patient — whether they make a difference in prolonging survival, improving quality of life and tolerance to treatment.

CONCLUSION

Cancer cachexia continues to be a difficult management problem. The literature is vast and confusing because the exact pathogenesis is not clearly established.

Cachectin receptors blockers and the use of recombinant human growth hormone with nutritional support may be the answers to the problem. The physician would be advised to keep an eye on these areas for further developments.

ACKNOWLEDGEMENT

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REFERENCES

1. Aderka et al. Cachectin production by cancer patients. Lancet 1985; (23): 1190.
2. Tracey et al. Cachectin induces cachexia, anorexia and inflammation. J. Exp Med 1988; 67 (3): 1211.
3. Warren et al. The acute metabolic effect of Tumour Necrosis Factor Administration In Humans. Arch Surg 1987; (122): 1396-1400.

4. Krause et al. Brain TRP and the Neoplastic Anoreixa — Cachexia Syndrome. Cancer 1979; (44): 1003-1008.
5. Bernstein. Etiology of anorexia in Cancer. Cancer 1986; (58): 1881-1885.
6. Klein et al. Total Parental Nutrition and Cancer Clinical Trials. Cancer 1986; (58): 1378-1386.
7. Chlebowski et al. Hydrazine Sulphate in cancer patients with weight loss. A placebo controlled clinical experience. Cancer 1987; 59 (3): 406-410.
8. Tisdale et al. Reduction of weight loss and tumour size in cachexia model by high fat diet. B J Cancer 1987; (56): 39-43.
9. Manson et al. Growth Hormone stimulates protein synthesis during Hypocalorie parenteral nutrition. Ann. of Surg 1988; (208): 136-142.

THE FIRST ANNUAL SCIENTIFIC CONFERENCE
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WHAT'S NEW IN DIABETES

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CHANGING PREVALENCE OF DIABETES MELLITUS IN SINGAPORE OVER A 10-YEAR PERIOD

1975 Ministry of Health Survey

(17,679 persons aged 15 and above)

Screening method of post-prandial glycosuria and diagnosis 2HBG 140 mg/dl (WHO 1965).

1.99% incidence (projected to the then census population of 2.2 million means that 44,000 persons in Singapore had DM).

50-54 years highest prevalence
Ethnic: Indians 6%
Malays 2.4%
Chinese 1.6%
60% were newly diagnosed
44% were overweight

Complications:		
	Hypertension	26.8%
	Nephropathy	9.9%
	Retinopathy	8.5%
	CAD	6.1%
	Skin infections	4.6%
	Neuropathy	3.3%

1985 National University Hospital Survey

(3731 persons aged 18 and above)

Prevalence:
4.7% of the adult population found to have DM
40 yrs and above 12.9%
32% newly diagnosed
Ethnic (males) — Indian 13.4 %
Malay 9.5%
Chinese 4.6%

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There is an impression that the prevalence of diabetes is increasing in many parts of the world.

An apparent increase in the prevalence rate from 2.0% to 4.7% is seen. However, this may be due to different screening and diagnostic criteria used.

PATHOGENESIS OF NIDDM

The pathogenesis of NIDDM has remained a controversy for many years.

Human diabetes is currently classified into 2 general categories:

Type I (IDDM) Type II (NIDDM)

IDDM is due to an absolute deficiency of insulin secondary to profound β-cell destruction.

In NIDDM, the cause of the abnormal metabolic state is less well understood. Although NIDDM is predominantly inherited, it is likely that metabolic and environmental factors determine expression of the disease, time of onset and perhaps severity.

At presentation NIDDMs are more obese than their nondiabetic counterparts. Shortly after the discovery of insulin, most diabetologists thought that insulin deficiency was the single abnormality in all diabetic states and that NIDDM was due to partial insulin deficiency with variable degree of residual insulin secretory capacity. Over the last decade, however, diabetologists have discovered that it is a heterogenous disorder characterised by abnormalities in tissue insulin sensitivity as well as a deficiency of the pancreatic β-cell.

It is now recognised that the situation is not so simple and there has been con-

siderable debate as to which is the predominant lesion responsible for glucose intolerance in NIDDM patients.

Major metabolic abnormalities co-exist and contribute to the hyperglycaemic state in NIDDM.

These include:

(1) Peripheral insulin resistance
(2) Impaired insulin secretion
(3) Increased basal hepatic glucose production

INSULIN RESISTANCE

Insulin resistance may be said to exist when even normal concentrations of insulin produce a less than normal biologic response.

In most cases, the insulin resistance is usually defined by the presence of endogenous hyperinsulinaemia in the face of normo or hyperglycaemia and by resistance to exogenous insulin.

Insulin resistance may occur as a result of any process that alters the availability of insulin in the bloodstream:

(a) abnormal β-cell product (abnormal insulin molecule or incomplete conversion of proinsulin to insulin)
(b) presence of circulatory insulin antagonists (GH, cortisol, glucagon, catecholamine, antibodies directed against insulin or its receptors)
(c) defect of insulin action at the target cell level (insulin-receptor defects or post-receptor defects).

In most cases, insulin resistance in NIDDM is due to abnormalities of insulin action at the target tissue. The target tissue abnormalities of insulin action can be divided into receptor and post-receptor defects, which produce characteristic changes in the shape of the dose-responsive curve for insulin. A decrease of insulin-receptor numbers leads to a shift of the dose-response curve to the right, with no change in peak insulin action = decrease in insulin sensitivity.

Animal studies show that in obesity, a decrease in insulin receptor numbers leads to decreased insulin binding, with no change in receptor affinity. The majority factor regulating the receptor in obesity appears to be level of circulating insulin.

The more insulin resistant the animal, the higher the basal insulin and the greater the decrease in insulin receptors. These observations led to the concept of "down-regulation" — i.e. hyperinsulinaemia causes an increase in the degradation rate of insulin receptors.

Insulin resistance can be partially reversed by 50-70% by:

(a) sulphonylureas which act by increasing insulin-binding due to an increase in the number of receptors, potentiating insulin action in target tissues.
(b) weight reduction.
(c) intensive insulin therapy.

Patients with Type II Diabetes Mellitus thus present combined insulin-receptor and post-receptor defects. The post-receptor defects involve a decrease in glucose transport activity plus possible additional intracellular defects in glucose metabolism.

Receptor defect leads to mild insulin resistance whereas the addition of a post-receptor defect results in the more severe insulin resistance commonly seen in NIDDM.

IMPAIRED INSULIN SECRETION

Insulin is secreted in 2 phases by the β-cell. An abrupt rise in plasma glucose level above 100 mg/dl causes a biphasic insulin response. The acute (1st) phase represents an early burst of insulin stored within the cell, followed by a second phase of newly synthesised hormone, which rises more gradually.

Type II DMs are characterised by a severe defect in that 1st phase of secretion which leads to the classic diabetic profile: a series of metabolic disturbances and a consequent inability to metabolise glucose. In general, the more severe the diabetic state, the greater the defect in insulin secretion.

Since the 1960's research workers have demonstrated defective 1st and 2nd phase insulin secretory responses to glucose in NIDDM.

Japanese workers (Kosaka) studied impaired glucose tolerance (IGT) subjects and reported that apart from the level of glycaemia, the best predictors of the ultimate development of DM were a diminished insulin response and obesity.

O'Rahilly (Radcliff Infirmary, Oxford) showed that insulin is secreted in 12-15 minute pulses and that this pulsatility is absent in NIDDM subjects and in persons who have a family history of NIDDM and in those IGT subjects who have FBG in the high-normal range.

Again, all forms of antidiabetic therapy i.e. sulphynoylureas, weight reduction and intensive insulin therapy are capable of partially reversing these insulin secretory defects.

INCREASED HEPATIC GLUCOSE PRODUCTION

Increased basal hepatic glucose production rates are a characteristic feature of patients with NIDDM and fasting hyperglycaemia.

The greater the degree of fasting hyperglycaemia — the greater the elevation in hepatic glucose production. Hyperglucagonaemia is commonly noted in NIDDM (Glucagon stimulates hepatic glucose production) — and 2/3 of hepatic glucose production is glucagon-dependent in NIDDM.

Hepatic insulin resistance may also play a role by diminishing insulin's normal effects to suppress hepatic glucose production and by allowing unopposed glucagon action. Enhanced gluconeogenesis from peripheral tissues also contributes to the increase in hepatic glucose production.

Sulphonylurea therapy, weight reduction and intensive insulin therapy in responsive patients can normalise these hepatic abnormalities in glucose metabolism.

PATHOGENESIS OF HYPERGLYCAEMIA

Overall glucose uptake is divided into:

(1) Non-insulin mediated glucose uptake (NIMGU)

(2) Insulin mediated glucose uptake (IMGU)

Because of the differences in the relative proportions of IMGU and NIMGU with fasting and feeding, the cause of **fasting hyperglycaemia** is different from that of **post-prandial hyperglycaemia.**

In the **basal state,** NIMGU predominates and accounts for 70% of overall glucose uptake. Therefore impairment in insulin mediated glucose uptake due to insulin resistance and/or decreased insulin secretion would have relatively minor effect on overall glucose disposal.

Hence hepatic glucose production is the main cause of fasting hyperglycaemia in NIDDM.

The cause of **post-prandial hyperglycaemia** is quite different. Recent data show that the majority of ingested glucose (70-79%) by-passes the liver and enters the peripheral circulation. In the post-prandial state, IMGU normally predominates (80-90%) and a decrease in IMGU due to insulin resistance and insulin deficiency will markedly reduce glucose disposal in NIDDM.

Hence post-prandial hyperglycaemia is due to decreased peripheral utilisation (primarily muscle).

THERAPEUTIC IMPLICATIONS

An understanding of the pathogenesis of Fasting (F) vs Postprandrol (PP) hyperglycaemia in NIDDM has significant implication for therapeutic regimes.

e.g. A therapeutic regimen able to restrain hepatic glucose production and bring it into the normal range would lower FBG to normal. But if such a therapy has no effect on insulin secretion/insulin action, IMGU would remain unchanged and control of PP hyperglycaemia ineffective.

Similarly, antidiabetic therapy is directed only to control of IMGU thereby controlling only PP hyperglycaemia and having no effect on lowering FBG levels.

An ideal form of antidiabetic therapy should lower both F and PP glucose levels. There is no current ideal therapy for NIDDM but the **2nd generation sulphonylureas** offer several advantages for Type II DM.

Stimulate insulin secretion
Correct 1st phase insulin release
? increase number of receptors
Reduce hepatic glucose production
Improve peripheral insulin action at receptor and post-receptor level

PROINSULIN IN THE TREATMENT OF NIDDM

Proinsulin is the single chain protein precursor of insulin. Cleavage of the C-peptide from proinsulin produces the insulin molecule.

Numerous studies showed that it was only 5-10% as potent as insulin. Proinsulin was thought to have no physiological or therapeutic importance.

However, recombinant DNA techniques have led to a better understanding of proinsulin metabolic effects and extensive studies using the englycaemic clamp technique suggested a preferential action of proinsulin in suppressing hepatic glucose output as compared with its effect in stimulating peripheral disposal of glucose.

Clinical studies have shown that, human proinsulin injected subcutaneously in patients with NIDDM, can control their hyperglycaemia, whether injected in the postabsorptive state at 9 am or at 10.30 pm.

When human proinsulin (HPI) was administered at bedtime, the FPG level declined to the normal range without the development of overweight hypoglycaemia.

The studies highlight several differences between proinsulin and regular insulin.

The onset of the metabolic effects of proinsulin is more gradual and subcutaneous injected proinsulin has a time course closer to that of intermediate acting insulins. Studies of the pathophysiology of NIDDM have identified peripheral insulin resistance, impaired insulin secretion and elevated hepatic glucose output as the major metabolic abnormalities underlying the hyperglycaemia of NIDDM and hepatic over productors of glucose is the major determinant of the magnitude of the FPG level in NIDDM.

Hence the properties of proinsulin suggest a possible role in the treatment of NIDDM.

COMPLICATIONS IN DIABETES MELLITUS

It is generally accepted that there is a relationship between diabetic control and the incidence of long-term complications. But few patients are able to maintain strict normoglycaemia for long periods of time with the current methods of insulin treatment.

The same long-term complications are seen in patients with Type II diabetes.

One possible mechanism involves the increased activity of the polyol pathway and its related abnormalities. Research in this area has expanded rapidly and many animal studies have demonstrated potential uses of the aldose-reductase inhibitors (ARI's) which block the conversion of glucose to sorbitol, the first step in the polyol pathway.

The discovery of sorbitol in the diabetic lens led to a search for aldose-reductase activity in other tissues affected by long-term complications. And it is now known that polyol-pathway activity is increased in those tissues susceptible to complications during hyperglycaemia and contributory to the aetiology of neuropathy, retinopathy, cataracts and other complications.

Another polyol, myo-inositol has been implicated a key link between hyperglycaemia and functional impairment in several tissues subject to diabetic complications.

Aldose Reductase Inhibitors (ARIs) not only prevent accumulation of sorbitol but also block the depletion of myo-inositol in the peripheral nerve and other tissues in diabetic animals.

Clinical trials of ARI's in diabetic patients have produced conflicting results.

In *Diabetic Neuropathy* — there is need for controlled studies in very early neuropathy. Majority of the published studies have been on patients with chronic neuropathy with a relatively long duration of diabetes.

In *Diabetic Ocular Complications* — there has been a suggestion that treatment with ARI's might reduce the number of microaneurysms and exudates and results are awaited of the several double-blind, randomised, multi-center trials in progress.

In *Diabetic Nephropathy* — the use of ARIs is a recent development. Early reports from clinical studies suggest that ARIs may have a beneficial effect on protein excretion.

SAFETY OF ALDOSE REDUCTASE INHIBITORS (ARIs)

SORBINIL has been associated with a high incidence of side-effects — immune-complex-mediated macular-erythematous rash with or without fever, pancytopenia and lympadenopathy usually appearing 6-14 days after starting therapy.

LIPID DISORDERS AND DIABETES

Lipid and lipoprotein abnormalities are common in the diabetic population as insulin deficiency and insulin resistance impinge on key enzymes and pathways in their metabolism.

In NIDDM there is insulin resistance and VLDL Production is increased:

(a) due to hyperinsulinaemia directly stimulating hepatic VLDL or production

(b) relative insulin deficiency at cellular level associated with insulin resistance.

Generally LDL levels vary according to glycaemic control. NIDDM patients are more likely to have elevated LDL levels than IDDM.

HLD-cholesterol concentration particularly HDL_2 (the subfraction most closely associated with vascular disease in an inverse fashion) tends to be low in NIDDM. Lower HDL levels may also be due to increased activity of hepatic lipase. In NIDDM there is altered HDL composition and reverse cholesterol transport may be impaired.

Because elevated cholesterol and elevated triglycerides are risk factors for macrovascular disease in NIDDM — intervention is necessary in the form of glycaemic control and diet. If significant hyperlipidaemia persists in NIDDM, and attempts to correct obesity not easy, as well as not being possible to achieve normoglycaemia, then the patient should be treated as for a primary hyperlipidaemia.

Plasma triglycerides are strongly related to vascular disease in diabetes. Increased trigylcerides + reduced HDL increases the risk for atherogenesis (Fibrates reduce triglyceride + increase HDL).

CARDIOVASCULAR DISEASE

The risk of coronary artery disease is high in diabetic patients. CAD is the commoner cause of death in diabetes. A 10-year prospective study (Munich) in Germany reported that defined key factors were associated with a high risk of macrovascular disease in diabetics:

— systolic hypertension (mean of 165 mmHg or more)

— hypertriglyceridaemia

— hyperinsulinaemia

Control of hypertension, lipids and smoking may be more important for the prevention of complications than just blood glucose control.

DIABETIC NEPHROPATHY

Diabetic nephropathy is the major cause of death in patients with Type I diabetes mellitus. Important functional and structural events occur in the kidney

of diabetic patients during the 10-20 years before onset of overt clinical proteinuria. This silent period is followed by a stage of early diabetic nephropathy. The only clinical manifestation of this stage of early diabetic nephropathy is an increased Urinary Albumin Excretion Rate (UAER).

If microalbuminuria is found, efforts should be directed toward improving glycaemia control and early intervention to maintain blood pressure.

SEXUAL DYSFUNCTION

Patients suffering from the debilitating diabetic complications of blindness, amputation, end-stage renal disease, diabetic diarrhoea and orthostatic hypotension are vociferous in their complaints. But when it comes to impotence, a significant majority suffer in silence. It is reported to affect 50-60% of the diabetic male population in both Type I and Type II Diabetes Mellitus.

A careful interview can substantially help in differentiating between impotence of primary psychogenic origin and that of organic origin.

In taking a history, one should be alert for symptoms of autonomic neuropathy involving other body systems especially the CVS, GIT and peripheral nervous system.

Similarly, a history of myocardial infarction, CVA, claudication, foot ulcers, alerts the physician to associated changes in the arterial system that might cause vascular impotence.

An important and overlooked component of history taking is the careful listing of all prescriptive and non-prescriptive drugs taken by the patient.

Because some patients may have more than one cause for impotence, a multidisciplinary approach is indicated. In a study by a group of endocrinologist, psychiatrist, psychologist, urologist and endocrine biochemist in Thomas Jefferson University, all subjects underwent an exhaustive evaluation. The results showed that impotence in diabetic men, although primarily vascular and/or neurological, may be associated with other pathophysiological mechanisms.

During the last 2-3 years, there has also been a significant shift of international opinion in the diabetes world. Recent research work in the non-enzymatic glycosylation of body tissues now makes it clear that levels of blood glucose constantly between 8 (144) and 11 mmol/l (198 mg/dl) are no longer aceptable.

50-60% of all deaths in diabetes are attributed to vascular disease. Antecedent hypertension, hyperlipoproteinaemia and hyperinsulinemia appear to be more strongly related to the atherosclerotic risk than hyperglycaemia.

Like cardiovascular disease, non-insulin dependent diabetes (NIDDM) occurs in relation to certain life-styles, the most obvious of which are obesity and rapid socio-economic development. Hence primary prevention of diabetes becomes increasingly important because of their significant morbidity and mortality and the human and economic costs associated with diabetes and its complications.

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WHAT'S NEW IN THE EYE IN DIABETES MELLITUS

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SUMMARY

Eye manifestations of diabetes mellitus vary in significance from transient refractive changes to total blindness from diabetic retinopathy. Diabetes affects almost all structures of the eye and the orbit. The corneal epithelium is more easily damaged. Iris pathology leads to pupil abnormalities and poor dilation to mydriatics. The lens changes which affects refraction comes with blood sugar level changes and this leads to transient blurred vision.

The 3rd, 4th or 6th cranial nerves may be affected and rarely severe orbital cellulitis develops. A more common and serious problem is cataract. It develops earlier and progresses more rapidly in diabetics than in non-diabetics.

But, by far the most important eye complication is diabetic retinopathy. This complication is important because it can cause blindness which can be prevented with early laser photocoagulation.

This paper highlights new developments in the management of laser photocoagulation for diabetic retinopathy and the management of cataracts with intraocular implants in diabetics.

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cataract
implants

DIABETIC RETINOPATHY

In Singapore, diabetic retinopathy has become a common ocular problem.[12] This is because a diabetic now lives longer as a result of better management. Unfortunately, the longer the diabetic lives the greater is his chance of developing complications, one of which is diabetic retinopathy.[4,13,18,19]

Fortunately, blindness from diabetic retinopathy can now be prevented with adequate argon laser photocoagulation. In 1977 multicentre randomised clinical trials proved that photocoagulation can prevent blindness in 60% of patients.[15-17] More recent reports indicated that probably up to 90% of blindness can be prevented provided the patients are treated early. This places a heavy responsibility on medical practitioners.

It is mandatory to regularly examine the retina of a diabetic with pupil dilated in a darkened room. Not only must the early changes of diabetic retinopathy be recognised but also dangerous changes which can be subtle.

Early diagnosis — Retinal Evaluation

An eye with normal vision may have changes indicating that it is at risk of becoming blind. Thus, normal visual acuity is not an indication that all is well. The only way to determine the presence of dangerous changes is with regular retinal examination.

Direct Ophthalmoscope

This is recommended for non-ophthalmologists who are not trained to use the indirect ophthalmoscope and who are unlikely to possess a retinal camera. To avoid missing dangerous retinal changes, pupils must be well dilated, and the examination done in a darkened room.

Fundal Camera

Photographs of the retina of patients with diabetic retinopathy provide an excellent record. A record of the posterior retina, most commonly affected by the disease, is made by a single photograph using the wide angle 60-degree (or 45-degree which is less satisfactory) fundal camera.

Fundal Fluorescein Angiography (FFA)

FFA has some value in the management of diabetic retinopathy but most of the significant changes can be detected without its use. The value of FFA moreover depends on its quality which in some 50% of cases is lacking due to opacities in the ocular media. FFA is useful in evaluating macular changes and in detecting new vessels as well as the presence of capillary non-perfusion.[1]

TYPES OF RETINOPATHY

There are 3 basic types of diabetic retinopathy:-

(1) *Background diabetic retinopathy* with and without maculopathy. (Fig. 1).

(2) *Pre-proliferative diabetic retinopathy* includes eyes with soft exudates, large haemorrhages, abnormal veins or looping veins and retinal oedema. (Figs. 2a & 2b).

(3) *Proliferative diabetic retinopathy* will be those with forward new vessels (Fig. 3) and subretinal haemorrhages.

The most common causes of blindness are due to traction retinal detachment, vitreous haemorrhage and severe maculopathy.

Argon Laser Photocoagulation

Laser photocoagulation is effective if treatment begins early.[2,3,5,6] Because of this, practitioners managing diabetics must recognise diabetic retinopathy early to give patients the best chance for retaining vision.[8,10,11]

It is emphasised that there is also no guarantee that through photocoagulation, vision will be maintained and no assurance that vision may not even deteriorate after treatment. Furthermore, patients require continuous follow-up to ensure that post-treatment changes can be recognised and treated early.

Background Diabetic Retinopathy

Although patients with background diabetic retinopathy are generally not treated, there are some exceptions: if the background changes are widespread or near the macula and may lead to maculopathy; or if the patient lives abroad and is unlikely to be able to return regularly for retinal evaluation; it may be safer for such patients to receive limited laser treatment rather than for them to reappear years later with irreversible retinal changes.

Proliferative Diabetic Retinopathy

Occasionally, the microangiopathic change is mainly occlusive, leading to retinal ischaemia.[7] The serious effect of retinal ischaemia is neovascularization. The ischaemic retina is believed to liberate a vaso-formative substance. This stimulates the formation of new vessels. 5-10% of diabetic retinopathy develop these proliferative changes. The main clinical features are the neovascularization of the disc and/or the retina and pre-retinal haemorrhage.

Disc new vessels is an ocular emergency. Vitreous traction may pull on these abnormal blood vessels and cause a pre-retinal (Fig. 4) and vitreous haemorrhage.

Initially, the haemorrhages may clear quickly. But large and recurrent vitreous haemorrhages take longer to clear. Even-

tually, the whole vitreous cavity may become filled with blood. Without treatment, 50 percent of the eyes will become blind within 2 years.

Neovascularization is usually accompanied by fibrous proliferation. This leads to traction retinal detachment (Fig. 5). Traction retinal detachment is not always disastrous because it may remain stationary for many years. If the macula is not threatened, there may be no need to intervene surgically.

The aim of photocoagulation is to destroy the ischaemic retina, as destroyed retina cannot produce the vaso-formative substance. New vessels regress if the ischaemic retina is destroyed.

In proliferative diabetic retinopathy, the treatment is peripheral retinal photocoagulation,[3,9] also known as pan retinal photocoagulation or ablation (Fig. 6). Prior to treatment, patients should be forewarned of visual changes such as the worsening of central vision due to macular oedema following peripheral retinal photocoagulation.

Advanced Diabetic Retinopathy

The indirect ophthalmoscope provides the best evaluation of advanced diabetic retinopathy with vitreous haemorrhage or traction retinal detachment. When the retina cannot be seen, however, ultrasound is a useful method of evaluation. The visual prognosis is poor for patients requiring vitrectomy or retinal detachment surgery[14] due to surgical difficulties as well as the recurrence of haemorrhage and fibrous tissue formation.

IMPLANT SURGERY IN DIABETICS WITH CATARACTS

Many previous contraindications of implant surgery after removal of cataract are no longer relevant. From controversial beginnings, it is now more accepted universally that a posterior chamber implant can be inserted in diabetics.

In Singapore an active diabetic retinopathy clinic for over a decade gave a unique opportunity for the study of implant surgery for cataract in diabetics.

Between January 1982 and September 1987, 2504 eyes were treated with extracapsular cataract extraction and posterior chamber intraocular lens implantation. Of these 525 were in diabetics, 146 were from overseas and were lost to follow-up, leaving 379.

Results

Table 1 gives the age and sex distribution. 160 patients were males and 219 were females ranging from 31-90 years.

TABLE 1
AGE/SEX DISTRIBUTION

Age	M	F	Total
31-40	3	3	6
41-50	9	5	14
51-60	13	47	60
61-70	85	109	194
71-80	47	49	96
81-90	3	6	9
	160	219	379

Table 2 shows the diabetic control. Note the few insulin dependent patients. The diabetic retinal status is summarised in Table 3.

TABLE 2
DIABETIC CONTROL

Treatment	No. of cases
Diet alone	31
Oral agents	299
Insulin alone	42
Both oral & insulin	7
Total	379

TABLE 3
DIABETIC RETINAL STATUS

Normal	225
Background	101
Maculopathy	50
Pre-proliferative	33
Proliferative	11
Total	420

(Total is more than 379 as some groups overlap)

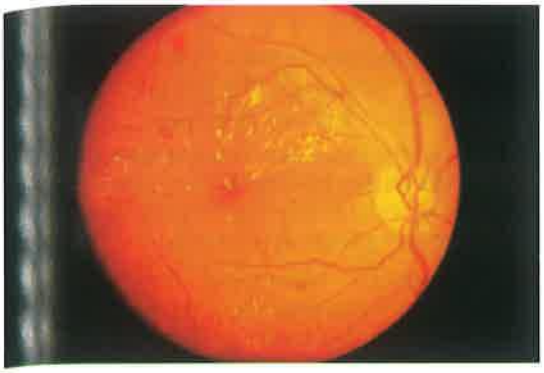

Fig. 1 Background diabetic retinopathy with hard exudates, microaneurysms and haemorrhages near the macula.

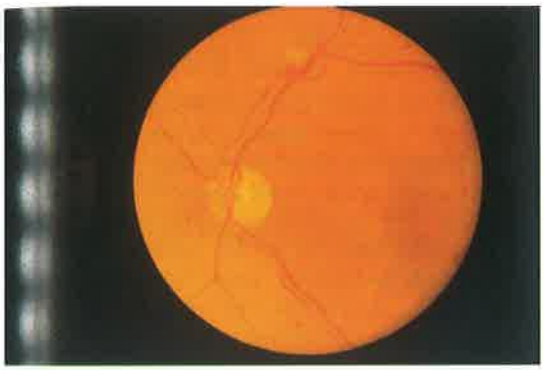

Fig. 3 Abnormal new vessels at disc can be subtle and difficult to see.

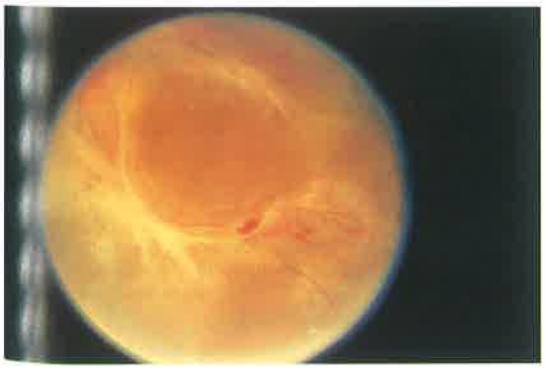

Fig. 5 Peripheral retinal photocoagulation. Entire retina treated except macular and disc.

Fig. 6 Vitreous haemorrhage and traction retinal detachment. Poor view of retina because of vitreous haemorrhage.

Fig. 2a Composite of pre-proliferative diabetic retinopathy with soft exudates, large haemorrhage and looping of veins above disc.

Fig. 2b Fundal fluorescein angiography shows widespread capillary non-perfusion.

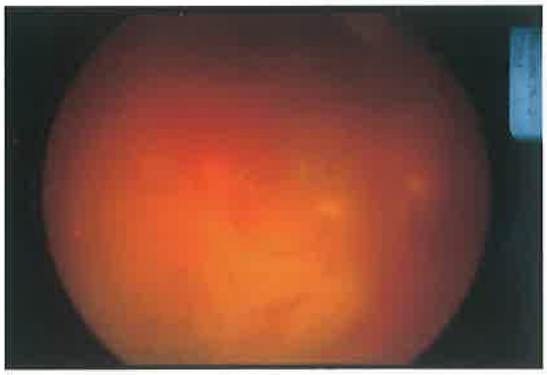

Fig. 4 Fibrous proliferation leading to traction retinal detachment.

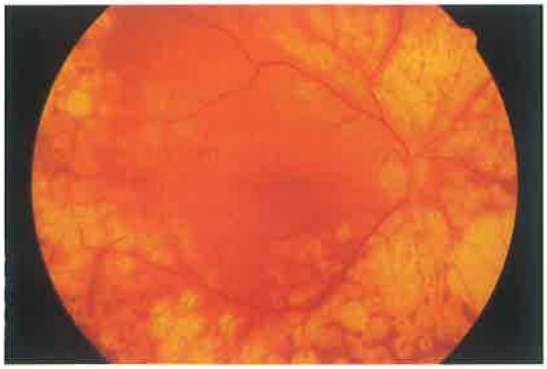

Table 4 shows the post-operative complications. Corneal abrasion and persistent iritis were common but transient problems. There is an increase in endophthalmitis (compared to the non-diabetics). An unusual complication is the development of fibrin over the pupillary area.

TABLE 4
POST-OPERATIVE COMPLICATIONS

	No. of cases
Persistent iritis	11
Corneal abrasion	7
Increased IOP (transient corneal oedema)	6
IOL malposition (pupil capture)	4
Pupillary fibrin	4
Endophthalmitis	3
Retinal detachment	3
Retinal vein occlusion	3
Signicicant pigment deposits on IOL	3

Table 5 shows that about 80% had 6/12 vision or better. However, if pre-existing diseases were excluded, 95% had 6/12 vision or better.

TABLE 5
VISUAL RESULTS

	Post-op (all)	Post-op (excluding pre-existing disease)
6/12 or better	304 (80%)	304 (95%)
6/18-6/24	32	5
6/36-6/60	14	3
	379	317

No one challenges the benefits of intraocular lens implant today and we believe that there must be strong reasons for not inserting an intraocular implant. With improved health care, diabetics today live longer. Diabetics sometimes have difficulty with contact lenses because of the poor quality of their corneal epithelium and the increased likelihood of infection.

RECOMMENDATIONS AND CONCLUSION

Our recommendations in managing diabetics with posterior chamber intraocular implant surgery are as follows:-

1. At operation — care regarding corneal epithelium and iris. A 7 mm implant inserted in-the-bag and avoid posterior capsule rupture if possible.
2. No special treatment for diabetics without retinopathy or with mild background diabetic retinopathy.
3. Eyes with maculopathy should have laser treatment, preferably pre-operatively, if not within a week of surgery. This is because cataract surgery can make untreated maculopathy rapidly worse.
4. Eyes with pre-proliferative retinopathy should have the retina treated, preferably pre-operativley.
5. Eyes with proliferative diabetic retinopathy (controversial) should be treated with laser photocoagulation and the condition stabilised before implant surgery. If possible, laser photocoagulation may be considered within a week of surgery. Pre-operative cryotherapy is an alternative.

The decision can be difficult. It will depend on many factors — the experience of the surgeon, the retinopathy, the patient's age and general health, the other eye and a host of factors which are important for a surgical decision in complicated situations. It is emphasised that the retina must be regularly reviewed and treated, if necessary.

REFERENCES

1. Ang B C, Lim A S M, Khoo C Y: Fundal fluorescein angiography in diabetic retinopathy. Proceedings of the XVI Singapore-Malaysia Congress of Medicine, 1982, 601-2.
2. Barrie T: Current options in management: proliferative diabetic eye disease. Trans Ophthalmol Soc UK, 1983, 103: 125-32.
3. Constable I J, Lim A S M: Laser — Its Clinical Uses in Eye Diseases. Edinburgh: Churchill Livingstone, 1981.
4. Klein R, Klein B E K, Moss S E: Visual impairment in diabetes. Ophthalmology, 1984, 91: 1-9.
5. L'Esperance Jr F A: Ophthalmic Laser: Photocoagulation, Photoradiation and Surgery. St Louis: Mosby, 1982.

6. Lim A S M, Khoo C Y, Ang B C: Diabetic retinopathy with special reference to photocoagulation. Proceedings of the X Singapore-Malaysia Congress of Medicine, Academy of Medicine, 1975, 269-76.
7. Lim A S M, Ang B C, Natural History of diabetic retinopathy: treatment with photocoagulation. Trans APAO VIII: 1979, 327-33.
8. Lim A S M, Ang B C: Prevention of blindness in diabetic retinopathy. Trans APAO VIII: 1979, 427-31.
9. Lim A S M, Khoo C Y, Ang B C: Some problems and limitations of laser photocoagulation in diabetic retinopathy. Trans APAO VIII: 1981, 648-53.
10. Lim A S M, Khoo C Y, Ang B C: Current methods in the evaluation and treatment of diabetic retinopathy. Proceedings of the XVI Singapore-Malaysia Congress of Medicine, 1982, 596-600.
11. Lim A S M, Khoo C Y, Ang B C: Diabetic retinopathy and laser photocoagulation. Asean Journal of Clinical Sciences, Monograph, 1982. 6: 162-7.
12. Low C H: Recent trends in the incidence and pattern of blindness in Singapore (1971-1980). Society of Ophthalmology Proceedings, Ophthalmology, 1982, 1: 83-97.
13. Low C H, Yeo P P B, Tan M H et al: Incidence of diabetic ocular complications in a general medical unit. Society of Ophthalmology Proceedings, Ophthalmology, 1982, 1: 67-75.
14. Noble K G, Carr R E: Diabetic retinopathy I. Non-proliferative retinopathy. In R E Carr (ed.) Disorders of the Fundus. Ophthalmology, 1983m 90: 1261-3.
15. The Diabetic Retinopathy Study Research Group: Preliminary report on effects of photocoagulation therapy. Am J Ophthalmol. 1976, 81: 1-14.
16. The Diabetic Retinopathy Study Research Group: Photocoagulation treatment of proliferative diabetic retinopathy: the second report of Diabetic Retinopathy Study findings Ophthalmol. 1978, 85: 82-106.
17. The Diabetic Retinopathy Study Research Group: Photocoagulation treatment of proliferative diabetic retinopathy: Relationship of adverse treatment effects to retinopathy severity. In: S L Fine et al, (eds.). Management of Retinal Vascular and Macular Disorders. Baltimore: Williams & Wilkins, 1983, 191-8.
18. The Wisconsin Epidemiologic Study of Diabetic Retinopathy: II Prevalence and risk of diabetic retinopathy when age at diagnosis is less than 30 years. Ophthalmology, 1984, 102: 520-6.
19. The Wisconsin in Epidemiologic Study of Diabetic Retinopathy: III Prevalence and risk of diabetic retinopathy when age at diagnosis is 30 or more years. Ophthalmology, 1984, 102: 527-32.

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WHAT'S NEW IN ASTHMA

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ABSTRACT

The definition of asthma must now recognise the inflammatory basis of bronchial asthma. It is inflammation that leads to bronchial hyper-reactivity which is a manifestation of a protective reflex. Inflammation mediated by mast cells is responsible for allergic asthma. Many stimuli and not only IgE antibodies can cause mast cell degranulation which leads to the release of performed as well as newly formed mediators. All these can give the early as well as the late asthmatic response. Platelet activating factor is the only known endogenous mediator causing bronchial hyperreactivity.

The concept of anti-asthma drugs is useful. Beta agonist drugs represent only symptomatic therapy for asthma. Anti-asthma drugs aim to prevent/treat the underlying inflammation. In view of the undesirable side effects of long term oral steroids, inhaled steroids must be effectively used. Patient education on the use of inhalers and self-monitoring of peak expiratory flow rates should be encouraged.

Keywords: airway inflammation, late asthmatic response, bronchial hyperreactivity, anti-asthma therapy.

INTRODUCTION

What is new in asthma? I would like to focus on five topics. The first is advances in the understanding of mast cell anatomy and function. The second is the importance of the inflammatory response in the airways in bronchial asthma. The third is the pathophysiology of the early and late asthma response and how treatment can help. The fourth is on the concept of bronchial hyperreactivity and its management and finally, the advances in the use of inhaled drugs.

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THE MAST CELL

Immune Triggers

The mast cell has all along been thought of as the prototype cell of type I immune-mediated reactions. Without its participation, there is no acute anaphylaxis IgE antibody was known since 1968 to be a potent mast cell degranulator once activated by antigen and it still is. However other triggers have been identified and these trigger the mast cell through Fc receptors on the mast cell. These triggers include lectin, anti-IgE antibody, anti-idiotype antibody, anti-Fc receptor antibody, IgG4 and cross-linked IgE antibody. So even among antibodies more than IgE can trigger mast cell degranulation.

Cell Populations

There are at least two different mast cell populations[1] — the mucosal mast cell (MMC) and the connective tissue mast cell (CTMC). MMC is T-cell dependent has more Fc receptors, less histamine and more prostaglandins and leukotrienes than CTMC. Histamine release is not inhibited by sodium cromoglycate or theophylline in MMC. These properties of MMC in bronchial mucosa may in part explain why asthma does not always respond to our conventional drugs.

BRONCHIAL REACTIONS

In terms of therapy, it has been observed that sodium cromoglycate inhibits both the immediate and the late phase bronchial reactions while steroids block only the latter. The immediate bronchoconstriction that occurs when antigens provoke an asthmatic attack occurs within 10-15 minutes. The late bronchoconstriction develops some 8 hours later. To explain this we need to examine mast cell degranulation.

Mast Cell Degranulation

The mast cell when degranulated discharges two groups of mediators. The first are the spasmogens responsible for bronchoconstriction. They are histamine, slow reacting substance (SRS), prostaglandins and platelet activating factor (PAF). These spasmogens cause both acute and late bronchospasm. The second group of mediators are the chemotactic factors, neutrophil chemotactic factor (NCF), eosinophil chemotactic factor (ECF-A), leukotriene B_4 (LTB_4) and PAF again. These cause an inflammatory bronchial response. Eosinophil through major basic protein is toxic to mucosal cells.

Another way of looking at the 2 groups of mediators released from mast cells is to classify those that are already preformed and stored in the mast cell grannules which when released act rapidly (eg histamine, NCF, ECF-A) while the second group are the newly formed mediators like LTB_4, PAF, LTC_4, LTD_4 and PGD_2. The latter result from activation of phospholipase A_2 which initiates the arachidonic acid into two metabolic pathways via either cyclo-oxygenase to give thromboxanes and porstaglandins or lipo-oxygenase to give SRS and leukotrienes.

Other Triggers

Besides immune-mediated triggers that act via the Fc receptor, the mast cell is susceptible to degranulation through two other direct mechanisms — anaphylatoxins C_3a and C_5a, and drugs like calcium, onophores, codeine and morphine. The sequelae of degranulation is the same as for immune-mediated triggers and bronchospasm and airway inflammation result.

THE INFLAMMATORY RESPONSE

Release of inflammatory mediators in the airway leads to bronchoconstriction, microvascular leak causing oedema and exudation, mucus hypersecretion and bronchial hyperreactivity. All types of inflammatory cells can do this to varying degrees. The mast cell as described above, the macrophage, the epithelial cell, the eosinophil, the neutrophil and the platelet do interact through hormonal agents and participate in augmenting the inflammation.

The eosinophil is the well-known companion cell of the type I immune response. It serves through its enzymes to mop up excess mast cell released mediators and so clamp down the response. However in bronchial challenge studies using antigen, some 6 to 7 hours after provocation when the late bronchoconstriction occurs, it has been observed that there is a more intense concentration of eosinophils than during the immediate phase reaction. This observation lends an important role to the inflammatory potential of the eosinophil which through its major basic protein can severely damage the bronchial mucosa[3,4].

Platelet activating factor (PAF) is a ubiquitous substance in the inflammatory endothelial and epithelial cells. It is not confined to platelets, as its name would suggest. It is now thought that PAF has a dominant role in the inflammatory response. It not only causes acute bronchoconstriction but also mucosal inflammation and through further eosinophil and platelet recruitment, damage and loss of bronchial epithelium. This denudation exposes irritant receptor nerves and contributes to the state of bronchial hyperreactivity, which is reflex mediated — both local reflexes and through the vagi. While other inflammatory mediators may heighten existing bronchial hyperreactivity, PAF is the only known endogenous substance to-date that can induce bronchial hyperreactivity de novo.[5]

BRONCHIAL HYPERREACTIVITY

What then is bronchial hyperreactivity? It could be defined as that state of the airways rendering it highly susceptible to bronchoconstriction at slightest noxious

stimulation. It can be seen as a protective reflex to prevent further damage to naked airways denuded of covering protective mucosa. Airways become "twitchy" and constrict to prevent noxious stimuli entering the lungs to cause damage.[6]

The presence of bronchial hyperreactivity strongly suggests the diagnosis of asthma in the absence of other factors such as 1) recent viral infection 2) adult respiratory distress syndrome 3) cystic fibrosis 4) sarcoidosis.

To test for its presence in the laboratory, certain substances like histamine or methacholine, or gases like cold air or sulphur dioxide, can be introduced into the airways in graded doses in a controlled manner to provoke bronchoconstriction. Bronchial hyperreactivity exists when minute doses of such substances, which in normal subjects have no effect, causes a significant bronchoconstriction.

PROPHYLACTIC THERAPY

A few points need to be made regarding the anti asthma drugs. Beta 2 agonists are very good for relief of bronchospasm. They are potent bronchodilators and nothing more. When there is acute bronchospasm, these drugs induce bronchodilation. But narrowed airways are due to other features besides bronchospasm. And airway inflammation contributes to this narrowing of airways.

Acute bronchodilator therapy is unsatisfactory for long-term prognosis of asthma. There is the need to treat the underlying inflammation in airways. There is also the need to try and reduce bronchial hyperreactivity through control of inflammation[7] and by other means. Only by so doing would there be successful prevention of the later possible development of irreversible airflow obstruction — this irreversible component is due to chronic inflammation in contrast to the easily reversed bronchospasm.

The prophylactic anti asthma drugs available include sodium cromoglycate, ketotifen, methylxanthines and glucocorticosteroids. Pure bronchodilators only release bronchospasm and nothing else so that when the drug wears off the patient is symptomatic again. Anti asthma drugs are given to try and prevent further attacks and patients who do not understand the rationale for their use, do not like them as they give no immediate relief during bronchospasm. Methylxanthines do have bronchodilator activity in addition to other functions so parenteral aminophylline does have a role in the treatment of acute asthma.

RATIONAL TREATMENT

As mentioned earlier, the early and the late asthmatic response have different pathogenetic mechanisms. The early response starts almost immediately, peaks in 10 to 30 minutes and is over by about 3 hours. The late response starts at 3 to 4 hours, peaks at 8 to 12 hours and lasts over 12 hours. The latter may lead to clinically significant increased bronchial non allergic responsiveness.

Treatment of the early response is best with beta 2 agonist drugs which not only reverses the bronchospasm but premedication can inhibit the response. The late response is only partially reversed by beta 2 agonists and premedication has no effect on it. Thus the use of pure bronchodilators working as smooth muscle relaxants can at best relieve bronchospasm. Sodium cromoglycate can inhibit both the early and the late responses. If its action on the mast cell preventing its degranulation is accepted, then this lends evidence for the central role of mast cells in allergic asthma. Glucocorticoids inhibit the late response and may partially inhibit the early response. The reason for this is thought to be its anti inflammatory property.

STRATEGY IN THE TREATMENT[6,7]

1. Heightened airway reactivity is a cardinal feature of asthma, as is bronchospasm.
2. The most popular hypothesis for this is that it is due to chronic airway inflammation.
3. The most convincing evidence supports the effects of sodium cromoglycate, inhaled and oral steroids reducing airway reactivity.

4. The common denominator is believed to be a reduction in the state of airway inflammation.

5. Patients will be better managed if the focus of treatment is changed from bronchospasm to inflammation.

In a recent study in Glasgow[8] the authors compared the management of asthma patients, 64 in a general ward whose doctors had an interest in asthma, with 86 in a general ward. The respiratory-biased physicians more frequently a) used oral steroids (83 versus 67 percent) b) monitored peak respiratory flow rates (73 versus 42 percent) c) asked the patient to return for follow-up (92 versus 56 percent) and d) tended to increase therapy (55 versus 28 percent).

As a result of these managerial decisions, the patients benefitted by experiencing less sleep disturbance (23 versus 41 percent) and less morning chest tightness (37 versus 55 percent). Asthma morbidity may decline with greater use of inhaled corticosteroids and sodium cromoglycate.[9]

INHALED THERAPY

Inhaled therapy[10,11] with metered dose inhalers (MDI) with drug delivered into the airways and lungs is the preferred mode of drug administration for patients when such drugs are available, when patients can be educated to successfully use them and when the bronchospasm is not so severe as to render the technique of using the MDI impossible. There are MDIs containing steroids, beta 2 agonists and sodium cromoglycate.

When correctly used, MDIs at best deliver about 9% of the dose of drug inhaled at the mouth into the airways and lungs. More than 75% of the drug is impacted in the oropharynx. With a nebuliser driven by oxygen or air, about 12% of the drug reaches the airways and lungs, with almost 70% of the drug lost in the apparatus. So when incorrectly used, very little if any drug is delivered to its intended site of action. Yet when properly done, the therapeutic effect is so tremendous considering the dose of drug is so minute. For example, a tablet of salbutamol contains 2 mg of drug but one puff of the MDI delivers at the mouth only 100 micrograms of salbutamol. No wonder that systemic side effects become minimal with MDI usage.

Therefore whenever possible patients should be educated to use MDIs especially if they can afford them. The introduction of "spacers" — big and now, smaller varieties that can be carried in the pocket or handbag — eliminates the skill of proper coordination between hand, mouth and breathing. Besides a slow deep inspiration, the patient must at the end of the inspiration hold his breath as long as possible to maximise entry of the aerosol into the deepest recesses of the airways. Too rapid a suction manoeuvre on inspiration means most of the drug is impacted in the oropharynx and larynx which leads to more frequent side effects and less therapeutic effect.

REFERENCES

1. Befers AD, Bienestock J, Denburg JA. Mast cell differentiation and heterogeneity. New York: Raven Press 1986.
2. Chung KF. Role of inflammation in the hyperreactivity of the airways in asthma. Thorax 1986; 41: 657-62.
3. Gleich GJ, Motojima S, Frigas E, Kephart GM, Fujisawa T, Kravis LP. The eosinophilic leukocyte and the pathology of fatal bronchial asthma: evidence for pathologic heterogeneity. J Allergy Clin/Immunol 1987; 80: 412-5.
4. Reed CE. Basic mechanisms of asthma: role of inflammation. Chest 1988; 94: 175-7.
5. Cuss FM, Dixon CMS, Barnes PJ. Effects of inhaled platelet activating factor on pulmonary function and bronchial responsiveness on man. Lancet 1986; 2: 189-92.
6. Cockcroft DW. Airway hyperresponsiveness and late asthmatic responses. Chest 1988; 94: 178-80.
7. McFadden ER Jr. Corticosteroids and cromoglycate sodium as modulators of airway inflammation. Chest 1988; 94: 181-4.
8. Bucknall CE, Robertson G, Moran F, Stevenson RD. Differences in hospital asthma management. Lancet 1988; i: 748-50.
9. Haj IFC, Higenbottam TW. Has the management of asthma improved? Lancet 1987; ii: 609-11.
10. Newhouse M, Dolorich M. Aerosol therapy: nebuliser versus metered dose inhaler. Chest 1987; 91: 779-80.
11. Clarke SW. Inhaler therapy. Quart J Med 1988; 67: 355-68.

HOME STUDY SECTION

ORAL HYPOGLYCAEMIC AGENTS

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INTRODUCTION

In considering the use of oral hypoglycaemic agents in the management of non-insulin-dependent diabetes mellitus (NIDDM), it is appropriate to review briefly the metabolic abnormalities that are found in this condition. The hyperglycaemia which characterise NIDDM arises as a result of overproduction of glucose by the liver, and decreased utilisation of glucose by peripheral tissues, especially muscle. Both deficient insulin secretion and resistance to the hypoglycaemic actions of insulin have been demonstrated in NIDDM and presumably are responsible for the abnormalities of glucose production and utilisation. It is appreciated from clinical, familial and population studies that NIDDM is a heterogenous disorder. Obesity frequently co-exist, and is a major factor in determining insulin resistance.

Ideally oral hypoglycaemic agents should correct the overproduction of glucose by the liver and its under-utilisation in peripheral tissues by correcting the dual abnormalities of deficient insulin decretion and insulin resistance. Given the different extent to which deficient insulin secretion and insulin resistance contribute to the metabolic disturbance in different individuals, drugs that are capable of modifying these processes independently should be available. Moreover, concurrent abnormalities of lipid metabolism, platelet function, coagulation factors and other features which may contribute to the development of atheroselerosis, microangiopathy and neuropathy should also be corrected. Serious side effects due to the drugs should not occur.

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So far, it has not been possible to develop agents that are capable of achieving all these goals. Thus, it is still preferable to attempt glycaemic and lipid control in patients with NIDDM by non-pharmacological means. Diet and exercise are the major components of non-pharmacological management of NIDDM, and their role cannot be over emphasised. However, this article will focus on the use of the two main groups of oral hypoglycaemic agents, namely the sulphonylureas and the biguanides.

SULPHONYLUREAS

Sulphonylureas have been used widely in the management of patients with NIDDM for over 30 years. Their hypoglycaemic effect was discovered incidentally in France during World War II in the course of investigations concerning the antibiotic properties of modified sulphonamides. Two generations of sulphonylureas are now available. First-generation sulphonylureas (tolbutamide and chlorpropamide) continue to be widely used. The second-generation sulphonylureas are more potent and include glibenclamide, glibonuride, gliclazide and glipizide. Despite the length of time that they have been in clinical use, controversy remains about the mode of action, indications for use, and the long term efficacy and safety of sulphonylureas.

Mode of Action

All sulphonylureas have the same mode of hypoglycaemic action. There is therefore no point in the concurrent use of more than one of these compounds. They depend on the presence of functioning pancreatic beta cells for their effect. Initially they stimulate the release of insulin by the pancreas. Whether this effect continues with the long-term use of these drugs is

still a matter of debate. More recent studies suggest that the long-term effect of sulphonylureas is to increase the number and affinity of peripheral insulin receptor sites.

Pharmacokinetics

The pharmacokinetic characteristics of sulphonylureas are summarised (Table 1). These drugs are in general well absorbed from the intestines and are highly protein bound in the blood which make them subject to drug binding interactions.

All sulphonylureas are metabolised to varying degrees in the liver and in the case of chlorpropamide a significant proportion of the drug is excreted unchanged by the kidneys. Oral hypoglycaemics that are extensively metabolised are susceptible to hepatic enzyme induction or inhibition, with the risk of hypoglycaemia in the latter case.

Care must be taken when these drugs are given to patients with chronic liver disease. Not only may drug metabolism be affected and the amount of carrier protein reduced but such patients are particularly likely to develop hypoglycaemia. Renal insufficiency may also have profound effects on the excretion of unchanged chlorpropamide.

Drug Interactions

Interactions between sulphonylureas and a number of commonly used drugs may result in either an attenuation or potentiation of the effectiveness of the oral hypoglycaemic agents. Potentiation of the action of sulphonylureas may occur from one of several mechanisms:

1) Displacement of the sulphonylureas from plasma protein binding sites, e.g. by long-acting sulphonamides such as sulphaphenazole; salicylates; coumarin anticoagulants such as warfarin; and pyrazolone derivatives such as phenylbutazone. However, displacement from protein binding sites is normally only of transient clinical significance, and commonly another mechanism (e.g. inhibition of biotransformation) is also involved in these interactions.

2) Inhibition of hepatic biotransformation of the sulphonylurea e.g. by cimetidine, long-acting sulphonamides, courmarin anticoagulants, pyrazolone derivatives and chloramphenicol.

3) Decrease in the urinary excretion of sluphonylureas e.g. by pyrazolone derivatives and possibly probenecid, salicylates and some sulphonamides.

TABLE 1: PHARMACOKINETIC CHARACTERISTIC AND DOSAGE REGIMENS OF INDIVIDUAL SULPHONYLUREAS

Drug	Elimination	Plasma half-life (hr)	Duration of effect (hr)	Initial dose (mg)	Maximum daily dose (mg)	daily frequency (doses)
First generation						
Tolbutamide (Rastinon)	Hepatic	3-25	6-12	500-150	3000	2-3
Chlorpropamide (Diabenese)	Renal/Hepatic	24-48	60	100-250	500	1
Second generation						
Gibenclamide (Daonil, Euglucon)	Hepatic	10-16	up to 24	2.5-50	20	1-2
Glibonuride (Glutril)	Hepatic	5-12	up to 24	12.5	50-100	1-2
Gliclazide (Diamicron)	Hepatic	12	up to 24	40-80	240-320	1-2
Glipizide (Minidiab)	Hepatic	3-7	up to 24	2.5-5.0	20-40	1-2

4) Pharmacodynamic interaction between the sulphonylurea and the drug, e.g. alcohol, salicylates, beta-blockers, levodopa and monoamine oxidase inhibitors.

Drugs which antagonise the action of sulphonylureas may also do so by several mechanisms:

1) Suppression of insulin release e.g. by diuretics such as thiazides and frusemide, phenytoin, propranolol, oral contraceptives and corticosteroids.
2) Hepatic enzyme induction of sulphonylurea metabolism e.g. by rifampicin, alcohol and barbiturates.

Not all the sulphonylureas are affected to the same extent by the various drugs mentioned above. The nature and extent of the interaction may be influenced to some extent by the degree of hepatic metabolism and urinary excretion. It is important to recognise that sulphonylureas affect the action of other drugs as well as being affected by them. For example, the interaction between the sulphonylureas and warfarin may also increase the anticoagulant activity of warfarin, and chlorpropamide may produce enhanced hyponatraemia when used with thiazide diuretics. Care should also be taken with drugs which may modify the physiological response to hypoglycaemia such as beta-blockers, clonidine and monoamine oxidaze inhibitors. As oral hypoglycaemic agents are used fairly commonly, more than the usual degree of caution needs to be employed before any new medication is prescribed.

Side Effects

Considering their widespread usage, significant adverse reactions to sulphonylureas are relatively uncommon and may be classified under four main groups:

1. Nonspecific Side Effects

These are primarily gastrointestinal and include symptoms such as nausea, vomiting, heartburn, flatulence and diarrhoea. Most of these are usually dose related, transient and respond to dose reduction. They rarely require discontinuation of medicine.

A disulfiram-like intolerance reaction to alcohol (facial flushing, palpitations, dizziness) occurs almost exclusively with chlorpropamide therapy. This genetically determined reaction occurs sufficiently commonly in patients taking chlopropamide to warrant them being warned of its possible occurrence when starting the drug. Water intoxication simulating an inappropriate antidiuretic hormone secretion syndrome occasionally occurs with chlorpropamide — and to a lesser extent with tolbutamide — but not with the newer agents, which may possibly be weakly diuretic.

2. Hypersensitivity Reactions

These usually appear within the first six weeks of treatment. They are relatively rare and are reversible. The hypersensitivity reaction may be discrete and confined to a single organ, or be generalised. Skin manifestations include pruritus, rashes, photosensitivity reactions, erythema nodosum, erythema multiforme, purpura, and exfoliative dermatitis. Blood features include leucopenia, thrombocytopenia, agranulocytosis, red cell aplasia and haemolytic anaemia. Gastrointestinal involvement may manifest as cholestatic jaundice. Cardiovascular involvement may present as a hypersensitivity angiitis.

3. Overdose Toxicity

Hypoglycaemia is the commonest adverse reaction of the sulphonylureas and may occasionally lead to a severe if not fatal outcome. The chief offender in this respect is chlorpropamide. Hypoglycaemia occurs most commonly in patients over 60 years, particularly in those with renal impairment. The second generation sulphonylureas may also cause hypoglycaemia but with the exception of glibenclamide this is usually short lived compared with chlorpropamide. Tolbutamide is a more appropriate choice for elderly patients at risk of developing hypoglycaemia. Drug interactions with sulphonylureas are also an important cause of hypoglycaemia.

4. Long-term Toxicity

The question of long-term toxicity of sulphonylureas was first highlighted by

the initial report of the University Group Diabetes Program (UGDP) in 1979. This was a 10-year prospective clinical study carried out in 12 university centres in the USA starting in 1961. The purpose of the study was to determine whether blood sugar control prevented or ameliorated the vascular complications of maturity onset diabetes mellitus. The results of this study were initially interpreted to show an increased risk of cardiovascular deaths in sulphonylurea treated patients. Although this study has since been criticised on a number of grounds, there is agreement, nevertheless, that maximum emphasis should be placed on diet and regular exercise with the use of the lowest possible dose of sulphonylurea.

Therapeutic Principles

Some general guidelines for sulphonylurea therapy are listed in Table 2. Sulphonylureas are most clearly indicated for the patient who is near the ideal weight and in whom diet fails to control symptoms and hyperglycaemia. Since these drugs tend to encourage some weight gain there is some reluctance to give them to obese patients. Nonetheless sulphonylureas may be useful in obese patients particularly when symptoms and hyperglycaemia persist despite adherence to diet. There is no convincing evidence that any one sulphonylurea has greater efficacy than the others (potency on weight for weight basis should not be equated with efficacy) but undoubtedly some patients who are not controlled with the drug may be controlled with another.

Sulphonylureas have no place in the treatment of patients with insulin-dependent diabetes. Furthermore, they should not be used to treat patients with gestational diabetes as they cross the placenta and may have dysmorphogenic effects. Under stressful conditions, for example, with severe infections, accidents or surgery, it may be necessary to temporarily transfer some patients to insulin therapy. This should be introduced early in a patient who is underweight or who has significant ketonuria either at the time of diagnosis or during follow-up.

TABLE 2: GENERAL GUIDELINES FOR SULPHONYLUREA THERAPY

1. Use in symptomatic NIDDM not controlled by diet alone.
2. Do not use in:
   a) Insulin-dependent diabetics
   b) Gastational diabetics
   c) Liver disease
   d) Impaired renal function
   e) Known allergy to sulphonamides
   f) Untoward outcomes during therapy eg. skin rash, cholestatic jaundice, dilutional hyponatraemia.
3. Ensure a proper trial of dietary therapy alone before starting a sulphonylurea.
4. Avoid long acting compounds in elderly patients.
5. No loading dose is required.
6. Do not use more than one sulphonylurea at a time.
7. Sequence of starting therapy:
   a) Starting dose 25% of maximal
   b) Measure degree of glycaemia control in 7 to 10 days
   c) Increase dose as necessary (until control or maximum dose is reached)
   d) Satisfactory response not likely if control is not attained in 3 to 4 weeks with maximum dose.
8. If primary or secondary failure develops, switch to insulin.
9. Early introduction of insulin should be considered if patient is underweight or showing ketones.
10. Ensure frequent review of the patient with emphasis on continuous dietary control and the lowest effective dose of sulphonylurea.
12. Be aware of possible interactions with other drugs.

Effectiveness and Efficacy of Sulphonylureas

It appears that the predictability of initial success with oral therapy is determined primarily by proper patient selection based upon the following 6 criteria:

1) Age at onset above 40 years.
2) Obesity at time of presentation.
3) Duration less than 5 years before initiation of treatment.
4) Absence of present or antecedent ketoacidosis.
5) Fasting blood glucose less than 200 mg/dl.
6) Insulin requirement less than 20 to 30 units daily (in patients under treatment with insulin and for whom a shift to an oral compound is under consideration).

In patients with diabetes of maturity onset (presumably mostly type — 2 diabetes), 20% to 40% of patients do not achieve satisfactory control with sulphonylureas. These are known as primary failures. Likewise a few patients — about 5% a year — although initially achieve satisfactory control will become secondary failures. Inappropriate patient selection, dietary non-compliance, the intervention of incidental infections and stresses, and the possibility of drug interactions, as well as the progression of the diabetic syndrome all conspire to lead to oral agent failure. With careful patient selection and dietary compliance, a good response has been reported over the first 5 years in 75% of patients, and successful therapy recorded for up to 20 years.

BIGUANIDES

Biguanides are guanidine derivatives. Their hypoglycaemic properties in experimental diabetes were first demonstrated in 1957 and shortly after this they were introduced into clinical use. The only biguanide in current use in Singapore is metformin. Phenformin has been withdrawn from use because of its liability to produce lactic acidosis, particularly in overdose, or in subjects with renal, hepatic or cardiac disease. Although this complication was rare, it was often fatal. Metformin has also been reported to produce lactic acidosis but it does so much less frequently than does phenformin and is safe in clinical practice.

Mode of Action

Although biguanides require the presence of insulin for their hypoglycaemic action, they do not stimulate insulin release and hence do not cause hypoglycaemia when given alone. The precise mode of action of biguanides in reducing blood glucose concentrations remains unclear but may include a degree of intestinal malabsorption, reduction in hepatic glucose production and particularly an increase in peripheral glucose uptake by making more receptors available to insulin.

Clinical Use

Metformin is as effective as chlorpropamide in reducing blood sugar concentrations in both obese and non-obese patients and treatment with metformin is associated with a notable reduction in weight. The cause of this weight loss may be partly related to an anorectic effect, malabsorption, and also perhaps a reduction in hyperinsulinaemia. Metformin is used in obese patients who fail to achieve satisfactory diabetic control with diet alone. It can also be used as an adjuvant to sulphonylurea therapy in patients who are not controlled adequately with sulphonylurea alone and in whom insulin therapy is not desired or is impracticable.

Pharmacokinetics

Metformin is not metabolised by the liver and is rapidly excreted by the kidneys by both glomerular filtration and active secretion, having a plasma half life of about 2 to 4 hours. Absorption is, however, slow and variable. Two or three times daily dosage (to a maximum of 2 gm) is necessary. Excretion is less rapid in patients with impaired renal function resulting in accumulation.

Side Effects

The most important untoward effect of metformin is gastrointestinal disturbance (nausea, vomiting, diarrhoea) and this may be reduced if patients take the tablets after meals and if the dose is built up slowly. In older patients there may be a reduced glomerular filtration rate and raised serum creatinine levels. Folate and vitamin B12 malabsorption can occur with long-term treatment.

Contraindications

Metformin should not be used in patients with renal failure and in those who are predisposed to develop lactic acidosis because of coexistent cardiovascular or hepatic disease. Metformin is also contraindicated in alcohol abuse, acute infections (especially respiratory or renal) and in the very old.

New Oral Agents in the Treatment of NIDDM

Acarbose is an inhibitor of alpha-glucosidase, and therefore slows carbohydrate digestion and absorption. It has been evaluated extensively, and found to have a minor but significant effect on glycaemic control in patients with NIDDM. Flatulence and intestinal bloating are common side effects. It is not yet available for general use in Singapore. New drugs which enhance the release of insulin (such as pirogliride) or increase the utilisation of glucose (ciglitazone) have been shown to be effective in animals, but side effects preclude their use in humans.

CONCLUSIONS

In spite of concerns about their long-term safety and efficacy, oral hypoglycaemic agents have an established place in the management of NIDDM. However, their use should not lead to the neglect of dietary compliance and regular exercise which are very important facets in the management of NIDDM. The decision to introduce insulin should not be delayed if oral agents have been unsuccessful in achieving control (primary failure), or have failed after a period of effective use (secondary failure).

REFERENCES

1. Asmal, A.C. and Marble, A.: Oral Hypoglycaemia Agents — An Update, Medical Progress, May 1986.
2. Beaven, D.W..: Antidiabetic Agents Today — Non-insulin-dependent Diabetes Mellitus, Current Therapeutics, January 1983.
3. Kolterman, O.G.: The Use of Oral Hypoglycaemic Agents in the Management of Type II Diabetes, Clinical Guide of Diabetes Mellitus, 1987.
4. Larkins, R.G.: The Use of Oral Hypoglycaemic Agents in the Treatment of Diabetes Mellitus, The Medical Journal of Australia, May 4, 1987.
5. Melander, A.: Clinical Pharmacology of Sulphonylureas, Metabolism, February 1987.

MULTIPLE CHOICE QUESTIONS

1. The following statement(s) is/are true of oral hypoglycaemic drugs
   - A they are used in the treatment of maturity onset diabetes mellitus which fails to respond to diet alone
   - B jaundice may be a side effect
   - C alcohol enhances their hypoglycaemic effect
   - D they are used in the treatment of a diabetic with a history of ketoacidosis
   - E they are useful when diabetic control deteriorates with infection.

2. In the treatment of diabetes mellitus
   - A metformin is no longer used because of the risk of causing lactic acidosis
   - B a sulphonylurea rather than a biguanide should be used in the obese patient
   - C chlorpropamide may cause prolonged hypoglycaemia
   - D cimetidine may potentiate the hypoglycaemic action of sulphonylureas
   - E oral hypoglycaemic agents should be withdrawn during pregnancy.

3. The following statements are correct
   - A hypoglycaemia is a recognised hazard of treatment with a biguanide given alone
   - B metformin increases peripheral glucose uptake
   - C the simultaneous use of glibenclamide and metformin is contraindicated
   - D a sulphonylurea may be used to treat early diabetes in childhood and adolescence

E hypoglycaemia may be masked by beta blockers.

4. Chlorpropamide
   A has a diuretic effect
   B is completely metabolised and inactivated in the liver
   C is particularly useful in the elderly
   D interacts with alcohol to cause profound facial flushing
   E is associated with the serious side effect of lactic acidosis.

5. Drugs that potentiate the hypoglycaemic action of sulphonylureas include
   A corticosteroids
   B warfarin
   C rifampicin
   D phenytoin
   E thiazide diuretics

6. Known adverse effects to oral hypoglycaemic agents include
   A diarrhoea
   B skin rashes
   C transient abnormalities of liver function
   D blood dyscrasia
   E hypocalcaemia

7. Metformin
   A is metabolised and inactivated by the liver
   B tends to suppress the appetite
   C common side effects are related to the gastrointestinal tract
   D is particularly useful in patients with renal failure
   E should be avoided in those with a heavy alcohol intake.

ANSWERS

1. A B C
2. C D E
3. B E
4. D
5. B
6. A B C D
7. B C E

HOME STUDY SECTION

X-RAY QUIZ

Dr K Param, *MBBS (S'pore), DMRD (Liv), FRCR (UK)*

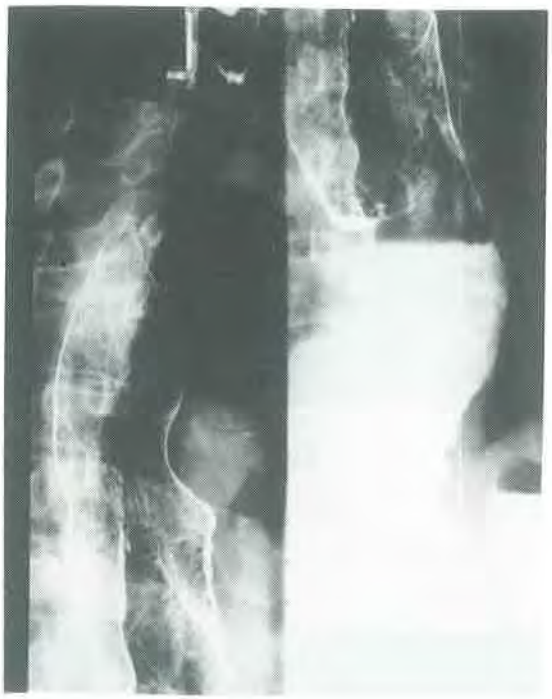


Figure I

A middle age Malay male presented with a fairly long history of regurgitation (1-2 years) dysphagia and weight loss. There was no loss of appetite. Figure I shows an x-ray of a barium swallow examination.

1) What abnormal features can you see?
2) What are the possible diagnoses?

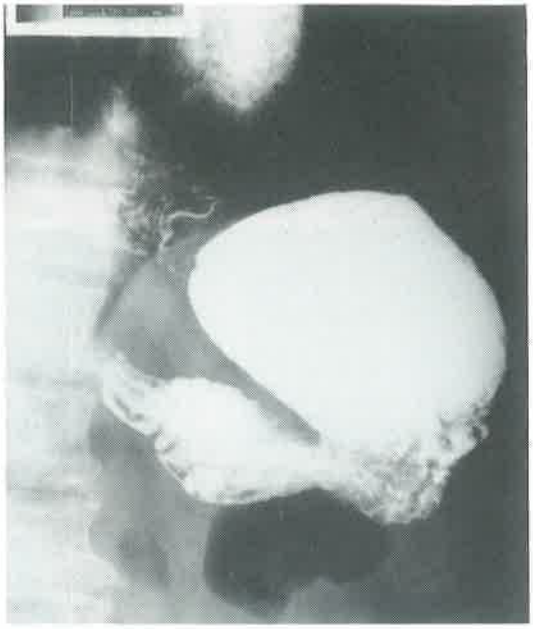


Figure II

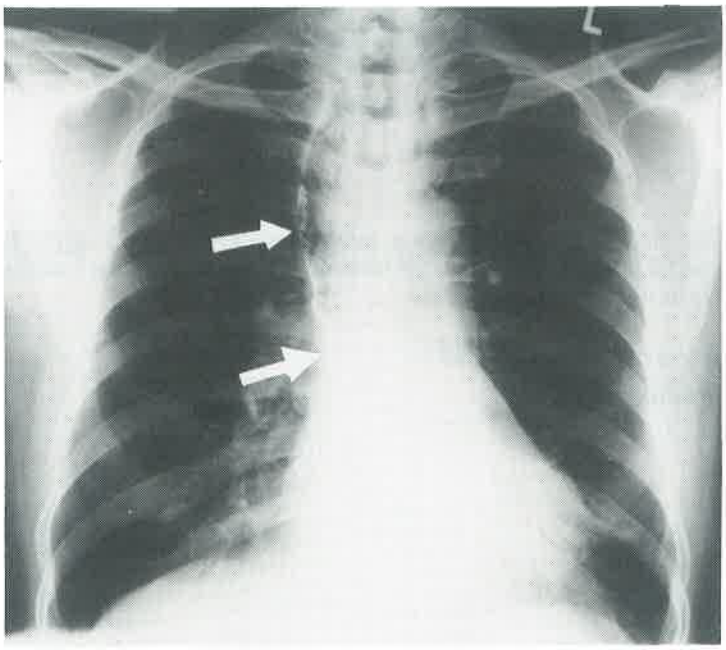


Figure III

ANSWER TO X-RAY QUIZ

Figure I shows a diffuse widening of the oesophagus with an air-fluid level. The distal end of the oesophagus tapers smoothly and has a 'bird-beak' appearance.

Figure II shows the dilated oesophagus with a smooth mucosa. There is little air in the stomach. The chest X-Ray in Figure III demonstrates a widened mediastinum due to the dilated oesophagus lined with barium (arrows).

DIAGNOSIS

Achalasia of oesophagus

DISCUSSION

There are a number of conditions that give rise to a diffusely dilated oesophagus. This could be secondary to a motility disorder or distal mechanical obstruction.

(A) Secondary to Disordered Motility

Achalasia
Post Vagotomy
Chagas Disease
Scleroderma
Systemic Lupus Erythematosus
Prebyesophagus
Diabetic Neuropathy

(B) Secondary to Distal Obstruction

Stricture (Reflux, Post-operative)
Neoplasm

Achalasia is a primary oesophageal motor disorder which consists of the inability of the lower oesophageal sphincter to relax fully after swallowing and loss of peristatic waves at the lower oesophagus.

The patients present with slowly progressive dysphagia and regurgitation. The dilated oesophagus has a tapered distal end (Bird-beak) with an intact mucosa.

Achalasia must be differentiated from other causes of a dilated oesophagus, particularly a malignant neoplasm. Endoscopy with biopsy as well as cytology are required to confirm the diagnosis of Achalasia. Complications of Achalasia include oesophagitis with or without ulceration and a higher incidence of squamour cell carcinoma. Achalasia is treated by pneumatic dilatation or surgically by means of the Heller procedure.

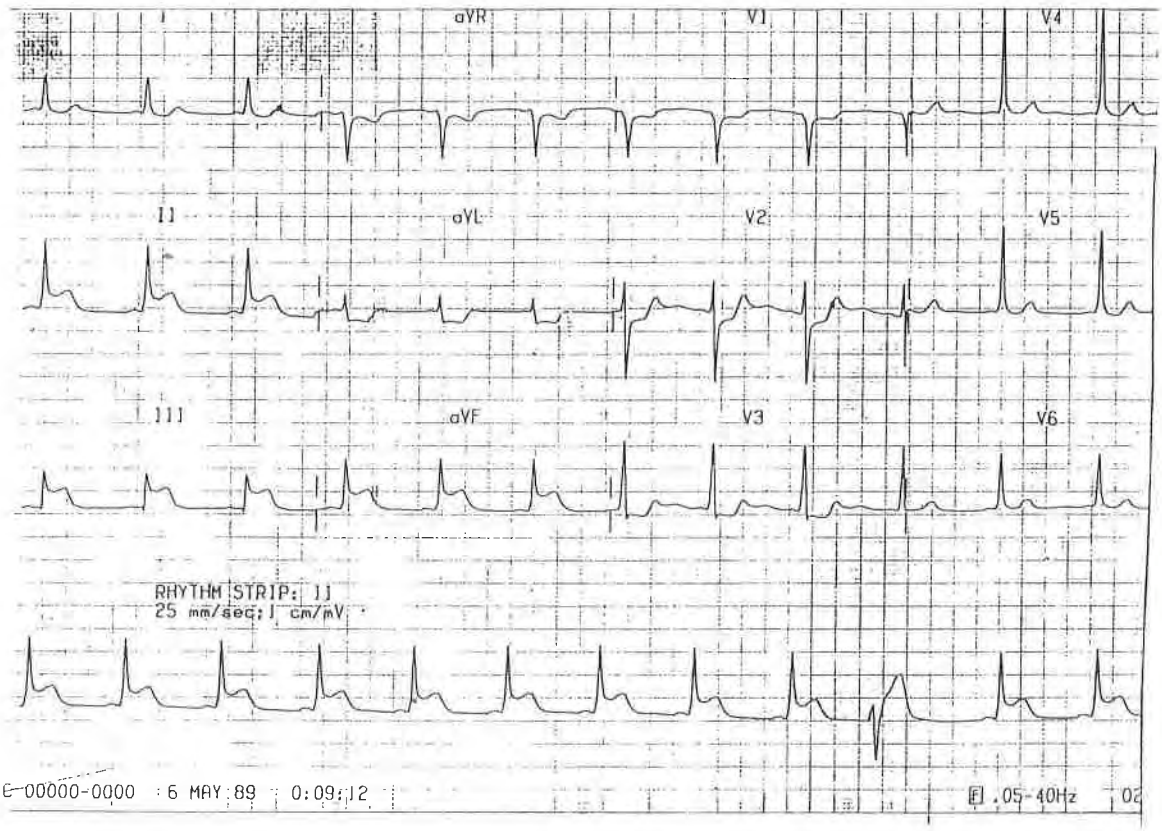
ECG QUIZ

Contributed by **Dr Baldev Singh,** *MBBS (S'pore), M Med (Int Med), MRCP (UK)*

The ECG shown below belongs to a 31-year-old Malay male who was seen by his Company doctor for chest pain. An ECG was done and reported as normal and he was given analgesics. That same evening he had more chest pain and was seen at a Government hospital A & E unit where ECG and cardiac enzymes were done. These were reported as normal and he was sent home. Pain subsided but two days later he had more pain and he saw his Company doctor again and was sent home with medicines. The next day he experienced severe chest pain in the evening and presented himself at a private hospital A & E.

The ECG shown was done in the Emergency Department and he was admitted to the ICU. The patient had no history of hypertension, diabetes mellitus or familial hyperlipidemia. He was a smoker since his early twenties and currently in his present job as a news editor smoked about 30 cigarettes a day.

What ECG abnormalities are seen and what is his most likely diagnosis?



ANSWER TO ECG QUIZ

The ECG shows saddle back type of ST elevation in II, AVF and reciprocal ST depression in I, AVL, V1 to V3. Saddle back ST elevation is commonly seen in acute pericarditis but can also be seen in ischaemia. The ST elevation in acute pericarditis is usually seen in most leads and especially so in anterior leads. Furthermore in pericarditis reciprocal ST depression is not seen.

This patient had acute inferior myocardial infarction. His SCPK was elevated to over 1000 and SCPK-MB was also markedly above normal.

In addition the ECG also shows a short PR interval and slurred upstroke of the QRS complex — delta wave. Hence this patient has a Wolff Parkinson White Syndrome as well.

COMMENTS

This patient quite clearly was having unstable angina prior to admission. The diagnosis was probably missed due to 2 reasons. Firstly, a low index of suspicion because of his fairly young age. A history of smoking is a powerful risk factor and any smoker presenting with chest pain, even if other risk factors are absent, should alert the doctor to possibility of coronary artery disease.

Secondly, a resting ECG is of very low diagnostic value in coronary artery disease unless it is done during a pain episode. Cardiac enzymes are similarly of no help if the patient has not infarcted and may be normal immediately after infarction.

BOOK REVIEW

SKILLS & MANAGEMENT IN FAMILY MEDICINE

Authors: **Drs EK Koh, LG Goh & P Kee**
Publisher: **Singapore: PG Publishing**

A medical book by local doctors is always an occasion for joy. When the local doctors are general practitioners/family physicians, known personally to the reviewer for their dedication and commitment to the ideals of general practice, the joy is multiplied.

They have not set out to develop new theories in general practice. The task they have undertaken is to bring together lines of thoughts and inquiry from many allied fields and arrange them in a pattern that can be understood in a clinical setting. The pattern becomes the key to unravel the psychodynamics of the family physician-patient relationship.

It is not suggested that they have merely collected the works of other authors into a compendium leaving the reader to take his pick from amongst the many titles and collection.

Their intention, though not expressed as such, is to absorb their colleagues into a kind of inquiry that cannot be obtained or inferred from the orthodox "doctor-patient" relationship taught to many generations of medical students by rigidly disciplined institutional medical teachers of the past.

It is not untrue to say that even without the benefit of the wisdom of the book under review, the bulk of general practice patients will continue to obtain adequate treatment in physiological or pathological terms. This book however adds the bonuses of intellectual and emotional satisfaction not only to the patients under care but to the care-givers, the GPs as well.

Severing the Gordian knot is fast becoming the standard way of solving a problem. The consequences however are that the resultant frayed ends become problems demanding attention themselves. There is nothing more satisfying than to be able to untwine and straighten a patient's problem without resorting to the quick "cut". There are alternative ways of untying the Gordian knot and this book has to do with these alternatives. They can be acquired and the authors are showing how.

As he goes through the book, the reader cannot fail but be entertained by a few Freudian slips. Referring to modern medical treatment as a warhead on a ballistic missile, the authors state,

"It is important if the missile is not directed and delivered to the right target."

I must protest with Freudian authority that a missile whether or not on target has never been regarded as an instrument of impotence but one of potent devastation. In another part of the book some 78 pages away, the authors suggest that,

"As one listens creatively to the patient, one develops an understanding of the patient's life situation, lifestyle, hopes, aspiration and fears."

I am not without imagination but I can't in all honesty "listen creatively".

There is more than the usual number of mis-spellings of words and names, missing alphabets and punctuation marks and

transposed columns in this book. The authors will do well to obtain the services of a good proof reader in the next printing.

Despite the "debut" defects which are in themselves amusing, this book is thoroughly recommended to all GPs who want to enjoy looking after their patients holistically. GPs must enjoy what they are doing and this book has added this extra dimension to their practice. Each patient has built up an intricate eco-system of relationships in his own life and he is very much in the centre of this. Until he has accepted the GP as being part of his eco-system, the claim to being his family physician is anything but real. This book helps the GP to find a place in his patient's eco-system and to merit his trust as his family physician. The prudent doctor will certainly not want this to happen by chance but will want to earn it. What better way to earn it than by learning and equipping himself with the much needed knowhow that this book provides!

LVC

AN APPRECIATION

LORD HUNT OF FAWLEY

CBE, DM, FRCP, FRCS, FRCGP, FCGPS

I first met Lord Hunt in 1968. He was Dr John Hunt then and he was President of the Royal College of General Practitioners on his way to Australia.

He was a tall man, had some difficulty with a stiff hip, but he was friendly and cheerful and most of all had a discerning mind which could assess every situation in life accurately.

Even before having met him I was aware of the tremendous work put in by the man in the establishment of the English College of General Practitioners. I told him of our problems then in setting up a similar academic body for our GPs in Singapore. He listened attentively and then shared with me the wealth of his experience.

He had a most trying time in his attempts to set up the English College. He told me that at one time all the Royal Colleges had lined up against him. A fellow of the Royal College of Surgeons even taunted him by saying, "It's absolute nonsense, you might as well found a college of ingrowing toe-nails."

Fortunately for the new college he had a valuable ally in Sir Henry Willink, a past Minister of Health who was later to write of his experience as "I always feel that the foundation of the College was one of the very best projects with which I have been involved in my life."

John Hunt impressed upon me the need of winning friends and allies to our cause. To set about doing this we climbed four flights of stairs to spend an afternoon with the Vice-Chancellor of the University of Singapore, Dr Toh Chin Chye in his office. He was supportive of the idea.

Next we had working lunches and dinners with all the medical top brass of the country and this included consultants from the hospitals, senior general practitioners, officials of the Academy of Medicine and the Ministry of Health.

Fortunately we had a better reception from our top medical people in Singapore than his experience with the "giants" in UK. They were all friendly and promised to help. One small factor which might have swung things in our favour was that he had a pleasant reunion with a fellow colleague of his at Barts, Prof Sir Gordon Arthur Ransome.

John Hunt worked hard for our cause. He spent the better part of one night writing an article supporting the need for an academic body for GPs in Singapore, an article which as editor of the SMA Medical Newsletter I was only too happy to publish it. He also told me that in his opinion we would be better off with an independent body of our own rather than be a faculty of any overseas college.

During his short stay here I also took him round to visit the medical establishments of the British Armed Forces stationed in Singapore. He had been a Wing Commander in the RAF during the war and was in the neuro-psychiatric unit where cases of head injury were under his care. This was not surprising as John Hunt had obtained his MRCP in 1934 while he was at Barts. He surprised the senior staff at St Batholomew's Hospital by going into general practice because many considered him destined for a "brilliant career as a neurology consultant."

Among his many other achievements he was also President of the Hunterian Society, the GP section of the Royal Socie-

ty of Medicine and a member of the general advisory council of the BBC. For his contribution to the medical world he was created a life baron by the Queen in 1973. For his work in helping us establish our own college he was made an honorary Fellow of the College of General Practitioners Singapore.

He has been to Singapore a few times since his first visit and I always look him up when I am in London. He had become an old friend and we would talk of many things other than on medical topics. Once he asked me to attend a seminar in Canada on Euthanasia. He was unable to go and he needed to know what went on as he was preparing to address the House of Lords on the subject. On my return we shared views over lunch in the House of Lords, a place which most tourists like myself seldom get to see.

Lord Hunt of Fawley died on 28 December 1988 after an illness most bravely borne. During his declining years his eyesight failed him and it was his wife Elisabeth who gave him moral and physical support. She was a pillar of strength and she served as his window to the world. Up to the end John's mind was keen and sharp and he always wanted to know what was happening around him and in the world. Besides his wife Elisabeth, he leaves behind twin doctor sons and two daughters.

Lord Hunt of Fawley has not left us. He has just gone to join the other medical immortals like Sir William Osler and Sir James Mackenzie. For me it was a privilege knowing him. I feel I have lived with medical history.

For all of us his name will always be a star in the medical firmament.

E K

NEWS FROM THE COUNCIL

1. TWELFTH COUNCIL – 1989/91

At the recent Annual General Meeting held on 14 May 1989, the following office bearers were elected:

President	Dr Koh Eng Kheng
Vice-President	Dr Alfred Loh Wee Tiong
Censor-in-Chief	Dr Lim Kim Leong
Honorary Secretary	Dr Soh Cheow Beng
Honorary Treasurer	Dr Wong Wee Nam
Council Members	Dr Chan Cheow Ju
	Dr Huan Meng Wah
	Dr John Lim Khai Liang
	Dr Richard Ng Mong Hoo
	Dr Arthur Tan Chin Lock
Honorary Editor	Dr Goh Lee Gan

2. 12TH WONCA CONFERENCE

Drs Alfred Loh and Goh Lee Gan represented the College at the 12th WONCA Conference held in Jerusalem on 28 May – 1 June 1989.

At the WONCA Council Meeting held from 26 – 27 May 1989 at the Zichron Yacov Conference Centre, the WONCA office bearers for 1989 – 1992 were elected:

Dr Douglas G Garvie (UK)	Chairman of Council
Dr Donald W Rae (Canada)	President
Dr Peter C Y Lee (Hong Kong)	President Elect
Dr Wesley E Fabb (Australia)	Hon Secretary & Hon Treasurer
Dr Goran Sjonell (Sweden)	Member at large
Dr Giora Almagor (Israel)	Member at large
Dr Alfred Loh (Singapore)	Vice-President, Asia Pacific Region
Dr Richard Inskip (USA)	Vice-President, America
Dr Giora Almagor (Israel)	Vice-President, Europe

A report of the Conference will be published in the next issue.

3. 1990 REGIONAL CONFERENCE

The 1990 WONCA Regional Conference will be held in Bali from 24 – 28 June. The theme is Family Practice Towards the Year of 2000: Prospects and Challenges. You can register through the College Secretariat (Te. No. 2230606).

4. 1992 WONCA WORLD CONFERENCE

The 1992 WONCA World Conference will be held in Vancouver in May. Details will be announced later.

5. 2ND ANNUAL SCIENTIFIC CONFERENCE

The 2nd Annual Scientific Conference of the College of General Practitioners Singapore will be held on 11 and 12 November 1989. The theme is "Teamwork in Health Care". Dr Dixie Tan, President MINDS and MP for Ulu Pandan has been invited to be the Sreenivasan Orator for 1989.

THE SINGAPORE FAMILY PHYSICIAN
Guidelines For Authors

Authors are invited to submit material for publication in the Singapore Family Physician on the understanding that the work is original and that it has not been submitted or published elsewhere.

The following types of articles may be suitable for publication: case reports, original research work, audits of patient care, protocols for patient or practice management and review articles.

PRESENTATION OF THE MANUSCRIPT

The whole paper

* Normally the text should not exceed 2000 words and the number of illustrations should not exceed eight.

  Type throughout in upper and lower case, using double spacing, with three centimetre margins all round. Number every page on the upper right hand corner, beginning with the title page as 1. Make all necessary corrections before submitting the final typescript.

  Headings and subheadings may be used in the text. Indicate the former by capitals, the latter in upper and lower case underlined.

  Arrange the manuscript in this order: (1) title page, (2) summary, (3) text, (4) references (5) tables, and (6) illustrations.
* Send three copies of all elements of the article: summary,text, references, tables and illustrations. The author should retain a personal copy.

The title page

* The title should be short and clear.
* Include on the title page first name, qualifications,present appointments, type and place of practice of each contributor.
* Include name, address and telephone number of the author to whom correspondence should be sent.
* Insert at the bottom: name and address of institution from which the work originated.

The summary

* The summary should describe why the article was written and give the main argument or findings.
* Limit words as follows: 100 words for major articles; 50 words for case reports.
* Add at end of summary: an alphabet listing of up to 8 keywords which are useful for article indexing and retrieval.

The text

The text should have the following sequence:

* Introduction: State clearly the purpose of the article.
* Materials and methods: Describe the selection of the subjects clearly. Give references to established methods, including statistical methods; provide references and brief descriptions of methods that have been published but are not well known. Describe new or substantially modified methods, giving reasons for using them and evaluate their limitations. Include numbers of observations and the statistical significance of the findings where appropriate.

  Drugs must be referred to generically; all the usual trade names may be included in parentheses. Dosages should be quoted in metric units.

  Laboratory values should be in SI units with traditional units in parentheses.

  Do not use patient's names, initials or hospital numbers.
* Results: Present results in logical sequ-

ence in the text,tables and illustrations.

* Discussions: Emphasise the new and important aspects of the research and the conclusions that follow from them. Indicate the implications of the findings and limitations. Relate the observations to other relevant studies.

Illustrations

* Diagrams, line drawings, photographs or flow charts are valuable but their use will be subject to editorial policy. Transparencies or prints are acceptable for colour reproduction at the authors' expense.
* Each illustration must carry its appropriate Figure number and the top should be clearly labelled.
* Figure legends, typed (double-spaced) and each on a separate page should be no more than 45 words.

Tables

* Any table must supplement the text without duplicating it.
* Each should be numbered, typed on a separate sheet with an appropriate title.

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Acknowledgements

Place these at the end of the text, before references.

References

These should be limited to the work cited in the article.

References should be double spaced and arranged alphabetically by author. Personal communications are not acceptable as references. Unpublished material should be included only if an address can be given from which a copy of the material cited is available.

Authors are responsible for accuracy of references, which should conform to the Vancouver style (see Further reading). List all authors (include all initials) when there are six or fewer; when seven or more list the first three and add et al. Give the title of the paper cited in full, the title of the journal abbreviated according to Index Medicus (if not listed by Index Medicus spell in full); the year; the volume number and the first and last page number of the article.

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Further reading

1. INTERNATIONAL COMMITTEE OF MEDICAL JOURNAL EDITORS. Uniform requirements for manuscripts submitted to biomedical journals. Ann Intern Med 1988; 108: 258-265.
2. Bailar III JC and Mosteller F. Guidelines for Statistical Reporting in Articles for Medical Journals. Ann Intern Med 1988; 108: 266-273.

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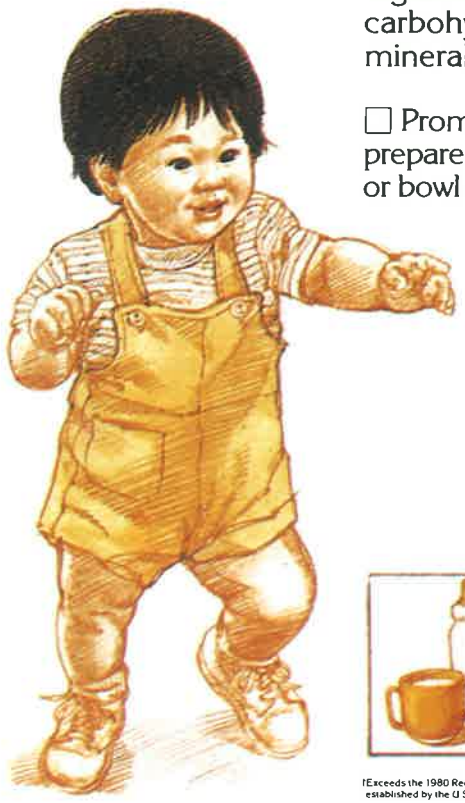

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Many men face the idea of going bald with equanimity, viewing it as a natural part of the aging process. But the others – the ones who come to you for consultation on hair loss therapy – see baldness as a real problem, a problem they would like your help in solving.

While many questions about the balding process remain unanswered, one thing has changed during recent medical history. Today, for the first time, there is an effective product for you to prescribe in the treatment of male pattern baldness: **REGAINE Topical Solution.**

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"De Villez and Olsen et al have shown in their respective studies that topical minoxidil prevents expansion or enlargement of the bald area in the majority of patients treated for 12 months. Our results confirm these findings and extend the time frame to 24 months. Diameter measurements of the bald area provided objective evidence of the prophylactic therapeutic activity of topical minoxidil."

Long-Term Efficacy Of Topical Minoxidil In Male Pattern Baldness

Harry Irving Katz, et al, *J Am Acad Dermatol 16:711-8 1987*

Stimulation of Terminal Hair Growth

"Treatment of subjects with topical minoxidil for 4 months resulted in a statistically significant increase in terminal hair growth in comparison with placebo therapy. No subject had a net hair loss in the target area during the study."

Topical minoxidil in early male pattern baldness

Elise A Olsen, et al, *J AM ACAD DERMATOL 13: 185-192, 1985*

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FIRST ANNOUNCEMENT

WONCA REGIONAL CONFERENCE ASIA PACIFIC REGION

June 24-28, 1990, Bali - Indonesia

THEME

Family Practice Towards the Year of 2000: Prospects and Challenges

Organized by:

The Indonesian College of Family Physicians

REGISTRATION FEE

	before 1 March 1990	after 1 March 1990
Participant	US$275	US$325
Accompanying person	US$150	US$175

ACCOMMODTION

- Pertamina Cottage (Congress venue)
- Surrounding Hotel

Please contact our College Secretariat Tel: 2230606 (Singapore) for further details.

Bactroban

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- Highly active against the causative pathogens.
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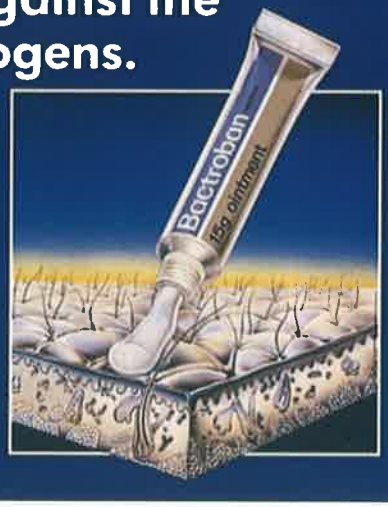
- 96% success in a variety of skin infections.[1]



PRESCRIBING INFORMATION

Presentation BACTROBAN ointment: mupirocin 2% w/w in polyethylene glycol base. 5g or 15g tubes.

Activity BACTROBAN is a topical anti-bacterial agent, active against those organisms responsible for the majority of skin infections, e.g. Staphylococcus aureus, including methicillin-resistant strains, other staphylococci and streptococci. It is also active at concentrations attainable on the skin against Gram-negative skin pathogens such as Escherichia coli and Proteus spp.

Indications Bacterial skin infections, e.g. impetigo, folliculitis and furuncolosis.

Dosage and Administration Adults and children: BACTROBAN should be applied to the affected area up to three times daily, for up to 10 days.

Precautions Avoid contact of BACTROBAN ointment with the eyes. Use BACTROBAN with caution in patients with moderate or severe renal impairment.

Use in Pregnancy: There is inadequate evidence of safety to recommend the use of BACTROBAN during pregnancy.

Contra-indications Hypersensitivity to BACTROBAN or other ointments containing polyethylene glycols. This BACTROBAN formulation is not suitable for ophthalmic or intra-nasal use.

Side-effects Some minor localised effects such as burning, stinging and itching have been reported.

Storage BACTROBAN should be stored at room temperature (below 25°C). Not all presentations are available in every country.

Further information is available from Beecham Pharmaceuticals, Brentford, England. BACTROBAN is a trademark.

Beecham Pharmaceuticals
INTERNATIONAL DIVISION

References 1. Contemporary Dermatology, 1987, **1** (2): 32. 2. Proc. Int. Symp. on Bactroban, Excerpta Medica, 1984, 190. 3. Int. J. Derm., 1987, **26**(7):472. 4. Curr. Ther. Res. Exp., 1987, **41** (1): 114. 5. Proc. Int. Symp. On Bactroban, Excerpta Medica, 4, 141. 6. Roy. Soc. Med. Int. Cong. and Symp. 80, 173.

International Division 001/34/2/14/89

CME UPDATE: SURGICAL & ORTHOPAEDIC MODULE

PROGRAMME

21.7.89 SWELLING IN THE NECK – DIAGNOSIS AND MANAGEMENT

Lecturer
Assoc Prof Walter Tan
Dept of Surgery, NUH

Moderator
Dr Soh Cheow Beng

28.7.89 NO LECTURE

04.8.89 CURRENT SURGICAL MANAGEMENT OF PEPTIC ULCERS

Lecturer
Mr Ng Boon Keng
Sr Surgeon/Head
Dept of Surgery, AH

Moderator
Dr Wong Wee Nam

11.8.89 "MINOR"ORTHOPAEDIC SURGERY

Lecturer
Mr Tan Ser Kiat
Sr Orthopaedic Surgeon/Head
Dept of Orthopaedic Surgery, SGH

Moderator
Dr Huan Meng Wah

18.8.89 SURGICAL MANAGEMENT OF COMMON ANO-RECTAL CONDITIONS

Lecturer
Mr Goh Hak Su
Head
Dept of Colorectal Surgery, SGH

Moderator
Dr Chan Cheow Ju

25.8.89 NO LECTURE

01.9.89 EARLY DIAGNOSIS AND MANAGEMENT OF CARCINOMA OF STOMACH

Lecturer
Mr Low Cheng Hock
Sr Surgeon/Head
Dept of Surgery II, TTSH

Moderator
Dr John Lim

08.9.89 PITFALLS IN THE MANAGEMENT OF COMMON HAND INJURIES

Lecturer
Mr Teoh Lam Chuan
Head
Hand Surgery Unit, SGH

Moderator
Dr Arthur Tan

15.9.89 PRINCIPLES OF MANAGEMENT OF COMMON SPORTS INJURIES

Lecturer
Dr Giam Choo Keong
Consultant/Head
Sports Medicine and Research Centre
S'pore Sports Council

Moderator
Dr Alfred Loh

22.9.89 CURRENT CONCEPTS IN THE CONSERVATIVE MANAGEMENT OF LOW BACK PAIN

Lecturer
Ms Soh Say Lim
Physiotherapy Dept, SGH

Lecturer
Mr Lee Eng Hin
Sr Lecturer/Consultant
Dept of Orthopaedic Surgery, NUH

Moderator
Dr Richard Ng

For further details contact the College Secretariat, Tel: 2230606.

FAMILY MEDICINE TEACHING PROGRAMME MODULE 6

	6	
	Sep 89 – Nov 89 (Aug 89 – Oct 89)*	
6A	**THE ADULT PATIENT**	
1	9 Sep	Problems of living
2	23 Sep	Harmful lifestyles
3	7 Oct	Occupational health
4	21 Oct	Fitness to work; statutory examinations
6B	**BONE & JT DISORDERS**	
1	16 Sep	Common rheumatic problems in general practice
2	30 Sep	Emergency medicine & CPR; the housecall
3	14 Oct	Sports injuries
C	**PRACTICE MANAGEMENT**	
6C	4 Nov	Setting up practice – Single or partnership – Location – Clinic design – Equipping the clinic

For further details contact the Secretariat Tel: 2230606.

NEW FROM ICI

ZESTRIL

lisinopril

An advance in ACE inhibition

Once daily

Full 24-hour control of hypertension

Well tolerated

ESCRIBING NOTES
nd tablets, containing 5, 10 and 20 mg of lisinopril drate coloured pink, pink and red respectively.

cations
ertension and congestive heart failure (CHF). In nts with CHF 'Zestril' is used as an adjunct to alis and diuretics.

age
pertension the usual effective maintenance dose mg once daily. 10 mg once daily can be used re a starting dose is appropriate. A lower starting (2.5 or 5 mg) is required in patients with renal irment, renovascular hypertension, volume or depleted patients and some elderly patients. reafter dosage should be adjusted according to d pressure response. The maximum dose d in long-term controlled clinical trials was 80 day. CHF 5 to 20 mg once daily, starting dose 2.5 mg.

traindications
ersensitivity to any component of this product.

cautions
e required in volume or salt-depleted patients, e previously treated with diuretics and those with renovascular hypertension as symptomatic hypotension may occur. In hypertensive patients in whom the diuretic cannot be discontinued initial dose of 'Zestril' should be 5 mg. Hypotension may occur during anaesthesia. Correct by plasma volume expansion. Renal impairment may occur in some CHF patients who experience hypotension on starting 'Zestril'. This is usually reversible. Dosage in renal impairment (and elderly) should be based on creatinine clearance.

Pregnancy
There are no studies in pregnant women.
Should only be used if potential benefit outweighs the risk to the fetus. Caution if given to nursing mother.
No paediatric experience.
Diuretics potentiate the antihypertensive effect of 'Zestril'. Symptomatic hypotension can be minimised by discontinuing diuretic prior to 'Zestril'. Avoid use of potassium sparing diuretics and potassium supplements with 'Zestril' especially in patients with renal impairment. If used concurrently, frequent monitoring of serum potassium is required.
Indomethacin may diminish the antihypertensive efficacy of concomitantly administered 'Zestril'. 'Zestril' ameliorates diuretic-induced hypokalaemia.

Side effects
Mostly mild and transient: dizziness, headache, diarrhoea, fatigue, cough, nausea, rash, hypotension, orthostatic effects, palpitation, chest pain, asthenia. Angioneurotic oedema has been rarely reported. If it occurs, discontinue 'Zestril' promptly. Treatment with antihistamines or adrenaline may be appropriate. Increases in blood urea and serum creatinine, usually reversible, have been seen. Small decreases in haemoglobin and haematocrit have occurred. Hyperkalaemia may occur.

Overdosage
No data. Correct hypotension with plasma volume expansion. 'Zestril' is dialysable.

'Zestril' is a trademark
Further information is available on request

ICI (Singapore) Private Limited
Finlayson House 4 Raffles Quay
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Telephone 224381

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ONCE DAILY

Oruvail 200

controlled release ketoprofen

STRIKING PERFORMANCE IN ARTHRITIS

Prescribing Information

Dosage Orally with food, 200mg daily. **Indications** Rheumatological disorders, including osteoarthritis, rheumatoid arthritis, ankylosing spondylitis and acute musculoskeletal conditions; dysmenorrhoea. **Contra-indications** Recurring history of/or peptic ulceration; chronic dyspepsia; use in children; in patients sensitive to aspirin or other non-steroidal anti-inflammatory drugs known to inhibit prostaglandin synthetase or with bronchial asthma or allergic disease, severe renal dysfunction. **Precautions** Pregnancy; lactation. Concomitant administration of protein-bound drugs. **Side-effects** Occasional gastro-intestinal intolerance. Very rare gastro-intestinal haemorrhage/skin rashes. **Presentation** 200mg capsules PL0012/0158; 100mg capsules PL0012/0143. Basic NHS cost (Jan. 1987) 28x200mg capsules in calendar blister pack 100x100mg capsules ORUVAIL is a trade mark. Further information is available from:

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