CHESTPIECE

Vol. 3 No. 7

APRIL '76

NEW

Canesten®

Broad-spectrum antimycotic with fungicidal and trichomonacidal action

eradicates fungi

Vaginal tablets
in infectious leucorrhea and vaginitis caused by Candida, Torulopsis, Trichomonas.

Therapy takes only 6 days

Cream and solution
in all dermatomycosis caused by dermatophytes, yeasts mould and other fungi.

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100 g cream/solution contain 1 g bis-phenyl-(2-chlorophenyl)-1-imidazolyl-methane.
Packing: Pack of 6 vaginal tablets. Tube of 20 g of cream. Plastic bottle of 20 ml of solution.

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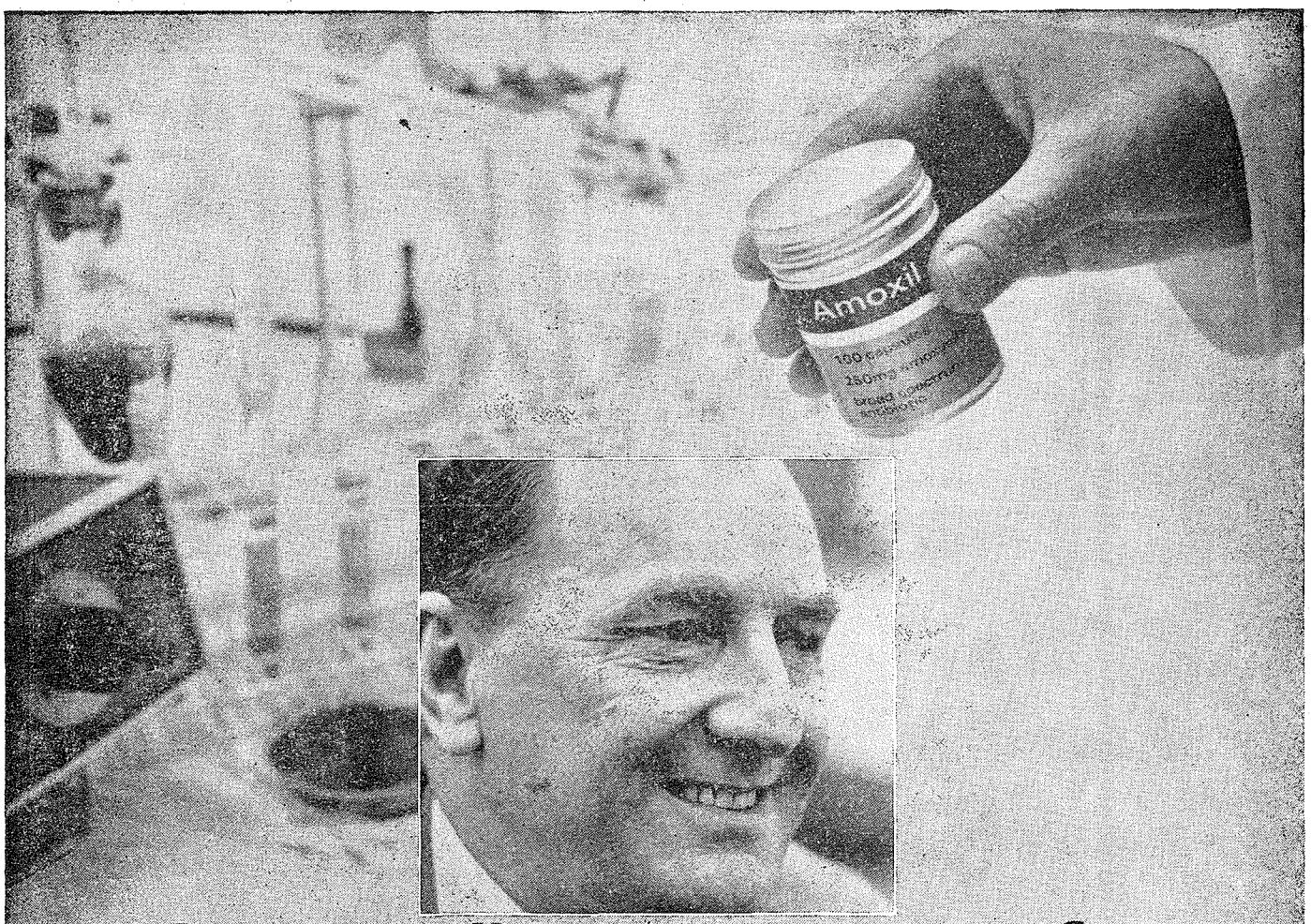

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▶ Amoxil t.d.s.

Amoxil t.d.s. – An excellent broad spectrum antibiotic in the treatment of respiratory tract infections.

Bencard *Amoxil (trademark) is a product of research from Bencard, Brentford, England.*

new

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chestpiece

april '76

journal of the malta medical students association

MALTA MEDICAL STUDENTS' ASSOCIATION

Committee for 1976

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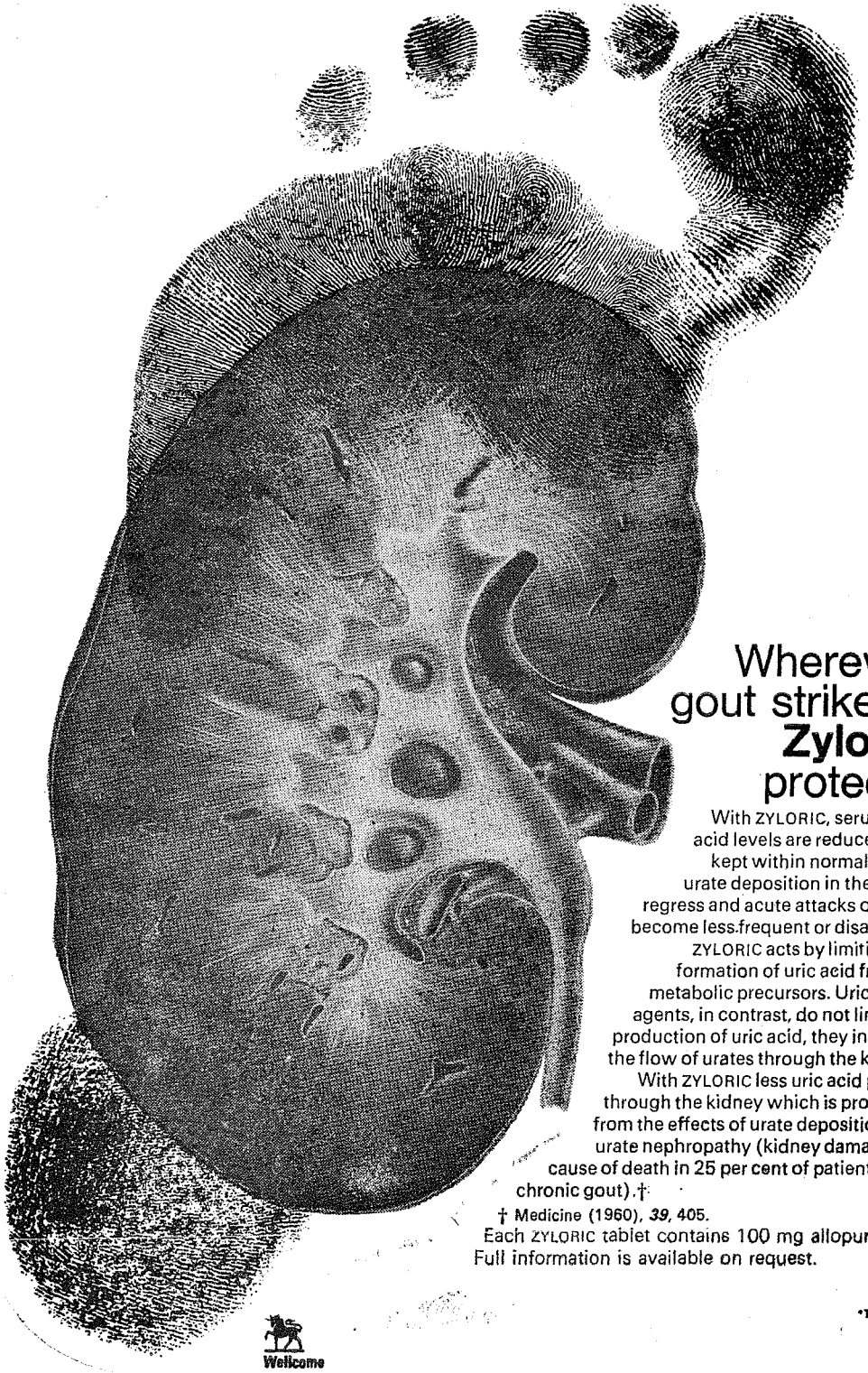

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With ZYLORIC, serum uric acid levels are reduced and kept within normal limits, urate deposition in the joints regress and acute attacks of gout become less frequent or disappear. ZYLORIC acts by limiting the formation of uric acid from its metabolic precursors. Uricosuric agents, in contrast, do not limit the production of uric acid, they increase the flow of urates through the kidney. With ZYLORIC less uric acid passes through the kidney which is protected from the effects of urate deposition and urate nephropathy (kidney damage is a cause of death in 25 per cent of patients with chronic gout).†

† Medicine (1960), *39*, 405.

Each ZYLORIC tablet contains 100 mg allopurinol.
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Wellcome

Burroughs Wellcome & Co. (The Wellcome Foundation Ltd.) **Dartford, Kent.**

Editorial

summer jobs

The recent announcement that financial assistance by the government will be given to students who are over 18 years of age has been welcomed by most of us. Up to now students who wished to enter University or the Polytechnic had to depend entirely on their parents' support for the duration of their studies. In several instances the more unfortunate ones had to deprive themselves of tertiary education because their parents could not afford to support them financially. So, although not all agree on the form which the government assistance should take, its introduction is a big step towards making tertiary education available to all.

It has been rumoured that Medical Students in their Final Course, will be given jobs connected with the clinical work at St. Luke's. We sincerely wish that this rumour is true because this would prevent a conflict with the regulations, which would otherwise arise if we are given jobs somewhere else. In fact the regulations state that, 'Practical and Clinical work will be carried out throughout the course, including the vacations.' This means that students in their clinical course, have to attend the out-patients department, ward-rounds and operating sessions at St. Luke's even throughout the summer holidays. Therefore by giving us such jobs at St. Luke's we will be able to benefit from the Government's assistance without conflicting with the Regulations.

The Association

One cannot but strongly deplore the negative attitude adopted by several medical students towards their association. If there had ever been the least suspicion that the elected committee members did not use their energies in the best interest of the medical students, one might be tempted to find justification for the reigning apathy. But the useful work done by all the committees, especially in the Students' Exchange Programme cannot be questioned by anybody. These colleagues merit our support and assistance and one notes with disapproval that their efforts are being given the cold shoulder by most students who do not even turn up at the Annual General Meeting, so that for the last four years the Annual General Meeting had to be held without a quorum. It is no wonder that not enough students accepted the nomination to contest this year's elections for the M.M.S.A. committee.

However, as soon as the applications for clerkships abroad are issued, those who had been most indifferent are the first to pester the Exchange Officers to obtain an elective post. And when in October the grants are announced they are the ones whi check and re-check lest they receive less than is is their due.

While desiring to avoid the word 'selfish', a more appropriate adjective does not easily come to mind.

The Journal

We must first apologize for the delay in the publication of this issue. However we tried to make up for this delay by giving our readers a varied issue with no less than thirty reading pages. We will be expecting comments and suggestions so that the standard of the journal will continue to improve, because we admit that there is still ample room for improvement.

We must once again urge students to send in articles for the next issue which we intend to publish in October. Let us hope that the majority of the articles will be written by medical students for after all this is a Students' Journal. So while wishing everybody the best of luck for the forthcoming examinations, you will hear from us again next October.

letters to the editor

NOTE: Opinions expressed in these letters do not necessarily reflect the views held by the editorial board.

Dear Sir,

I was one of the few who attended for the M.M.S.A. party on the 17th November, during which Travel Grants were given to the many students who went abroad this summer.

I would like to congratulate the M.M.S.A. for offering quite a handful of cheesecakes, and pizza and enough alcohol to make you happy (far from causing post-alcoholic cirrhosis!!). However, as usual there is always someone who complains, not so much for the sake of complaining, but for what seems to me a room for improvement.

Although we were asked to dress in a jacket and tie, and someone even decided to come in D.J.!, I have to say that the atmosphere was completely lacking. Would it not have been possible to find a more adequate place. I think last year's 'Griffin' was much better.

It is true, drinks last year were a bit expensive but could not the M.M.S.A. have issued tickets, say for 1 or 2 free drinks, and in my opinion would be cheaper than offering drinks free for all, and so the price for the hiring of the hall would not be so 'sky high' as described.

As usual, Medical students and one guest for each person were invited. Could I know what are the M.M.S.A.'s objections for students getting along as many guests as they want? As things are, those who have their girl-friend stay with her, as if they are at a disco on a Sunday, and those who are still 'spinsters and bachelors' gather together and chat about the usual jokes, lectures, nurses, etc., etc., etc.

If more people are present, one can make new friends and who knows, someone may get 'love at first sight'.

One last comment. I think it is a shame (or a pity) for certain members of the committee not attending such a party. I think this shows how interested certain members are.

Well, keep it up and please do improve.

Yours truly,

DISSATISFIED.

Dear Sir,

May I show my appreciation for the efforts you and your editorial board, as also the ex-editor Dr. Mark Agius, M.D., have put into making possible the re-publication of 'Chestpiece'. The attitude of your predecessors had in fact not only deprived us medical students of our journal for many months, but had also made many of us fear it would never rise to its feet again. At one time we had been told that not enough articles had been submitted to the editor; when some students made sure there were enough articles by presenting their own contributions (even at the expense of working on articles only fifteen days prior to the Intermediate Examination), the cost of paper and printing suddenly rose and not enough adverts could be collected to meet the cost.

But, now, may I ask: How did the new inexperienced members of the present committee (editorial board) manage to achieve within two months what their predecessors failed to achieve within two years? In my opinion logic can only provide one answer: the new members did not accept their posts for the sake of being on the editorial board, but did it with the firm intention of doing their utmost to bring 'Chestpiece' back to its former glory. You and your collaborators, by overcoming the very big difficulty of reviving 'Chestpiece' from the dead, have proved that our journal can be kept alive as long as enough effort is put into the task. I sincerely hope that your successors, when it will be time for them to take over, will follow on your footsteps and that all medical students will contribute their support by presenting articles for publication. As for you and the other members on the Editorial Board, I congratulate you again and urge you to keep it up.

But, alas, I have to point out also that very few other students seem to share your spirit and enthusiasm. Only those who do not have eyes to see and ears to hear can fail to behold among us the greatest affliction which could have hit any student body, namely, the ever-growing apathy being shown by the vast majority of medical students towards what is done for them by the few who have not yet contracted this chronic disease. How often have I seen you, in your efforts to get into 'Chestpiece' as many articles by student authors as possible, ask students to submit their contributions only to be told that it was too laborious and hence too time-consuming? But-then, was it just as demanding of M.M.S.A. to ask them to attend some of its activities?

I think that the least M.M.S.A. could have expected in return for its fruitful work was the presence of a quorum at its Annual General Meeting. Not only was such a quorum missing (forcing a suspension of the rules for the meeting to open), but most of those present decided they should leave before the end of the first day of the meeting and then not to attend at all on the second; among these were also some members of the Committee, including one whose report was under discussion and another whose report had not been read at all. Admittedly one

must excuse (!!!) those who, year after year, unfortunately continue to have an important appointment just on the day of the meeting (and, this year, also on the second day of it!), and those who just could not make it because they had to watch 'Show de Cologne' on television in the next room to where the meeting was being held. I still wonder how such students invariably manage to turn up at the yearly M.M.S.A. grant-giving ceremony to pick up their money-cheques, never failing to avoid all other appointments on that day! This would explain the fact that this ceremony, of all the M.M.S.A.'s activities, continues to attract the largest number of students; only a minimal number of students not receiving the money-cheques do attend it. More deplorable is that even some M.M.S.A. committee members did not even deem it their duty to attend this ceremony (but, then, some committee members did not deem it their duty to attend more than half of the M.M.S.A. committee meetings!).

In my opinion, it is not at all surprising that this year a small number of students decided to contest the M.M.S.A. elections. Most students could not care less; others were, and rightly so, dissuaded from entering the candidature knowing that their efforts would not be appreciated; a very small minority may admittedly have had other valid reasons. By this I do not intend to encourage the prevailing apathy; I only wish to point out that this chronic progressive disease that is ravaging among us is inevitably leading us into a very dangerous, vicious circle. It is time that all of us, particularly those who so far have refused to do so, realise our situation and decide to take the bull by the horns before it is too late.

Sincerely yours,
ONE WHO CARES.

Dear Sir,

Allow me to dedicate this letter to the many active members of our association.

Don't come to the meetings.

If you do come, come late.

If you still have something to study, don't think of coming.

If you do attend meetings find fault with the officers and other members.

Never accept office as it is easier to crtic-ize than to do things.

Do nothing more than is absolutely necessary but when others willingly and unselfishly use their ability to help matters along, howl that the meetings are being run by a clique.

Don't read the noticeboards and then find excuses.

Don't ever come when you can contribute but when you intend to go abroad or have just come back, open your hands wide open and pull out your empty pockets.

Sincerely yours,
DISGUSTED.

M.M.S.A.

STATEMENT OF POLICY 1976 COMMITTEE

Report

March 1976

The MMSA started this session in a definite mess. To start with, senior members adopted a generalised *laissez-faire* attitude and none was willing even to stand for elections. The result was that all nominated members were elected unopposed and even after a by-election, a full committee cannot be constituted. Yet members were surprisingly co-operative and understanding on individual levels. The main complaint was that MMSA's general meetings were fast deteriorating into sessions of incomprehensible, often meaningless interplay of rules and regulations between the chairman and a few members who seem well informed in student unionism, and most members feel real benefits that could come from such exercises were not commensurated with real loss of time and effort. Some see everything wrong with the statutes and would want every word altered. It is on this background that the present executive took over. However, we feel that the handicap was not insuperable and that with hard work we could tidy the MMSA over this acute exacerbation of a chronic problem. The committee does not intend to depart tremendously from the policy of its predecessors. We hope to keep the Malta student body within the universe of the IFMSA and to participate — as much as funds allow us — in its activitieas including active exchange of students.

On the local level, we hope to organise lively get togethers, symposia and a cocktail dinner.

By the time our tenure of office is over, we hope to have instilled in the minds of our fellow members that it is sweet and fit to give one's service for one's own fatherland.

queries

Question: *Why do parietal cells stain red in haematoxylin and eosin sections if they are acid secreting?*

Reply: The hydrochloric acid secreted by the parietal cells is formed on the cell membrane i.e. outside the cells. Hence the hydrochloric acid takes no part in the staining properties of the cytoplasm of the parietal cells. Furthermore the the hydrochloric acid is completely dissociated into free ions and is never bound to the tissues, so that it is readily washed away by aqueous solutions used in tissue processing.

The cationic radicals responsible for 'acidophilic' staining of cytoplasms are usually the amine radicals (NH^+_3) which are present on most proteins. In the pareital cells the numerous, large mitochondria present in the cytoplasm appear to be responsible for the strong 'acidophilic' staining.

Dr. A. Cuschieri M.D.; Ph.D.(Lond).

Question: *What considerations should be taken into account when results of serum calcium estimations are interpreted?*

Reply: Most of the methods used in the routine clinical laboratory estimate total serum (or plasma) calcium. This includes the ionisod calcium [Ca++] (50 — 65%), protein bound cal- (30 — 45%), and the remaining (5 — 10%) fraction that is complexed with organic ions. The total calcium ranges between 8.5 mg to 10.5 mg per 100 ml (2.12 — 2.62 mmol/l). Of the three fractions, it is the ionised calcium [Ca++] which is the most important physiologically, by affecting neuromuscular excitability, and influencing parathormone secretion.

In interpreting results of calcium estimations, the concentration of the serum proteins is of great relevance. Total serum calcium levels alter in parallel with changes in serum proteins, e.g. in hypoproteinaemia serum calcium may be much reduced as the serum proteins, but the ionized fraction [Ca++] is not. Correcting factors for changes in serum proteins have been suggested, but are generally not safely applicable.

Binding of calcium to protein increases with a rise in blood pH and vice versa, so that serum [Ca++] falls. Such a change is produced by the i.v. administration of bicarbonate, or as a result of overbreathing. Lowering of the blood pH has the opposite effect. A return to normal level is achieved by compensatory parathyroid activity, or if the change in blood pH occurs slowly.

Intravenous administration of chelating agents as EDTA (usually as tri-sodium edetic acid) that may be used as an anticoagulant for donor's blood, leads to disturbance of the equilibrium between the three calcium fractions and causing a fall in serum [Ca++]. Such chelation leads to a wider distribution of calcium into the extracellular fluid.

Interpretation of results should be made only after taking these inherent facts ino account.

More obvious safeguards that too often are disregarded concern the technique of sampling. Results become dependable only if the proper technique is rigorously observed. This is particularly essential if serial estimations are to be meaningful. Blood taken from the patient in a fasting state avoids post-prandial fluctuations.

It is absolutely necessary that the blood must not come into contact with any form of calcium, as may occur with residues on repeatedly boiled or sterilised syringes. Disposable syringes and blood sample containers, or the use of vacutainers, are essential tools.

The site for venous sampling should be so selected as to avoid possible venue stasis, and the use of a tourniquet is best avoided. Prolonged venous stasis causes the protein bound fraction to increase by increasing the concentration of protein that results from 'ultrafiltration' of the blood in the capillaries of the forearm, and more specifically of albumin to which calcium is bound. If at all necessary, the tourniquet, applied briefly, should be released after the vein is punctured, and the sample is withdrawn only after an interval to allow for a free circulation. The site should also be well away from that where there is an intravenous infusion. This may account for an ambiguous hypocalcaemia that is more likely to be misinterpreted, considering that true hypocalcamia is more common than hypercalcaemia.

Dr. J.L. Grech, M.D., F.R.C. Path.

Question: *What is the special pre-operative, operative and post-operative care of a patient who is being operated for phaeochrmocytoma?*

Reply: Phaeochromocytoma was an invariably fatal tumor until the first successful removal by Mayo (1927). Successful excision relieves all clinical abnormalities in the majority of patients but this procedure used to have a high mortality of the order of 25%. The prognosis has greatly improved since the advent of adrenergic blocking agents, of safe anaesthesia and application of blood transfusion during surgery.

Pre-operatively it is essential to pay particular attention to the following points:

a) Establishing the diagnosis of phaeochromocytoma — this is most accurately done by demonstrating increased exretion and secretion of cathecolamines or their major urinary metabolites vanillimandelic acid, metnoradrenaline and metadrenaline.

b) Attempting to localise the site of the tumor usually by the use of radiography including X-ray chest (which may demonstrate intrathoracic phaeochromocytomas), i.v. pyelography, pre-sacral oxygen insufflation, arteriography and venography.

c) Controlling hypertension and arrythmias by the use of phenoxybenzamine and propanolol.

The dangers experienced **during operation** are:

a) **Hypertension** before and during induction of anaesthesia and handling of the tumor. Hypertension can be controlled by the use of alpha-adrenergic blocking agents (e.g. phentolamine, phenoxybenzamine.)

The anaesthetic agents cyclopropane and trichioethylene should be avoided as they release cathecolamines from phaechromocytomas. Tiopentone, halothane or a nitrous oxide-oxygen-ether mixture are usually used.

b) **Hypotension** following the removal of the tumor which removes all vasoconstrictor influences thus expanding the vascular space with a sudden elimination in blood volume. Careful monitoring of pulse, blood pressure, E.C.G. and C.V.P. is of utmost importance and should commence before anaesthesia. Adequate blood transfusion is essential and may be life-saving.

c) **Arrythmias** may occur due to the effects of increased cathecolamines upon the myocardium sensitised by anaesthetic agents and hypertension as well as the use of alpha-adrenergic blocking drugs. This is largely abolished by beta-adrenergic blockade using propranolol.

Post-operative blood transfusion and monitoring is continued until the cardio-vascular system is stabilised.

Mr. L. Cutajar, M.D., F.R.C.S.

Question: *What are your views on routine bacteriological examination of urine of pregnant women for asymptomatic bacteruria.*

Reply: Kass clearly demonstrated that acute pyelonephritis of pregnancy is particularly liable to develop in patients with asymptomatic bacteuria and early treatment of this asymptomatic state can substantially reduce the development of this serious complication. A relationship between untreated bacteruria and complications of pregnancy, including premature delivery, has also been suggested. Hence early detection of asymptomatic bacteruria and treatment in obstetrics can do much in the field of preventive medicine if acute severe symptomatic infections and other possible complications are to be reduced. Whilst, failure of recognition and therefore of treatment may ultimately lead to chronic irreversible disease.

The incidence of asymptomatic bacteruria, that is usually reported in pregnant women, is between 5-6.5%. During pregnancy symptoms such as frequency, nocturia and urgency are complained of just as often by non-bacteriuric patients as by those with confirmed bacteruria. Hence, the importance of bacteriological examination of urine in all cases.

Therefore **all** antenatal patients, **should** be screened for significant bacteruria (its economic practicability has been established even in a very busy clinic) in the hope of preventing an attack of acute pyelonephritis, which after all is the most important factor involved, and of treating this adequately. Thus the progress of a potentially chronic and fatal disease is arrested, as much as possible, at an early asymptomatic stage.

Dr. A. Gatt, M.D., M.R.C.O.G.

St. John's Instructor: 'Outline the steps to be taken in the rescue and resuscitation of a drowning man.'

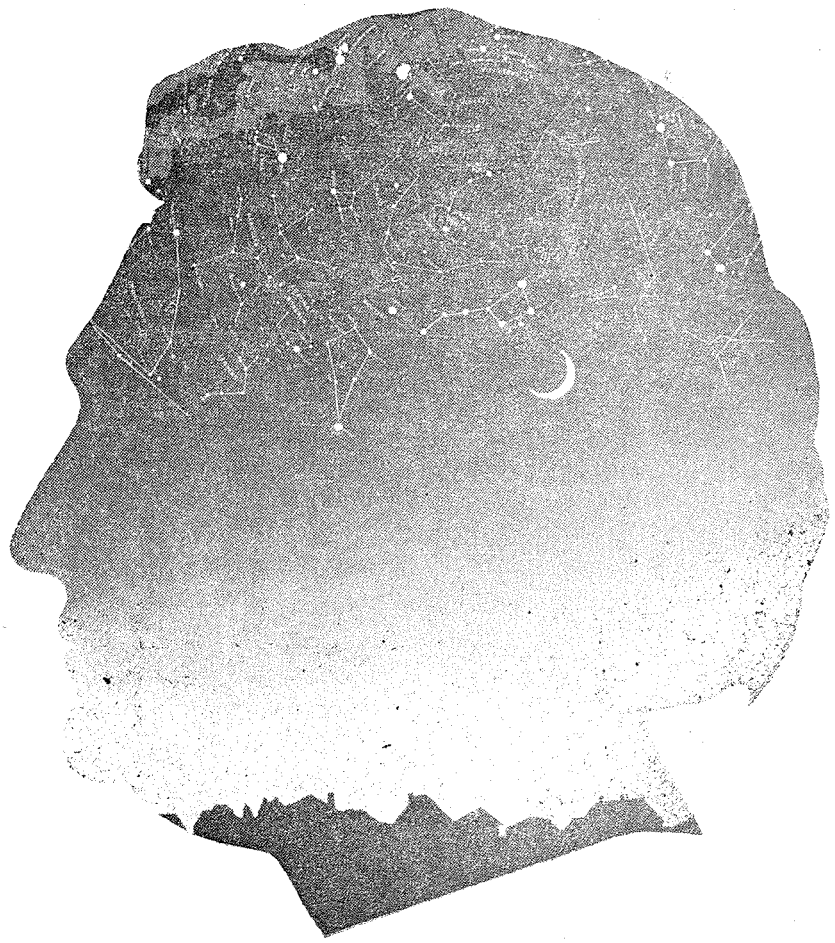
Keen pupil: 'One — get the man out of the water
Two — get the water out of the man.'

A young lady asked her doctor if he could recommed an absolutely safe method of contraception.

'The only sure method I know of, Miss Brown,' the doctor replied coldly, 'is a glass of unweetened lemon juice.'

'Thank you very much doctor,' fluted the girl. 'Just a glass of lemon juice. Before or after?'

'Instead of.'



Fast Asleep

Dalmane gets patients to sleep in less than half the time.[1] Reduction in sleep latency has been observed in the home,[1] and the hospital,[2] as well as the sleep laboratory[1,3] where objective studies have consistently confirmed the patients' subjective assessments. Add to this a less disturbed night[1,4] with Dalmane and you have a powerful treatment for insomnia, remarkably free from the problems of a barbiturate.[5,6]

DALMANE

a powerful treatment for insomnia

ROCHE

References 1. Kales, A., *et al.*, Arch. gen. Psychiat., 1970, *23*, 226 2. Feffer, H.L., and Gibbons, B., Med. Times (N.Y.), 1973, *101*, 130 3. Kales, J.D., *et al.*, Clin. Pharmacol. Ther., 1971, *12*, 691 4. Dement, W.C., In 'The Benzodiazepines', Ed. Garattini, S., *et al.*, Raven Press, New York, 1973, p599 5. Lasagna, L., In 'Drugs of Choice 1974-75', Ed. Modell, W., C.V. Mosby Co., St. Louis, 1974 6. Johns, M.W., Drugs, 1972, *4*, 290

a clinical problem

(the clinical case for this issue was prepared by victor cassar pullicino.)

A 45 year old nun was referred to hospital for investigation. She complained that for five years she had become progressively easily fatigued, with marked weakness and lassitude, to the extent that now she had marked difficulty in waking up in the morning and as it was continuous in nature it necessitated bed rest at various times throughout the day. These symptoms were enhanced and accompanied by a feeling of faintness after meals. She had lost her appetite with consequent loss of weight and complained of vague gastrointestinal upsets including occasional vomiting, abdominal pain and alternating episodes of constipation and diarrhoea. For the past year especially, she experienced an increasing difficulty in coping with the duties in convent due mainly to dyspnoea and a fainting feeling on moderate exertion and in fact on two occasions syncope during mass.

In the past she had an appendicectomy at 14 years of age and suffered from pulmonary T.B. when 25 years old for which she was subsubsequently given chemotherapy. She had been well after this but five years ago after a cholecystectomy operation she developed an increasing persistent tanning of her skin. She had found this strange because although her operation was in summer, she had had such a remarkably slow recovery after the operation that she had not gone out much and was not in the habit of sunbathing either.

On examination she looked ill, fatigued and slightly anaemic but was not cyanosed, dyspnoic or orthopnoic. There was no finger-clubbing or jaundice and no lymphadenopathy. She was generally pigmented especially in the neck, axilla, palmar creases and groin, with melanotic patches on the tongue and buccal mucosae. There was also a generalised loss of body hair especially marked in the axillary and pubic regions. She had a rapid small pulse, a blood-pressure of 90/60 and a temperature of 97°F.

The apex beat was impalpable, heart sounds were faint with an abrupt third heart sound but no murmur could be heard. Her cervical veins were distended with a paradoxical increase in the jugular venous pressure on inspiration. On inspection her abdomen was distended and there were two well-defined scars: a whitish appendcectomy scar which contrasted markedly with the highly pigmented cholescystectomy scar. There was a three finger hepatomegaly, a palpable spleen and ascites. There was also slight dependant oedema.

QUESTIONS:

1. What unusual dietary habit should be specifically asked for?
2. Mention some causes of mouth pigmention.
3. What is the importance of the splenomegaly?
4. What is your differential diagnosis?
5. Is the past history relevant?
6. What is the probable diagnosis?
7. What is so diagnostic of the different appearance of the two scars
8. Can you think of a possible explanation with regard to her symptoms being worsened in the morning and after meals?
9. What are the contributing factors to her episodes of syncope?
10. What two simple investigations may prove to be pathognomonic of her condition?

Answers on page 42

'I do like your uniform,' prattled the young charmer, 'tell me, what do you do exactly?'

'I am a naval surgeon, miss.'

'Really?' the young lady replied, wide-eyed. 'How you doctors speciallize . . . . '

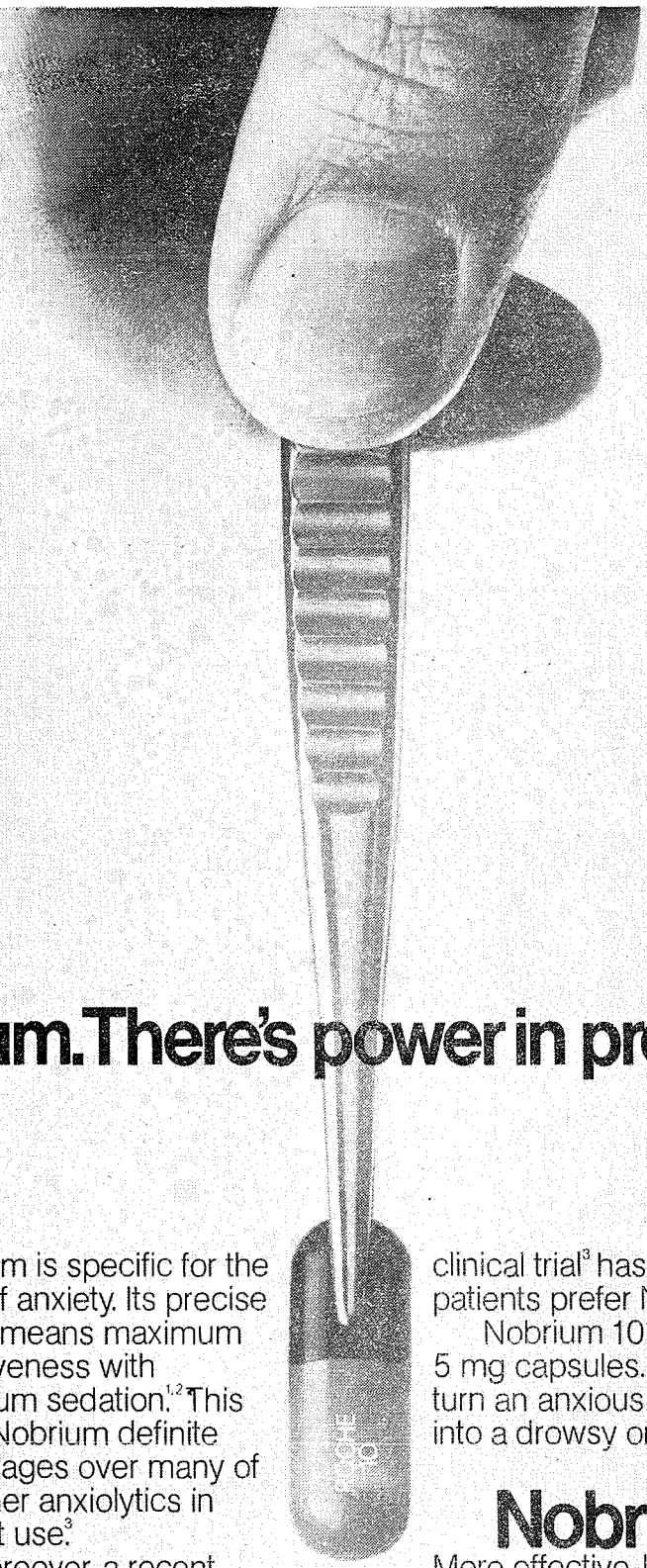
A dim but well-meaning young man called at the registry office to report his father's death.

'When did he die?' asked the registrar.

'Oh, he ain't dead yet,' replied the youth, but he will be before morning, so I thought I'd see you in good time.'

'I'm afraid it's out of the question,' the registrar explained. 'You see, your father might live for days yet, or even years.'

'I don't think so, sir,' replied the young man dubiously, 'doctor says he won't and he knows what he has given him.'



Nobrium. There's power in precision.

Nobrium is specific for the relief of anxiety. Its precise action means maximum effectiveness with minimum sedation.[1,2] This gives Nobrium definite advantages over many of the other anxiolytics in current use.[3]

Moreover, a recent clinical trial[3] has shown patients prefer Nobrium.

Nobrium 10 mg and 5 mg capsules. Don't turn an anxious patient into a drowsy one.

Nobrium

More effective, less sedative

ROCHE

Further information is available on request. Roche Products Limited, PO Box 2LE, 15 Manchester Square, London W1A 2LE.
Nobrium is the trade mark for pharmaceutical preparations containing medazepam.

References: 1 Kerry, R.J., and McDermott, C.M., Brit. med. J., 1971, **1**, 151. 2. Lopez Vazquez, R.M., Galicia clin., 1972, **90**, 783. 3. Lader, M.H., *et. al.*, Psychol. Med., 1974, **4**, 381.

J609071/975

Agents: Messrs Cherubino, 89 Archbishop Street, Valletta.

pulmonary surfactants

george galea.

General Considerations And Definitions.

Pulmonary alveoli of mammals are lined by by a single layer of epithelial cells forming the alveolar wall. The continuity of the cells which rest on a basement membrane, is interrupted occasionally by pores of Kohn. The alveolar wall contains two types of cells:

1) attenuated cells that are extremely thin (0.1-0.7u). These are the TYPE I cells known also known as the Surface Epithelial cells or Membrane Pneumocytes.

2) large round cells (7-14u). These are known as TYPE II cells or Great Alveolar cells or Granular Pneumocytes. (Figure 1).

On one side of the alveolar wall is the interstitium of the alveolar septum containing capillaries, lymphatics and connective tissue and on the other side between the wall and the alveolar air is the acellular 'Alveolar Lining Layer'. It covers and is somewhat adherent to the alveolar wall. It is a complex mixtures of lipids, proteins and carbohydrates and is termed the 'Surfactant System Of the Lung'. The highly surface active components of this system play an essential role in determining the normal mechanical properties of the lung, as first suggested by VON NEERGAARD (1929). They are indispensible to normal pulmonary function and may be altered either primarily or secondarily in certain pathological conditions.

Histochemistry.

Histo-chemical studies have identified some of the chemicals components of the lining. Their reactions with fluorochrome dyes show that they consist of lipids and mucins. They stain positively with Acid haematin, Alcian blue and Hales colloidal iron stain. Therefore it was concluded that pulmonary surfactants consist of a mixture of phospholipids, acid polysaccharides and mucopolysaccharides. Their reaction with phosphomolybdic acid showed that there are lipids which contain choline.

Origin.

The site of origin of the surfactant system is still very controversial. KLAUS et al (1961), have suggested that the surface active materials are secreted by the Type II cell. This theory has also been put forward by BUCKINGHAM et al. (1962), who are demonstrated using C^{14} that palmitate was concentrated in the great alveolar cells. There are in these cells spiral bodies known as Lamellar Osmiophilic Bodies (LOPB's) and they are thought to be secretory granules. Other investigators show evidence that surfactant originates in the LOPBs themselves. Klaus et al. (1961) think that these bodies are transformed mitochondria, because under experimental conditions of stress, many of the Type II cells transform into spiral bodies.

NIDEN (1967) has pointed out that vacuoles in the Type II cells could represent ingested surfactant, which has been synthesised elsewhere. He showed that these cells are phagocytic, although the process is slow and remarkably selective. CORRIN (1969) has found lytic enzymes (eg., phosphatidic acid phosphatase) in the same location, and this could well be taken to support Niden's view that Type II pneumocytes are concerned with the disposal rather than the synthesis of surfactant. However proposers of the theory, that pulmonary surfactant is secreted by the Type II cell, argue that these lytic enzymes may in fact, contribute to a synthetic process, because these may break chips of a larger molecule. So much so, that ABRAMS (1966) is of the opinion that the surface active phospholipids are part of a lipoprotein molecule. According to Niden, the Clara cells (terminal cells in the smaller bronchioles) are the secretory cells. Corrin (1969) has modified his theory and postulated that both Type II cells and the Clara cells are sites of surfactant secretion.

Chemistry.

The surfactant system, is as already indicated above, a complex mixture of lipids including neutral and phospho-lipids. These lipids may be associated with carbohydrates including, glucose, galactosamine, fucose, and other monomers. Any association between lipids and proteins in the surfactant system appears to be a loose one. Chemicals studies by Klaus et al. (1961) have confirmed that surfactants include: phosphatidyl cholines (choline phosphoglycerides); phosphatidyl ethanolamines (ethanolmine phosphoglycerides); sphingomyelins; phosphatidyl inositols and lysophosphatides.

KING and CLEMENTS, (1972) isolated 4 fractions of surface active materials from dogs' lungs extracts, using differential and density gradient centrifugation. They studied their chemical composition and their results are shown in Table 1.

TABLE 1

Composition Of Surface Active Material (% Of Dry Weight)

	Protein	Lipid	Sugars	Nitrogen	Phosphorus	Nucleic Acid
Fraction	11	81	≯ 1.5	3	3	≯ 0.5

(Modified from King and Clements: American Journal Of Physiology: 1972)

As can be readily observed all fractions are composed of lipids and protein and contain less than 2% sugars. The 4-formed fractions differed from each other in protein content but did not differ significantly in lipid composition.

Biosynthesis.

Phospholipids are synthesised rapidly in the lung. In fact, it has been demonstrated that recovering (using C^{14}) occurs within 2-4 minutes Of the phospholipids synthesised in the lung only phosphatidyl cholines' metabolism has been studied in detail. 3 main pathways are thought to be involved:

(a) the incorporation of a diglyceride and CDP (cytosine diphospho) choline to yield a phosphatidyl choline.

(b) 3 step methylation of a phosphatidyl ethanolamine.

(c) the acylation of a lysophosphatidyl choline.. A scheme of phospholipid biosynthetic pathways in the lung is shown in figure 2. SALISBURY-MURPHY and other co-workers (1969) showed that rabbit lung slices oxidized glucose to glycerol and fatty acid moeities of glycerides. The major plasma fatty acid is palmitic acid and it has been found out that dipalmitoyl phosphatidyl choline is the major component of the surfactant system. Experiments worked out by SALISBURY et al. (1969) show that plasma palmitate did not effect oxidation of glucose but increased its incorporation into glycerol moeity of the glycerides and inhibited lipogenesis from glucose.

Lipid metabolism in the lung differs in several respects from that of other tissues such as liver and adipose tissue. As already indicated, the mitochondria are thought to actively synthesise lipids, which is a task most efficiently performed by microsomes and supernatant fluid in adipose tissue and in liver.

Turnover.

Of interest are certain observations that the turnover rate of phospholipids in the alveolar lining is different from that in the pulmomary parenchyma although both are extremely rapid. It has also been postulated that transmethylation of a phosphatidyl ethanolamine to a phosphatidyl choline may take place in the lining directly.

By specific activity studies, i.e. using radioactive precursors and measuring the ratio of radioactivity to quantity of the compounds concerned TIERNEY, CLEMENTSand TRAHAN (1967) showed evidence of more than one pool of dipalmitoyl phosphatidyl choline (or dipalmitoyl lecithin-DPL).

The postulated that:

(a) there could be a a slow entry of precursors from other minor metabolic pathways within the lung itself,

(b) there could be a slow entry into the lung from other tissues e.g. muscle. It has been shown conclusievly that DPL exists in many other organs besides lung,

(c) there could be multiple pools of surface active material and these are secreted at different rates e.g. 2 cell types may secrete DPL at different rates,

(d) it could be possible that not all DPL is incorporated into surface active material. One fraction of newly syntesised DPL with a short half-life may supply DPL to the surface and the remaining portion may be incorporated into structures such as membranes and have a longer half-life.

Physical Properties.

Isolated fractions of surface active material should have physical and chemical properties consistent with the behaviour of alveolar surfaces. KING and CLEMENTS (1972) from very accurate experiments in vitro, with substances they themselves isolated, brought into light some of the physical properties of alveolar surface active molecules:

(a) it is thought that surfactant exists in 2 functionaily different components; an outer layer composed of densely packed phospholipids and an inner layer containing phospholipids in a different phsico-chemical configuration probably linked to proteins.

(b) the material isolated in vitro was capable of lowering the surface-tension of a sub-phase (constituted of approximately the ionic composition of ECF) to less than 10dyn cm^{-1} when spread on the surface in quantities that approximate those of duplex films of lipid and protein. (A duplex film in this context is defined as a film in which the lipid portion of the surface active material is at the the air interphase as a monomolecolar layer with a protein portion adsorbed beneath it).

(c) the amount of material that was recovered was sufficient in quantity to cover the alveolar surface with at least one duplex film of lipid and protein.

(d) the compressiblity of a surface film of surface active material measured at 10-15 dyn cm^{-1} surface tension was less than 0.09 cm dyn^{-1} at 37°C.

(e) surface active material adsorbed on an air-liquid interface at a rate comparable to those observed in physiological studies.

(f) surface active, material, as compared to whole lung, was enriched in dipalmitoyl phosphatidyl choline (0.5mg/gm).

Certain remarks could be made out of these physical properties. The marked lowering of surface tension is due probably to, the packing of molecules into a close -ordered array at an interphase Phospholipids are amphiphilic and arrange themselves in aqueous solution in a manner that minimizes contact between their hydrophobic portions (esterified fatty acids) and water. The minimum free energy configuartion accomplishing this objective is a large myelinic aggregate in which the hydrophobic portions of the molecule are in a non-polar environment while the polar portions (glycerol backbone and esterified alcohol) are exposed to the aqueous phase (figure 3).

The fact that it can adsorb readily on adequate surfaces fits in with current thinking, which suggests that a reservour of surface active materials exists in the alveolar subphase which can readily be absorbed to the alveolar surface as needed.

PHYSIOLOGICAL SIGNIFICANCE OF THE SURFACTANT SYSTEM.

(A) Pulmonary Mechanics and Alveolar Stability.

3 factors help to stabilize an alveolus:

(a) tissue forces,

(b) geometrical stability,

(c) changes in the lung surface tension with change in alveolar area (surface elastance)

From experiments with lung extracts of pulmonary tissue demonstrated that surface tension varies directly with area and approaches 0 at very small areas.

When a normal lung is inflated from the degassed state or from the liquid-filled state an interphase is established between the oncoming air and the material present in the airways and lung units. The pressure required to open the terminal units is related to surface tension developed at this interphase according to the Laplace relationship $P=2T/r$ where,

P is the pressure tending to resist inflation or produce collapse,

T is the surface tension at the interphase,

r is the radius of the terminal units.

At the tension found in the ECF i.e. 50 dyn cm $^{-1}$ in a surface with a radius of only 0.05mm, the pressure exerted against the air in the alveplus would be quite high (20cm of H_2O). As figures 4 indicates, the behaviour of surfactant shows a hysteresis pattern. In an expanded airspace the layer of surface active agent is attenuated and the surface tension is increased accordingly. The increase in tension is partly offset however by the increase in the radius of the airspace. As the interspace contracts to perhaps one-half its expanded size. the increasing amount of surfactant now available, reduces the surface tension, and so the pressure in the airspace is decreased.

The concentration of surfactant in the interface of tissue fluid and air at small and large alveoli is different. This is because areas of greater curvature produce the greatest suction force. This brings about a homogenuos distribution of pressure. Thus by varying the elastance, surfactant ensures that the smaller alveoli do not collapse, especially at low lung volume.

The inter-relationships of surface forces and the mechanical properties of the lung can be summarised by their contribution to volume-pressure hysteresis. (figure 5). During inflation, of the air-filled lung there is a critical opening pressure below which no air enters the lungs. This is a function of the size of the alveoli and the tension at the alveolar surface. The lung then inflates with only a small increase in pressure. There is an increase in the total number of alveoli showing an increase in volume, as well as in the size of those already open. The largest alveoli will open first. The pressure increase is also influenced by tissue elasticity. During deflation the alveoli remain open over a much larger volume range than during inflation. The greater the number of alveoli sharing a given volume, the smaller will be the retractive force developed by the lungs. All pressures during inflation therefore exceed those during defation. CLEMENTS (1973) suggested that 'surface-area/tension' hysteresis contributed to this 'volume-pressure' hysteressis by extending the volume range over which the airspaces would remain stable during deflation, as well as by producing hysteresis of individual airspaces

(B) Alveodar-Liquid Balance.

There are various forces which influence the circulation of liquid at the alveolar-capillary level. Air pressure within the alveoli and the colloid osmotic pressures tend to move liquid out of the alveolar spaces. Capillary hydrostatic pressure and intra-thoracic pressure tend to move liquid out of the capillaries. (figures 6) The lymphatic system plays a role in maintaining liquid equilibrum by draining liquid from interestices. Surface tension, plays an important role here as well. It produces a suction force which is transmitted to the alveolar wall.

If surface tension is similar to that of plasma (50 dyn cm^{-1}) there would be a net pressure differential of approximately 20mmHg. favouring transudation, when considering all pressures affecting movement. However, if surface tension were negligible, the balance of forces would favour alveolar 'dryness' during most of exhalation as surface tension approaches O. This however would favour transudation into the alveoli during most if inhalation, as surface tension increases to a maximum (approximately 40 dyn cm^{-1}). However certain investigators are of the opinion, that surface tension increases between breathing cycles from the mimimum value obtained at the end of exhalation to an intermediate or equilibrium value that is well below maximum.

(C) Pulmonary Capillary Flow.

The possibility that the suction effect produced by alveolar surface tension might reduce pericapillary pressure, and thus effect capillary blood flow has been tested by BRUDERMAN, PAIN and WEST, (1967) They indicate that the higher the surface tension, the lower the perfusion pressure required to support pulmonary flow. Thus the air-inflated lung with presumably the highest surface tension requires smaller perfusion pressures, than does the air deflated lung (lower surface tension) and the latter requires less pressure than the liquid filling lung, surface tension being virtually absent. Surfactant also affects regional blood distribution in the lung. Capillary perfusion in the superior portions of the lung is enhanced during inhalation when surface tension is highest. In effect, surface tension counteracts to some extent the opposition to flow due to gravity.

(D) Clearance Of The Alveolar Surface.

Surfactant molecules at the air-alveolar lining interphases tend to move in the plane of the surface from areas of low surface tension to areas of high tension. Such spreading may provide a clearance mechanism for the removal of extraneous material, like cellular debris or foreign particles, from the alveoli, and for the distribution of surfactant among alveoli.

(E) **Reaction To Infection.**

SHIFRINE and GOULRAY (1965) produced antibodies, to Mycoplasma mycoides, a micro-organism that causes contagious bovine pleuropneumonia and demonstrated that the antiserum preciptated both phenol extracted carbohydrate from M. mycoides and pneumogalactan, a polysaccharide from bovine lungs. Animals infected with contagious bovine pleuropneumonia produce antibodies which react with pneumogalactan and the carbohydrate from M.mycoides. The cross-reactivity indicates that the carbohydrate polymers have common linkages. The authors suggested that pneumogalactan may play a role in the pathogenesis of bovine pleuropneuomia, possibly by localising the organisms in the lungs through an antigen-antibody reaction. SCARPELLI, CLUTTARIO and TAYLOR (1967) have postulated the presence of a galactan in the alveolar lining layer of rabbits' and dogs' lungs. If indeed a galactan is part of the surfactant system, the localisation reaction of Shifrine and Gourlay would take place at the alveolar surface. The implications of these suggestions are of major importance since the mode of infectivity of micro-organisms is poorly understood at present and since it is possible that other micro-organisms have similar antigens.

(F) **Determination Of Alveolar Configuration.**

Most investigators agree that alveoli are either round or polygonal and that surface forces play a significant role in determining this configuration. The irregularities of the cell surface appear to be filled in and smoothed out by the hypophase (the part of the lining facing the alveolar cell membrane) of the lining layer.

Foetal And Neo-natal Physiology.

By the sixteenth week of intra-uterine life lung epithelial cells although undiffrentiated, are already sythesising and secreting pulmonary surfactants.

Before the onset of breathing, Type II cells line most of the alveoli and inclusions are full and dense. This suggests that surfactant is stored in the greatest relative amount at birth. The greatest demand for it, is at this stage, because a large area of lung surface must be covered with surfactant as the animal begins breathing. After 1½ hours of breathing, most of the Type II cells inclusions disappear and the number of recognisable Type II cells is greatly diminished. These morphological changes, suggest that stored surfactant is released during the first 1½ hours of life. By 24 hours a thin non-cellular surfactant lining is present.

CLUCK et al. (1967) provides a correlation to these morphological changes, by biochemical studies. At about 1-1½ hours of life is a peak of DPL secretion, and this as can be readily seen, coincides with the maximum number of free lamellar figures seen in the alveolar spaces.

Physiological Effects Of Reduction In Lung Surfactant.

Severe reduction in lung surfactant in the living organisms occurs almost exclusively in newborn humans and animals. The lungs at birth are filled with liquid which is displaced from the airspaces during the first breath into the interstitial spaces where absorption takes place via the lymphatics and directly into the circulation. At the end of the first breath the ability of retain air in the lung during expiration and form a 'Functional Residual Capacity' (FRC), depends upon the presence of surfactant in the air-liquid interphase in the alveoli. If surfactant is deficient expulsion of air during expiration can be complete. With each successive breath the alveoli have to be reopened from the collapsed state and the removal of liquid from the lung is impeded.

Gross interference with lung function follows with development of hyaline membrane disease (idiopathic respiratory distress syndrome of the newborn). In this condition deep retractions of the chest wall are present, durng inspiration, together with cyanosis and a fast respiratory frequency. There is a total alveolar atelectasis and the dilated terminal airways are lined with eosinophilic hyaline membranes composed largely of plasma proteins and epithelial debris. NORMAND thinks that the presence of plasma proteins in airspaces, implies increased permeability of the lung lining.

Measurements of lung mechanics show that lung compliance, FRC and Total Lung Capacity (TLC) are greatly reduced while airway resistance is little affected. Pulmonary vascular resistance is raised because of pulmonary vasoconstriction probably caused by the combined effects of atelectasis, hypoxia and acidosis.

Effects Of Some Physical and Chemical Factors On Pulmonary Surfactants.

Since volatile general anaesthetics must penetrate the alveolar lining layer and come into direct contact with the surfactant system, their effects on surface tension properties of lung extracts have been studied. No abnormality of surface tension was shown following exposure to anaesthetics in normal quantities either in vivo or in vitro.

Lipids analysis reveal no quantitative difference between smokers and non smokers, but the total lipid content was several times less in smokers. MILLER et al. suggest that cigarette smoking may lower tension without affecting the rate of surfactant production. However this finding is disputed.

Alterations in oxygen tension affects pulmonary surfactant. Hypoxic hypoxia reduces the number and size of inclusion bodies in Type II cells. Hyperoxia reduces the concentration of surface active phospholipids. Inhalation of 15% carbon dioxide by guinea-pigs results in hyaline membrane formation.

Surfactant formation before birth is known to be impaired by several factors, such as, aspiration of gastro-intestinal fluids, or excessive interchange with extrapulmonary fluid as, during respiratory movements. In foetal lungs there is an appeciable amount of albumin. Its function is thought to disperse the relatively insoluble phospholipids in foetal pulmonary fluid.

Surfactant concentrations may vary by alterations in the alveolar liquid environment, alterations in pulmonary blood flow, by pulmonary infections and certain surgical purocedures.

Surface tension in pulmonary extracts in-

creases when temperature is raised to 40-42°C and it is possible that the physiological properties of surfactant are altered significant during high febrile states in vivo.

Present Status And Future Prospects.

Current investigations on animals suggest that administration of suitable drugs to the preterm foetus may accelerate lung development and permit early delivery when there are appropriate obstetrical indications.

Current work also suggests that surfactant flux is under a significant measure of nervous and humoral control. This concept has far reaching implications for the role of surfactant in adjustment of the lung to varying physiological and pathological conditions. A case in point is derived from the work of REDDING (1972), who suggests that thyroxine may be a potent regulator of lung surfactant. His investigations indicate that thyroxine administration to rabbit foetuses accelerates the appearance of osmiophilic lamellar inclusions within the Type II pneumocytes.

CONCLUSION

Although not generally appreciated, the exocrine function of the lung may be its most vital function.

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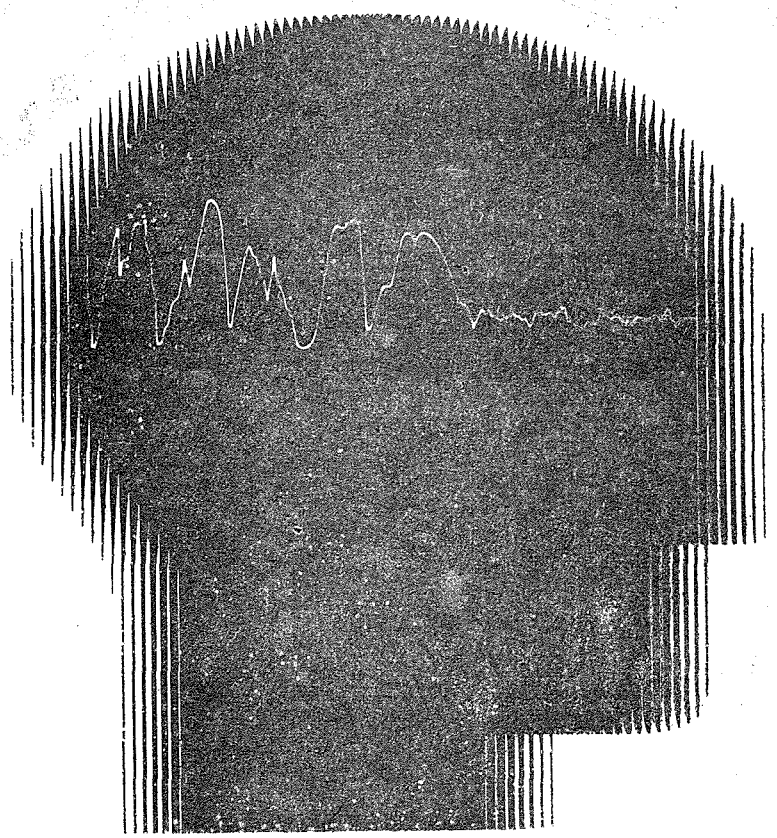

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the sympto-thermic method of family planning

dr. alfred gatt m.d., m.r.c.o.g.

Many are dissatisfied with, unsuitable for, or unwilling to use artificial means of family planning. This is why there are so many demanding a **natural** method, which is "safe" and practicable. The sympto-thermic method I am about to describe is the best solution available for these couples. It makes use of the symptoms and signs detectable at and around the time of ovulation.

Prior to ovulation the secretion of mucus by the cervical glands increases and the mucus thins out and is detectable on the vulva. It looks exactly like the white of an uncooked egg. This mucus if caught between the fingers can be pulled out into strings (Spinnbarkeit). This mucus favours the longevity of sperms by diminishing the vaginal acidity. It is also believed to act as a nutrient for sperms and when it thins out, as just mentioned, it favours the migration of sperms via the cervical canal.

After ovulation has occurred, the mucus thickens and doesn't gravitate out of the vagina. It blocks the cervical os.

Some patients complain of mid-cycle pain in the middle of lower abdomen (Mittelschmer). This is believed to be due to some blood spilling out of the burst follicle and acting as an irritant to the peritoneum. When this symptom is complained of, it is another pointer to the time of ovulation. Breat fullness and mid-cycle spotting when present, are other pointers to the time of ovulation.

The persistent rise in the basal body temperature **after the cessation of the cervical mucus** is the **best** sign that ovulation has occurred. It does not matter whether the temperature is taken orally, rectally or vaginally as long as it is always taken under standard conditions.

Not all temperature curves show a temperature rise which is easily recognisable. Often it is difficult to determine correctly the beginning of the hyperthermic phase. At a W.H.O. meeting in 1966 the following definition was formulated:

"The change from the hypothermic to the hyperthermic phase is spoken of as the 'shift'. A significant shift is one that occurs in 48 hours or less and in which three consecutive daily temperatures are at least 0.4°F. higher than the last six daily temperatures prior to the shift. Sometimes a difference of only 0.2°F. is sufficient to recognise the beginning of the hyperthermic phase".

If there is any doubt about the significance of any temperature rise one should relate it to the cervical mucus. Any rise, as previously stated, for 3 consecutive days, higher than the previous 6 days, and occurring **after** the cessation of mucus is diagnostic of ovulation.

The post ovulatory period is the period of **absolute** sterility. There is however a period of **relative** sterility prior to ovulation and various methods have been devised at detecting this:

a) **The calendar method** — this is accompanied by high failure rate.

b) **Temperature method** — take the basal temperature for 6 cycles; deduct 6 days from the day of the cycle which shows earliest rise of temperature and you get the last day of the relatively infertile period. This is more reliable than the calendar method.

c) **Method of Dr. Josef Rotzer of Austria:** He considers the first 6 days of a cycle as being infertile as long as the previous cycle showed a biphasic curve. This is a very reliable method.

d) A woman who can observe the mucus discharge early enough may rely upon the infertile days up until the first appearance of the mucus discharge. This is especially important in long and irregular cycle, where the mucus symptoms are usually longer lasting.

The above mentioned procedures allow the determination of the pre-ovulatory infertile period for almost all couples. The post ovulatory period gives a high degree of reliability but demands very long abstinence. Therefore couples have to be taught about means of detecting the pre-ovulatory infertile period. The symptothermic method described offers the best answer. But, it is important that the couples are not allowed to use this method before understanding it well and before they have confidence in it.

It has been estimated that on an average it takes a woman up to 6 months of observations and charting for her to understand all these observations about herself. Most women do not find any special difficulty in detecting cervical mucus (clear, slippery, like uncooked egg white, can be pulled out into strings) and can distinguish it from any abnormal vaginal discharge, including seminal discharge. They first notice a sensation of wetness in the region of the vulva and on cleaning themselves notice the stretchy egg white-like, clear mucus.

Conclusion: The aim of this paper is to present a reliable natural method of family planning. The symptothermic method is the best one available and the only factor which makes it impossible to use is unwillingness on the part of one partner to be involved in periodic abstinence from intercourse.

pope benedict xiv — friend of the medical profession

rev. m. jaccarini, lic.d., lic.th., m.a. (oxon.)

In the Wellcome Institute of the History of Medicine in London, there is an old microscope which once belonged to Prospero Lambertini, later Pope Benedict XIV. Born in Bologna in 1675, he became a priest and a canon lawyer, worked in Rome as advisor to various Congregations and Popes and as a member of the Congregation of Rites, was made Bishop of Ancona, and later Cardinal Archbishop of his native city from where he was unexpectedly elected Pope in 1740.

Reading his life I was struck by the number of resemblances he bore to Pope John XXIII, so that I said to myself, "Here was a Pope John of the 18th century". But it is not on this that I wish to dwell here. What interests us here is his patronage of medicine and surgery, as well as the sciences.

In an age when there was not yet the separation between the "two cultures" of C.P. Snow and when narrow specialisation was not yet possible, besides being a humanist, Lambertini was also interested in astronomy, electrical research (then in its infancy) and geology. He was particularly fascinated by medicine and surgery and by what is now called parapsychology. He developed these interests especially when he was Devil's Advocate, so called, in the Congregation of Rites. This official's duties in the processes of beatification and canonization is to make all-out efforts to prevent the process from continuing by trying to discover proofs against the heroic holiness of the candidate, or if this is established, to show that alleged miracles never happened but were exaggerations or distortions. Lambertini's duties as Devil's Advocate obliged him to consult men learned in anatomy, medicine, physics and parapsychology as well as to study these sciences for himself. For example we know that he read Harvey and Boyle.

Perhaps his interest had already started in Bologna as his native city possessed one of the most famous of medical schools (founded in 1200) especially prominent in anatomy and surgery. Always on friendly terms with the University, in his eagerness further to encourage the study of anatomy and surgery, Cardinal Prospero Lambertini, when Archbishop of Bologna, had published an edict meant to facilitate the supply of cadavers for the purpose of dissection. In it he declared that though it had always been considered permissible to dissect the bodies of men executed for their crimes, there had arisen some confusion over dissection in general. This was due to a ruling of Pope Boniface VIII in 1299 being wrongly interpreted. He argued that that ruling had nothing to do with dissection for purposes of medical training, but was directed against such practices as grave robbery. Ordinary dissection for medical purposes had begun with papal approval already in 1315, while Clement VII in 1531 had issued further regulations concerning it. He recalled that St. Francis de Sales had wished to donate his body for dissection to the Medical School of Padua.

In Bologna, Lambertini founded a school of anatomy and commissioned and paid for a number of models to be used in instruction in the Anatomical Museum set up in the Institute of Sciences, while on various occasions he donated sets of surgical instruments to the school. Prospero Lambertini insisted that though other subjects might be taught "in a speculative and theoretical manner" anatomy could not. Lectures in his school were to be followed, as far as possible, by dissections made by "a qualified anatomist" and in all cases to be followed by a practical demonstration of all points the lecturer had spoken about.

Of course, Lambertini's interest in medicine and surgery was not due principally to his scientific bent. He encouraged them because, as was his duty, he was concerned about suffering people, especially the ill. In fact, he also endowed hospitals and added new wings to them; visited the ill in them and formed associations of priests and laymen to visit them.

On the other hand, as Pope he refused to make inoculation against small-pox obligatory by law in the Papal States, as was suggested to him. Unlike vaccination against small-pox, which method had not yet been discovered, inoculation was sometimes dangerous. This was the reason why, although he advised his subjects to be inoculated against small-pox, he refused to oblige them by law.

Quite remarkable for the age, was his encouragement of girls to study. Thus he encouraged a certain Laura Bassi in her lectures in "natural philosophy" as the natural sciences were then called, at a time when an academic career was very unusual for a woman. Laura continued teaching even after she married a doctor and had several children. At his suggestion too, Maria Gaetana Agnesi was offered the Chair of Mathematics by the University of Bologna. Urging her to accept the Chair he wrote to her, "We are most happy to see your sex drawn to illuminate both science and your own talents".

In ecclesiastical circles, Prospero Lambertini is best known for his book, "Of the Beatification of the Servants of God and of the Canonisation of the Blessed" still the standard authority in its line. In it, he shows that far from being eager to accept miracles, the Church carefully and sceptically sifts any marvellous happenings using the services of independent doctors and scientists. An anecdote is an example of Lambertini's attitude. He was once

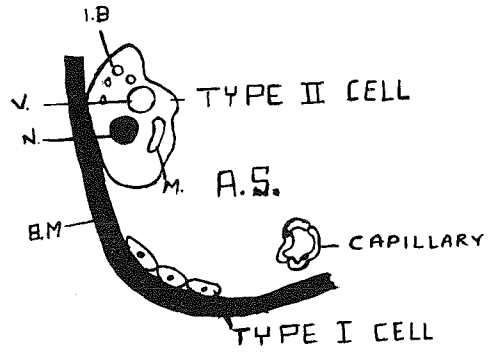
sitting on a commission investigating the case of a nun who insisted that she was living without food. In the course of the proceedings he put her the blunt but logical question whether she had bowel movements every day. Following her reply in the affirmative, he went on to show her up as a fake. This attitude pervades his book which is full of interesting examples of events and phenomena on which he gives common sense and scientific conclusions.

Like Pope John, he was a very loveable man, with a genius for making friends. Unassuming in his manners and a reformer in Church matters, a good priest, bishop and Pope he was never quite able to overcome his quick temper as he himself acknowledged. After his death, in 1758, Prospero Lambertini was described by Horace Walpole as "beloved by Papists, esteemed by Protestants . . , a man whom neither Wit nor Power could spoil".

I have culled the above items, interesting to medical men, from the gripping biography by Renée Haynes which appeared a few years ago under the title of "Philospher King: the Humanist Pope Benedict XIV".

PULMONARY SURFACTANTS

FIGURE. 1

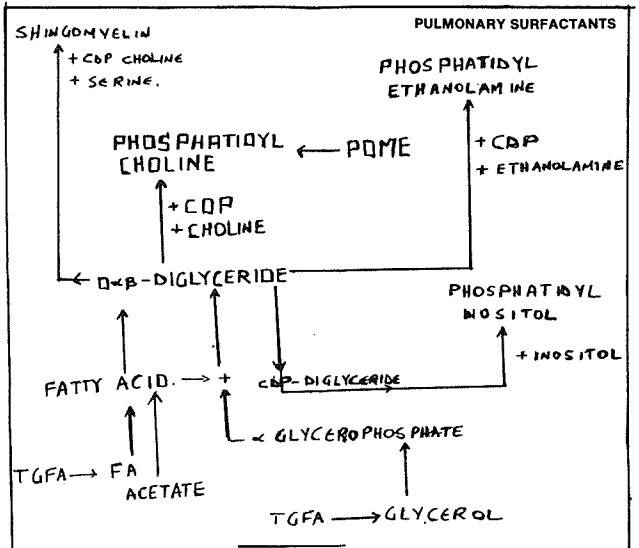


V. = VACUOLE.
I.B. = INCLUSION BODY.
N. = NUCLEUS
M. = MITOCHONDRION
B.M = BASEMENT MEMBRANE.
A.S. = ALVEOLAR SPACE.

NORMAL TYPE I AND TYPE II CELLS OF ALVEOLAR SPACE. (×8200)

(MODIFIED FROM SCARPELLI. E.M. - THE SURFACTANT SYSTEM OF THE LUNG. - 1968)

PULMONARY SURFACTANTS



(MODIFIED FROM SCARPELLI E.M.. "THE SURFACTANT SYSTEM OF THE LUNG -1968)

FIGURE 2.

PULMONARY SURFACTANTS

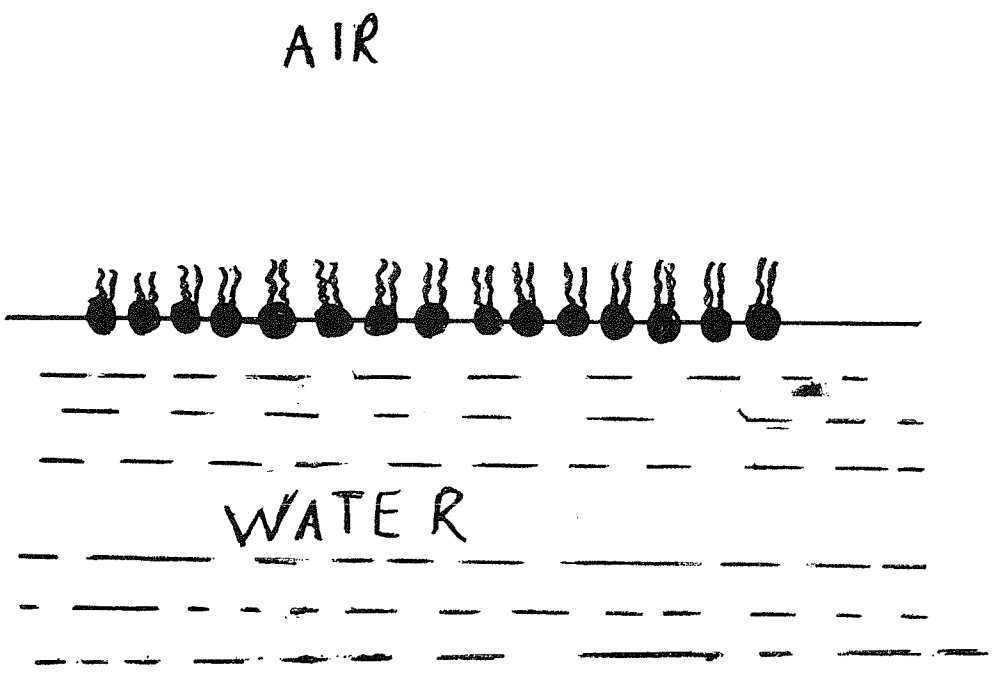
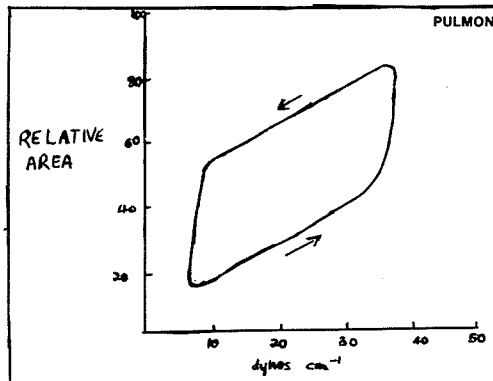
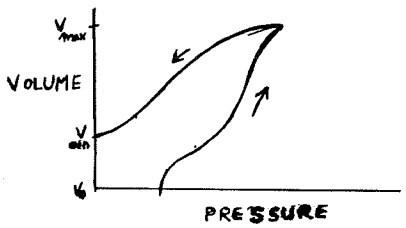


FIGURE 3



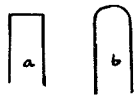


THE MAX. PRESSURE REQUIRED TO OPEN THE TERMINAL UNIT IS DETERMINED BY THE SURFACE TENSION AND THE MIN. RADIUS OF THE UNIT ONCE THE TERMINAL UNITS ARE OPENED THEY CONTINUE TO EXPAND AS INFLATION OF THE LUNG PROCEEDS. DURING DEFLATION THE LUNG CONTAINS A LARGER VOLUME OF AIR AT ANY GIVEN PRESSURE, COMPARED TO THE VOLUME IT CONTAINED DURING INFLATION. (HYSTERESIS)

FIGURE 4.

INFLATION RETRACTIVE FORCES.

1. RECRUITMENT OF INDIVIDUAL UNITS.



a. P_{min} r_{max}.
b. P_{max} r_{min}.

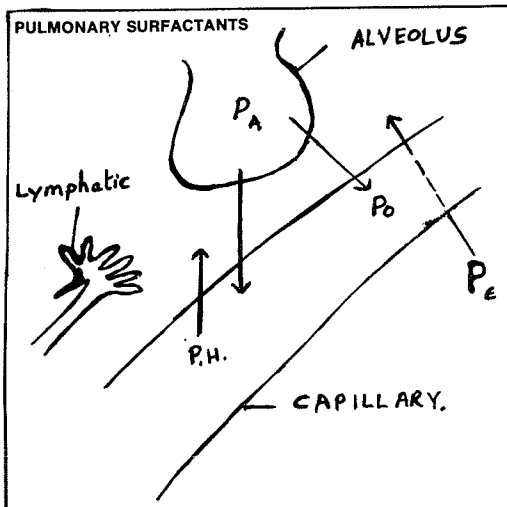
2. EXPANSION OF UNITS BEYOND HEMISHPERICAL CONFIGURATION.

3. TISSUE ELASTIC FORCES.

SKETCHES REPRESENT TERMINAL LUNG UNITS i.e. ALVEOLI AT THE END OF THE CONDUCTING UNITS (TERMINAL AIRWAYS AND DUCTS). P_{min} and P_{max} ARE THE MINIMAL AND MAXIMAL PRESSURES IN INDIVIDUAL TERMINAL UNITS. r_{min} and r_{max} ARE THE MINIMAL AND MAXIMAL RADII OF CURVATURE OF INDIVIDUAL TERMINAL UNITS.

(MODIFIED FROM SCARPELLI E.M. -THE SURFACTANT SYSTEM OF THE LUNG).

FIGURE 5



P_A - PRESSURE CAUSED BY AIR IN ALVEOLUS.

P_O - OSMOTIC PRESSURE OF PLASMA PROTEINS.

P_H - HYDROSTATIC PRESSURE WITH IN THE CAPILLARY

P_E - INTRATHORACIC PRESSURE

FIGURE 6.

CYCLIC AMP: THE UBIQUITOUS HORMONE

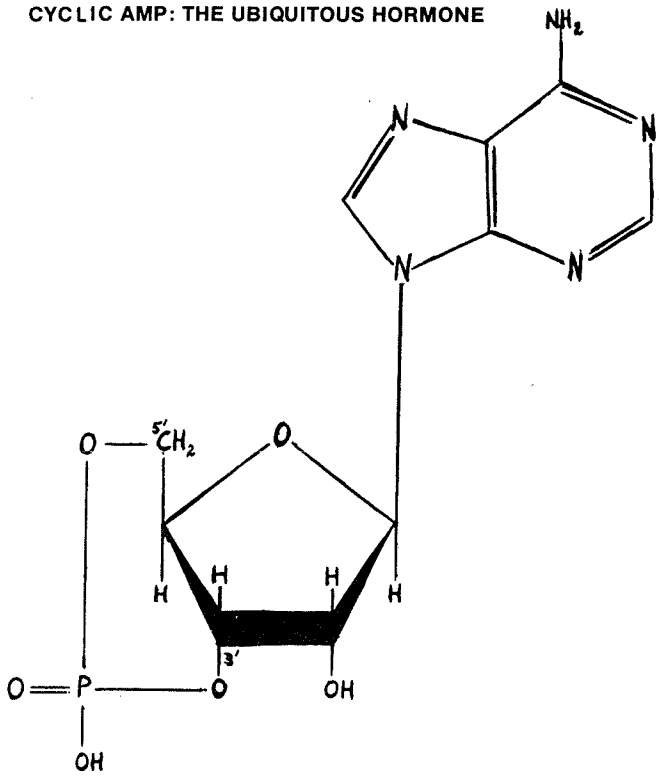


Fig. 1. Cyclic Adenosine 3',5'-Monophosphate.

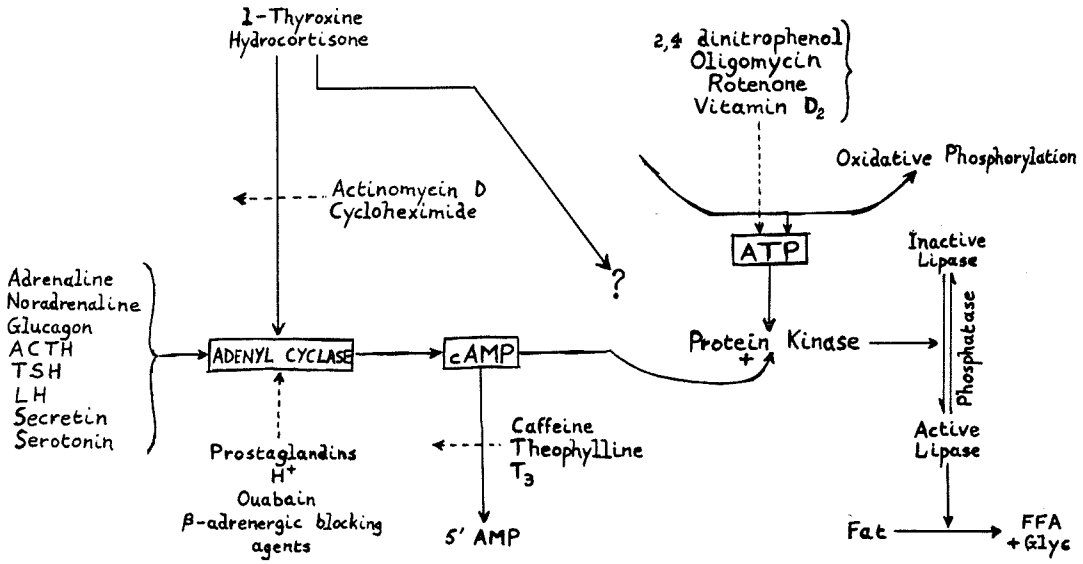


Fig. 2. Role of cAMP in lipolysis. Solid lines indicate stimulation, broken lines inhibition by cAMP. T_3 is Triiodothyronine. (Reproduced from Jost and Rickenberg: Cyclic AMP. Ann. Rev. Biochem. 40: 741-74, 1971).

CYCLIC AMP: THE UBIQUITOUS HORMONE

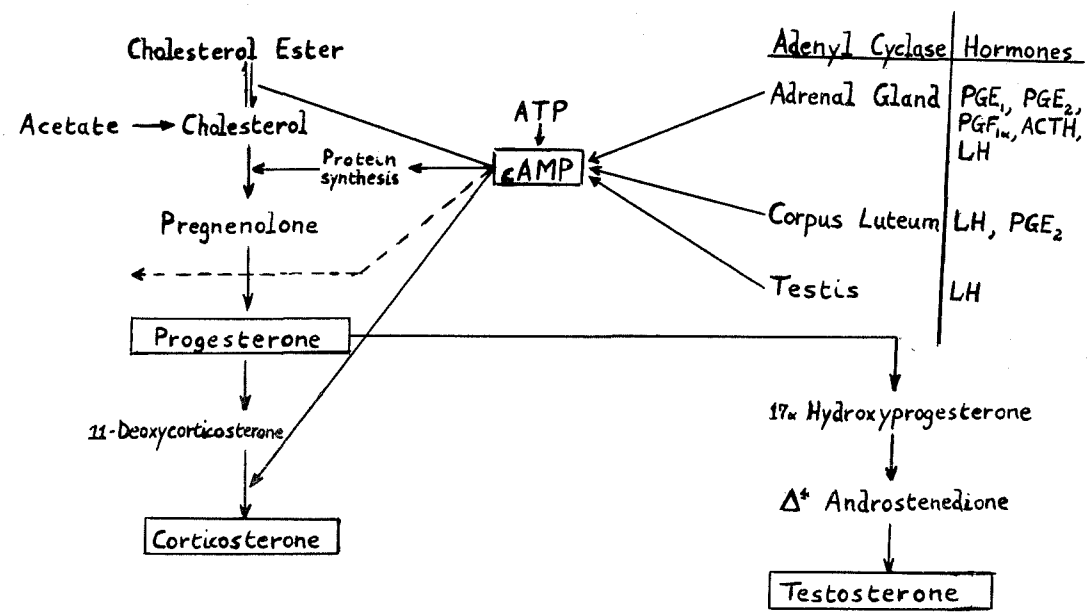


Fig. 3. Role of cAMP in Steroidogenesis. Solid lines indicate stimulation, broken lines inhibition by cAMP. (Reproduced from Jost and Rickenberg: Cyclic AMP. Ann. Rev. Biochem. 40: 741-74, 1971).

CYCLIC AMP: THE UBIQUITOUS HORMONE

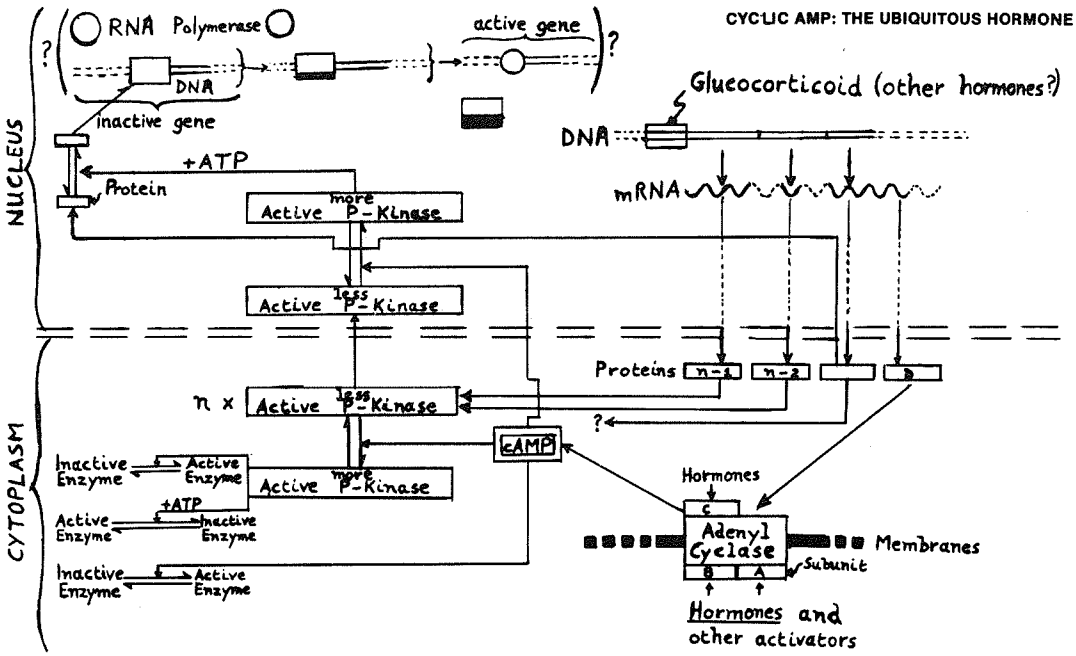


Fig. 1. The permissive (presently unexplained) effect of glucocorticoids. P-kinase denotes protein phosphokinase. (Reproduced from Jost and Rickenberg: Cyclic AMP. Ann. Rev. Biochem. 40:741-74, 1971).

A FEW FACTS ABOUT THE EBV

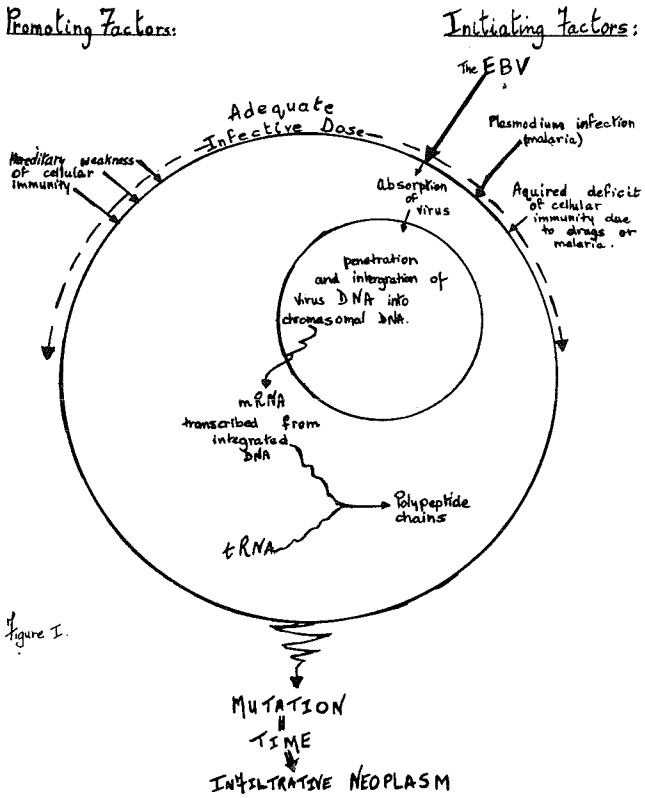
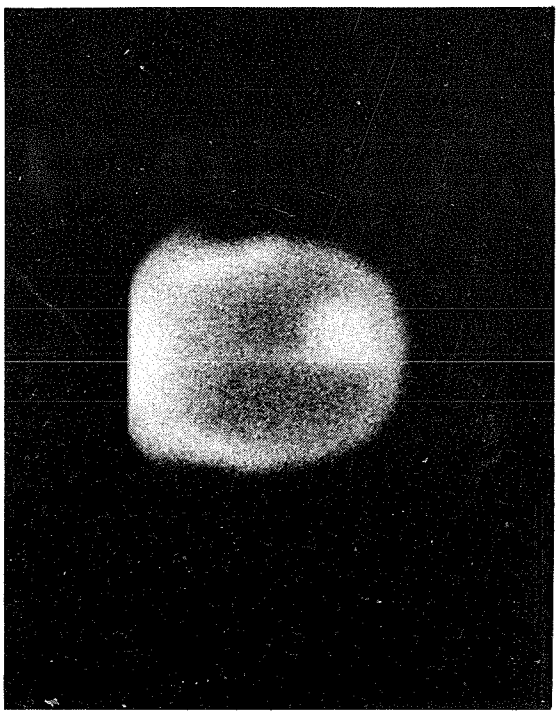


Figure I.



MENINGIOMAS

a new look at amputations and amputees.

Mr. R.O. Parnis M.B.E., M.D., F.R.C.S.

This is a talk given by Mr. Parnis at the Medical School Conference Hall on the 24th January, 1975. Mr. Parnis was the first local holder of the BMA-RUM Travelling Scholarship.

Malta is a country where one talks of impressions, where rumours abound and where facts, pure facts are quite hard to come by. There are several reasons for this state of affairs: if we limit ourselves to medical matters the main ones are a lack of a proper records system and the difficulty of looking up figures and suchlike on account of one's many other commitments. Trollpe says somewhere or other that happiness consists of having twelve hours work to do and only six hours to do it in. We are in this sense extremely happy: in fact we are laughing, but research is not carried out under these conditions.

Since my return to Malta three years ago I gradually formed the impression that amputees are not receiving the attention due to them. Amputations, I am now referring specifically to lower limb ones, are done by general and orthopaedic surgeons and their registrars and after their operation the patients vanish, to a grave, to another hospital, to a courageous wife or husband or occasionally to our one and only limb fitter whose advice we never seek and whose results we never question. I therefore thought it would be a good thing if I were to spend a while in a first class unit dealing with amputees, see what could be learnt and try and carry away the good news back home to be put, I hope, to equally good use. I was therefore very happy and most honoured to have been chosen as the first BMA-RUM Travelling Fellow of local origin.

The destination of the journey was Roehampton where I spent three weeks at the limb-fitting centre seeing and doing what I chose, with the fullest co-operation of the whole staff. The hospital nearby, Queen Mary's Hospital, is a general hospital in the Westminster Group and it was an old friend, Professor Ellis, who arranged things so well for me. The limb-fitting centre at Roehampton is not, however, a part of the hospital service but comes directly under the Ministry of Health. There are historical and developmental reasons for this divorce, which is not considered a good thing and which will in the foreseeable future be changed, following the recommendations of the Committee on Prosthetic and Orthotic Services of the British Orthopaedic Association.

There are 25 limb fitting centres in England and Wales catering for some 70,000 lower limb amputees and 13,000 upper limb ones. 5,000 amputees are referred there each year, 70 per cent of whom are over 65 years old. Roehampton is by far the largest as it serves the whole of London and the Home Counties. At the centre there are seven limb-fitting surgeons and it was with four of them, headed by Dr. Vitali, that I sat most of the time I spent there. In England the place of the medical man in limb-fitting, as distinct from the limb-fitter or prosthtist, receives rightly or wrongly more emphasis than probably in any other country. The limb-fitting surgeons work a nine-to-five 5 day week and during the day see about 15 patients. There is thus ample time to listen to what the patient has to say about his artificial limb, to arrange for minor adjustments, to order a new limb or to discuss particular problems with the limb-fitter.

These patients are patients for life and a close bond is formed between them and their surgeon so that prize winning exhibits at the local Women's Institute are brought to be admired, advice about their daughter's boyfriend is is solicited and gardening exploits related. Patients are allowed two limbs each, a somewhat wasteful procedure as we shall see, but unlike most other countries no amputee goes without a limb for financial reasons. Limbs were ordered by numbers, the most frequently prescribed ones being a No. 2 for an above knee stump and a No. 8, a patellar tendon wearing one, for a below knee one. Whether a patient brought forth many complaints or not depended mainly on his or her age. A young amputee usually managed very well and had little or nothing to report. As one of the surgeons told me "if a young man has both his legs off and he breaks his prostheses he will surely find some way to go out and meet his girl". On the other hand the elderly amputee often had his troubles due to passing years and increasing respiratory insufficiency and he tended to put the blame on to his artificial limb "I cannot use the limb for long distances as I used to". Even earache was on occasion blamed on to an above knee prosthesis! The date of delivery is metalled on to the limb and it is intended to serve for five years. However, in many cases it remains useful for much longer if well cared for and the advice given to patients is this: if it is comfortable keep it.

One of the limb fitting surgeons, Dr. Fletcher, with whom I sat, deals mainly with upper limb amputees of whom he has unrivalled experience. The main reasons for these amputations are congenital and industrial and road accidents, especially brachial plexus injuries in motor cyclists. Patients become one-handed very quickly and upper limb prostheses are in the main used by people at work or for cosmetic reasons or in double amputees. A rubber hand is stiff and strong for work while a dress hand has plastic stiff fingers for carrying or foam rubber for better cosmesis. The most impressive patient I saw was a black Jamaican with bilateral tru'knee amputations and short arms over which he wore prostheses when he wanted to look good. He played the piano well and was training to be a teacher.

In the hospital ground adjacent to the Centre are the factories of Messrs. Hanger and

Company under whom our Mr. Attard trained and with whom he keeps in close albeit sometimes irritated relationship owing to the delays in despatching the limbs he asks for. There are also small workshops belonging to two other firms Vessa and Blatchford whose actual factories are some distance away: so there are three firms dealing with lower limb prosthesis of which Hanger's is by far the largest. I shall mention Blatchford again later on as they have pioneered the MAP, the modular assembly prosthesis. Steepers have the monopoly of upper limb prostheses and monopolies are not usually good things.

I spent two sessions at Hanger's visiting their factory which is large and noisy and divided into several sections, leather, plastic, wood etc. The limb fitters who are employed by the firm see a patient initially three times. On the first occasion measuring and casting with plaster of Paris takes place and the patient is asked to send the shoe that he will wear. On the second occasion there is fitting with major or minor adjustments, trimming, making the leg vertical and so on and lastly the limb is delivered and put on and it has to be approved by the limbfitting surgeon. There are two snags here. The first is the length of time the patient has to wait before the limb is delivered. At present it is rare for a patient to receive any sort of appliance of factory construction in less than three weeks and a definite limb may take two months or more. This of course is bad because the remaining life span of the majority of amputees is limited and every day lost increases the difficulty of establishing walking patterns. The other snag is that the limb is approved when the patient has used it for a very short while and is happy with it. It is really only when he goes home and uses it for several days that he can say that all is well.

The training of a limb fitter takes four years, a quarter of the time being spent at the Paddington Technical College and the rest at Hanger's in the status of an apprentice. The trainees who are usually picked from promising workers at the factory have to be presentable and to get on well with people. The course is called Certificate Prosthesist and it is run by the British Institute of Surgical Technicians. There were several Commonwealth trainees at Hanger's. A fitter usually looks after a particular patient indefinitely and a question often asked of patients by the surgeon was: 'who is your fitter?' There are similar fitting arrangements in all the provincial centres; should an amputee move from one part of the country to another his medical notes and the manufacturers prosthetic file are transferred with him so that complete continuity is maintained.

Now I would like to deal with the very important subject of physiotherapy. Treatment should be carried out in the department and not in the wards and it starts ideally a fortnight before the operation. During this time we aim to achieve maximal fitness and functional activity. I will mention some of the points which are attended to. Hip and knee contractures are guarded against and if present they are corrected by exercise and positioning plus gentle stretching. The patient is taught how to walk with elbow crutches, how to bear weight on one leg and how to balance and walk on a posthesis by the use of a preamputation limb, a kneeling pylon. Exercises are given to strengthen the grip and the muscles of the trunk and of the arms for crutch walking. Naturally we must not forget breathing exercises and showing the patient the most effective method of coughing in order to prevent post-operative complications. Deep vein thrombosis is guarded against. The immediate post operative period sees the continuation of everything we have already noted and by the third or fourth day the patient can sit in a chair and learn sitting balance and trunk stabilising exercises. Soon after he goes to the Physical Medicine Dept. wearing normal clothes and a well-fitted shoe on the sound foot and here he practises balancinig and walking between parrallel bars. On the twelfth day the sutures are removed and firm stump bandaging starts as soon as it, the stump, has healed. The purpose of this is not as some might think, to produce a conical stump but to reduce the oedema and to accustom the stump to the firm all-round pressure which it will experience when an artificial limb is worn. When patients are finally on their own they are given a bandaging leaflet which explains the correct technique and they are told to reapply the bandage 3 times a day until a limb is worn all day. If they have to stay in bed for a few days on account of illness later on, they are told to resume the same constant bandaging of the stump until they are up and about and wearing their artificial limb.

The patients graduate from the bars to crutch walking and functional activities are practiced such as getting in and out of a bath and going to the lavatory. Ideally a pylon leg should be given to a patient within a few days of his operation but as I said delivery is not usually so quick.

When the pylon leg arrives the patient goes to the walking training school, attending daily or at least three times a week, travelling on his own or by ambulance if he lives fairly near. Otherwise he may be admitted to one of the rehabilitation wards of the nearby hospital. The walking training school at Roehampton is an impressive sight, with the newly fitted amputees moving on from parrallel bars to walking frames, tetrapods and sticks. There are twenty of them in action at one time. A home visit may be needed if it appears that there are barriers to the patient's independence; the physiotherapist and the occupational therapist may make suggestions for structural alterations and the medical social worker will see that the local Authority has the work carried out.

You may wonder at this stage why I have not mentioned the immediate fitting of a prothesis after operation. In 1965, Professor Marian Weiss of Constantia in Warsaw, whom I had the pleasure of meeting in Ghana in the same year, visited Roehampton and gave a demonstratiton of his method of the fitting of an immediate prosthesis to an above knee amputee. A similar

method was being employed at the same time by Dr. Burgess in Seattle. Enthusiasm was kindled and the method was used in many centres including Roehampton. It was abandoned mainly on account of common or garden sepsis but cases of gas gangrene necessitating amputation at a higher level and of tetanus also occured. I think it is fair to say that the method is used today only in specially selected cases even in Constantia and Seattle.

In the case of the minority of amputees which are still at work there will be a number who will be unable to continue at their job and interviews are arranged with the Resettlement Officer of the district to discuss future training and placement in suitable employment and to plan the timing of this. As regards bilateral amputees these will follow a similar programme but they cannot of course stand or crutch walk. Emphasis is put on increasing the strength of their upper limb and trunk muscles, on reachieving a stable sitting balance and on the ability to transfer on their own from bed to wheel chair and from this to bath and lavatory. Wheelchairs are ordered for these patients and they are fully trained in their use. As regards upper limb amputees graded manually resisted exercises for the muscles controlling the shoulder blade and joint are started straight away, also for the muscles working on the elbow joint in below elbow amputees. Work using pulleys and weights comes next.

Movements of the oppostie shoulder and shoulder girdle will control the artificial limb so these are given work to increase strength and mobility. Inbalance often tends to cause faulty neck and upper limb posture and this should be corrected. Firm bandaging is started when the sutures have been removed and the wound has healed. A leather cuff to which is attached cutlery or a pencil is strapped on to the bandage whatever the length of the stump. This encourages the patient to use the stump actively and will prevent him from becoming one-handed minded. There is an arm training school at Roehampton under the supervision of an occupational therapist. Here amputees are shown how to play draughts, to do carpentry, to work on machines, operate a switch board and do other jobs.

In 1967 a new building situated between the limb-fitting centre and Queen Mary's hospital was formally opened by the Minister of Health. It houses the Biomechanical Research and Development Unit, known as Bradu, where work takes place which aims at improving the current design of protheses and the total treatment of the amputee. Some of the work taking place at present includes controlled environment treatment for an amputation stump. Work on this started after the failure of the immediate fitting of a prosthesis. Here a transparent flexible pressure bag sealed incompletely by a Hovercraft skirt is filled with warm sterile air above atmospheric pressure, between 10 and 50 mm of mercury. The pressure varies, the high reading controlling the oedema the low one allowing blood to enter the stump.

As the air is warm it is of course drier. Early results from London and Seattle are very good and there are at present ten machines in use. A Mark 2, quieter and neater, is now ready. The bags are made commercially and the cost is now down to £3. This treatment is of course useful in other limb wounds not only amputation ones. The second impressive project of Bradu design is a huge carbon dioxide cylinder for foolproof recharging of the smaller units used for powering upper limb movements. The recharging takes place at night and the units are in action throughout the day. Movements are initiated by valves and there are usually three, one for the arms and two for the fingers and hooks. Work was also taking place in the clinical section, on sockets.

Finally, I would like to end this talk by leaving you this statement to chew on: an amputation is not simply an operation of destruction. Rather one of construction, to form a new organ of locomotion and so make the patient mobile again. It is only by the combined effort of all members of the team that the maximum restitution of function can be achieved. The amputee must understand that he is a member of this team, the most important member in fact, and that only by his help and full co-operation will the final objective of amputation which is mobility be achieved.

I do hope that this visit to Roehampton and the lessons that I learnt there will be of value to us in Malta and that as a result the lot of the amputee will be more cheerful. The man who needs most help is of course the elderly man and on another occasion I hope to deal more fully with the problems peculiar to this age group and at the same time to pinpoint modern trends in amputations and in prostheses.

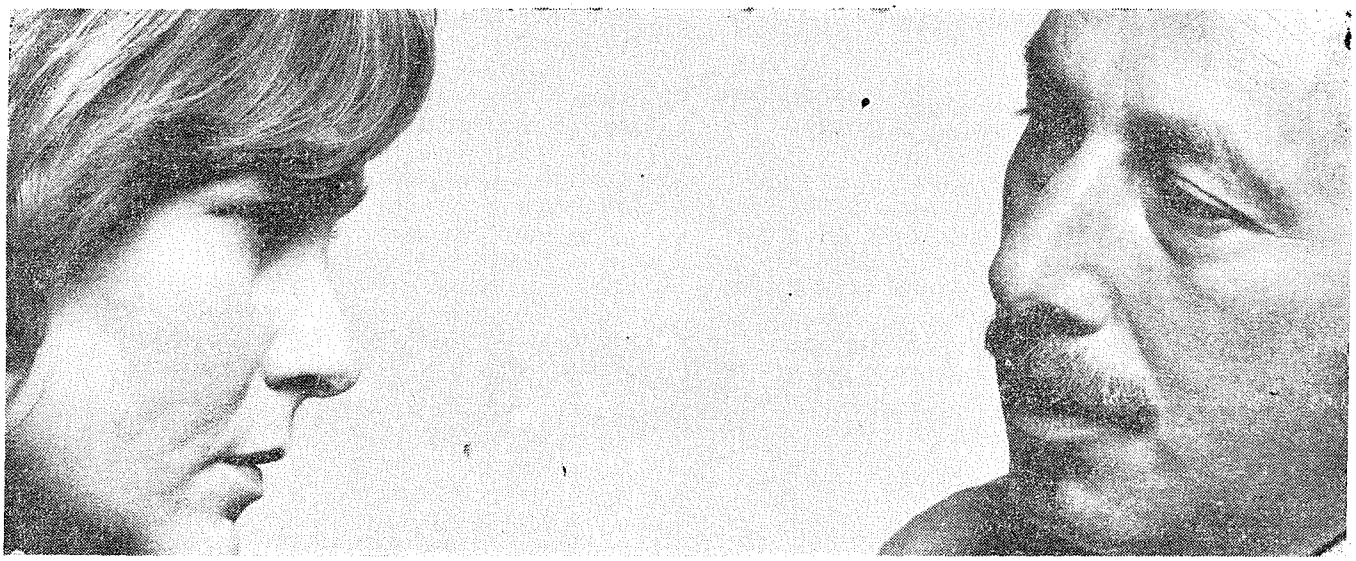
Doctor: 'Did you tell that beastly young man of yours my opinion of him?'

Daughter: 'Of course, Daddy.'

Doctor. 'Good. And what had he got to say to that?'

Daughter: 'Nothing much. Just that your diagnosis was as bad as ever.'

Peace of mind for your patient... and for you



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J954083.675/06

cyclic amp: the ubiquitous hormone

by john fsadni

It is now being claimed that many hormones act by way of a two-messenger system. The hormones may be regarded as first messengers which travel from their cells of origin to their target tissues to stimulate the formation therein of a second, intracellular messenger. Although one cannot exclude that other second messengers will eventually be discovered, the only one identified so far is cyclic adenosine 3', 5' monophosphate, or cyclic AMP (cAMP, Fig. 1). The function of this cyclic nucleotide as second messenger mediating the effects of a variety of hormones and other biologically active agents has now been definitely proved. Since the recognition of its physiological role, from the discovery that it mediated the hyperglycaemic effect of adrenaline and glucagon by stimulating the conversion of inactive to active glycogen phosphorylase, work in many laboratories has established both the ubiquity of cAMP in living organisms and the large number of its regulatory mechanisms.

ADENYL CYCLASE AND cAMP-DIESTERASE

The level of cAMP inside the cells at any given instant depends upon the activities of at least two enzymes: adenyl cyclase and phosphodiesterase.

Adenyl Cyclase. Adenyl cyclase catalyses the formation of cAMP and pyrophosphate from adenosine triphosphate (ATP) in a reaction which requires Mg++ :

$$ATP \longrightarrow cAMP + PPi$$

It is present in both nucleated and akaryotic cells where it is associated with either the cytoplasmic (e.g. in fat-cells, liver), mitochondrial (e.g. in skeletal muscle) or endoplasmic membrane (e.g. in fat-cells). Its profound metabolic importance resides in the fact that its activity responds to a wide variety of hormones (TABLE I) and other pharmacolgically active compounds.

The mechanism of its hormonal activation is generally assumed to involve an allosteric interaction between the hormone and either the adenyl cyclase or the membrane with which it is associated. The same adenyl cyclase may be stimulated by different effectors; conversely, the adenyl cyclases of individual tissues may vary in their response to the same effectors. Thus there arise problems as to the reasons for the hormonal specificity of adenyl cyclase.

It would appear that the molecular configuration of at least part of the adenyl cyclase system must differ from one tissue to another, or even within the same cells. The existence of distinct adenyl cyclase-receptor complexes in the various parts of the kidney (Marumo and Edelman, 1971) and of two distinct adenyl cyclases in the liver has been claimed. Most evidence supports the hypothesis that stimulation by different effectors is mediated by separate specific receptors at the outer surface of the plasma membrance; some of the receptors are at least partially proteinaceous. Competition between activators of differing efficacy probably also occurs; prostaglandin E_1 (PGE_1), a less potent activator of renal medullary adenyl cyclase than antidiuretic hormone (ADH), decreases ADH-mediated increases in cAMP production by competing with ADH for the receptors which influence adenyl cyclase in rat medulla (Beck et al., 1971). Cyclase stimulation decreases with age.

cAMP-Diesterase. Phosphodiesterase catalyses the hydrolysis of cAMP to 5'-AMP; it is specific for the 3', 5' diester-bond. Its distribution parallels that of adenyl cyclase and may occur, in some cases (e.g. in brain cortex) even in the same cell, in soluble (e.g. in liver) as well as in particulate form. The activity of the enzyme increases with age.

PLASMA cAMP

Under basal conditions, the plasma level of cAMP, whose turnover is known to be rapid, seems to be maintained by mechanisms that involve both uptake and release by tissue, metabolism within tissue, urinary excretion, and possibly other mechanisms (Blonde et al., 1974).

The small intestine is a site of net production of cAMP, and so may be the lungs (Wehmann et al., 1974); the kidneys are responsible for about 5% of the total rate of entry into plasma of cAMP (Blonde et al., 1974). Nevertheless, renal elimination accounts for 30% of the plasma clearance rate of cAMP, 10% as a result of metabolism within the renal tissue and 20% accounted for by urinary excretion; 30-55% of the urinary cAMP is derived from production and release by the renal parenchyma, the rest from glomerular filtration (Blonde et al., 1974). The liver is also one important site of elimination of plasma cAMP; a balance between uptake and secretion by this organ may exist (Blonde et al., 1974). However, plasma cAMP is present in such low concentration relative to intracellular concentrations that it is unlikely to be acting as a hormone by penetrating cell membranes of selected tissues (Blonde et al., 1974).

cAMP AND THE SYNTHESIS OF PROTEINS

Synthesis of a number of enzymes in various organs is stimulated by cAMP which appears to stimulate either the transcription to the specific messenger or its transmission from nucleus to cytoplasm.

Effect of cAMP on the transcription of genes. The mechanism by which cAMP stimulates the synthesis of functional messenger is unknown. The hypothesis that the phosphorylation of histones and other nuclear proteins mediates the differential transcription of genes is supported by the finding that cAMP stimulates the phosphorylation of purified liver histone kinase. Furthermore, cAMP increases the rate of

TABLE I. INTERACTIONS BETWEEN HORMONES AND ADENYL CYCLASES*

Organ producing hormone	Hormone	Adenyl Cyclase of
Adrenal medulla	Adrenaline	Brain Lung Spleen Pineal gland Salivary gland Ocular tissue Heart Aorta Diaphragm Skeletal muscle Liver Erythrocytes Fat cells Oviduct or uterus
	Nor-adrenaline	Fat cells Aorta Brain Pineal gland Hypophysis Salivary gland Oviduct or uterus Ocular tissue Melanocytes
All mammalian tissues	Prosta-glandins	Hypophysis Thyroid Lung Diaphragm Heart Aorta Skeletal muscle Spleen Blood platelets Kidney Adrenal cortex? Corpus luteum
Testis	Testosterone	Testis?
Intestine	Secretin	Fat cells
Pancreas	Glucagon	Heart Liver Blood platelets Fat cells
Placenta	Gonadotropin	Testis
Ovary	Oestrogen	Oviduct and uterus
Kidney	Erythropoietin?	Bone marrow
Neuro-hypophysis	Antidiuretic hormone	Aorta Kidney Urinary bladder
	Oxytocin	Urinary bladder
Hypo-thalamus	Hypothalamic extract	Hypophysis
Para-thyroid	Para-thyroid hormone	Skeletal muscles Bone Kidney
Thyroid	Triiodo-thyronine	Heart Corpus luteum Spermatozoid
	Thyro-calcitonin	Kidney Bone
Adeno-hypophysis	Luteinising hormone	Fat cells Corpus luteum
	Adrenocort-icotropin	Adrenal cortex Fat cells
	Thyroid stimulating hormone	Thyroid Fat cells
Pars intermedia	Melanocyte stimulating hormone	Melanocytes
	Phytohaem-agglutinin	Lymphocytes

*Reproduced and modified from Jost and Rickenberg: Cyclic AMP. Ann. Rev. Biochem. **40:** 741-74, 1971.

RNA synthesis in purified rat liver and the increase is preceded by phosphorylation of non-ohistone proteins and f_1 histones. Moreover various observations suggest that interactions of tissue-specific nuclear protein kinases, substrate and cAMP may be important in the tissue-specific regulations of RNA synthesis and chromatin function (Kish and Kleinsmith, 1974).

Effect of cAMP on the translation of mRNA. Besides the effect on the transcription of certain genes, an effect of cAMP on the translation of a bacterial messenger has also been claimed. The synthesis of tryptophanase is controlled at the level of the polysome. The ribosomal G-factor (a protein which participates in the translation of the nascent polypeptide chain) binds cAMP in the simultaneous presence of guanosine triphosphate (GTP). It has been suggested that cAMP regulates the movement of ribosomes along the messenger RNA (mRNA), so as to slow its hydrolysis by RNase V.

cAMP and inhibition of protein synthesis. Inhibition of protein synthesis by cAMP has been reported to occur in liver and muscle fibers.

EFFECT OF cAMP ON THE ACTIVITY OF ENZYMES

Glycogen phosphorylase. cAMP regulates glycogen metabolism at two sites. At the first it acts as an allosteric cofactor in a reaction in which a protein kinase, phosphorylase b kinase kinase, catalyses the phosphorylation of seryl residues of inactive phosphorylase b kinase converting the enzyme into its active form; ATP serves as phosphate donor in this reaction which is completely dependent on the presence of cAMP. The active phosphorylase b kinase catalyses the activation of glycogen phosphorylase b to phosphorylase a:

2 Phosphorylase b + 4 ATP
(inactive)
| Active Phosphorylase b Kinase
↓
Phosphorylase a + 4 ADP
(active)

Under certain conditions cAMP reduces the activity of phosphorylase a phosphatase which catalyses the inactivating dephosphosphorylation of phosphorylase a to b in the reaction

Phrosphorylase a + 4 H_2O
(active)
| Phosphorylase a phosphatase
↓
2 Phosphorylase b + 4 Pi
(inactive)

Glycogen phosphorylase. cAMP regulates glycogen metabolism at a second site. Here it stimulates the conversion of the active, dephosphorylated I form of glycogen synthetase to the inactive, phosphorylated D form by activating glycogen synthetase kinase which catalyses the reaction

Synthetase I + ATP
(active)
| Active Synthetase Kinase
↓
Synthetase D + ADP
(inactive)

Insulin blocks glucagon-stimulated glucose release from liver mainly by diverting glucose into glycogen (Mayo Johnson et al., 1972) and probably acts at this site by antagonising the cAMP production mediated by glucagon, which in turn acts by activating hepatic adenylate cyclase. (Liljenquist et al., 1974).

Phosphofructokinase. cAMP plays a complex role in activating phosphofructokinase, the enzyme catalysing the rate-limiting step in glycolysis. At least in mammalian heart it exerts two distinct effects. It overcomes the inhibition of phosphofructokinase by ATP at subsaturating concentrations of fructose-6-phosphate in a partially competitive manner, and also appears to participate in the activation of the inactive form of phosphofructokinase, this activation involving subunit aggregation.

Miscellaneous enzymes. cAMP counteracts the effect of ATP on the susceptibility of glyceraldehyde-3-phosphate dehydrogenase to inactivation by chymotrypsin. It stimulates the oxidation of glutamate, alpha-ketoglutarate, and pyruvate by brain homogenates and mitochondria. It also overcomes the inhibition of pyruvate kinase by ATP.

Protein kinases. cAMP stimulates protein kinase activity by dissociating the kinase into an inhibitory and a catalytically active subunit; the inhibitory component binds cAMP. In human erythrocytes both protein kinase components are localised on the inner, cytoplasmic surface of the plasma membrane (Rubin et al., 1973). A heat-stable protein which inhibits activation of muscle kinase by cAMP has been isolated from skeletal muscle; little is known about its mode of action.

cAMP AND LIPOLYSIS

cAMP mediates the effect of a number of lipolytic hormones (Fig. 2) and stimulates lipolysis in white and brown fat cells. Where various lipolytic hormones act on the same tissue (e.g. fat cells), the different hormones either interact with different sites or subunits of the same adenyl cyclase or different hormonal discriminators interact in the membrane with the same adenyl cyclase. Low K+ concentrations inhibit lipolysis, possibly by decreasing the affinity of the enzyme for hormones; it has been shown that K+ stimulates, but is not essential for, the activation of lipolysis in white fat cells.

Lipolysis is also severely inhibited if oxidative phosphorylation is blocked; Fain et al. (1973) found a good correlation between the ability of catecholamines and serotonin to affect cAMP accumulation, lipolysis, and respiration in brown fat cells. Thus stimulation of lipase activity by cAMP requires ATP and therefore may be effected by phosphorylation.

High concentrations of triodothyronine enhance the sensitivity of adipose tissue to the action of lipolytic hormones, whilst hydrocortisone is required for the maximal stimulation of adenyl cyclase by catecholamines and ACTH. Beta-adrenergic blocking agents are able to block the formation of cAMP in response to catecholamines but not to other hormones. The lipolytic and most other effects of catecholamines are decreased by acidosis and increased

by alkalosis. Whereas prostaglandins stimulate the adenyl cyclase of the adrenals and of the corpus luteum, PG_1, PGA and PG_2[a], inhnibit that of fat cells. The lipolytic effect of glucagon may be obscured in vivo by the antilipolytic effect of insulin whose release it tends to stimulate.

cAMP AND STEROIDOGENESIS

Several steroidogenic hormones, including ACTH, luteinising hormone (LH) and prostaglandins (E_2, E_7, F_1[a]), stimulate the adenyl cyclase of their steroidogenic target tissues (e.g., adrenal cortex, testis, and corpus luteum) and the cAMP, in turn, activates different steps of steroidogenesis (Fig. 3). Only a small fraction of the cells' potential to synthesise cAMP need be activated to achieve maximum steroidogenesis (Schulster et al., 1972).

cAMP appears to stimulate three different steps in steroid biosynthesis. The first step, the conversion of cholesterol ester to cholesterol, does not require protein synthesis, but the second, the conversion of cholesterol to pregnenolone, does; Mahaffee et al. (1974), however, suggest that cAMP stimulates steroidogenesis by regulating the mitochondrial precursor pool of cholesterol, rather than through a direct effect on the mitochondrial enzyme system that transforms cholesterol to pregnenolone. Stimulation of the third step, the conversion of 11-deoxycorticosterone to corticosterone, appears to involve an activation of the C-11 beta-hydroxylase. cAMP also inhibits (competitively with NAD) the two enzymes which catalyse the conversion of pregnenolone to progesterone: D^5 - 3beta - hydroxysteroid dehydrogenase and D^5 - 3 - ketosteroid isomerase. A cAMP-binding protein has recently been purified from the adrenals.

Current concepts for the complicated mechanism whereby ACTH stimulates corticosteroidogenesis therefore involve the following aspects: ACTH binding at cell-surface receptors, activation of adenyl cyclase and increased production of intracellular cAMP, activation of protein kinases with increased phosphorylation of ribosomal protein, induction of labile protein(s) implicated in the rate-limiting step of steroidogenesis and intracellular translocation of steroid intermediates that influence cholesterol conversion into pregnenolone (Schulster et al., 1972). Rubin et al. (1972) propose that ACTH activates adenyl cyclase by displacing calcium from some site on or near adenyl cyclase. They also suggest that the translocation of this calcium fraction into the cell interior to some active site — possibly the endoplasmic reticulum of mitochondria — which couples steroid production and release may be responsible for initiating steroid release. Angiotensin interacts synergistically with ACTH in elevating cAMP levels to stimulate steroidogenesis in bovine fasciculata cells, but not in human cells owing probably to the use of safely-low doses. (Peytremann et al., 1973).

cAMP AND CHOLESTEROL AND FATTY ACID SYNTHESIS

Bricker and Levey (1972) suggest that cAMP, probably under the control of some unknown primary hormone, may be involved in regulating acetyl-CoA incorporation into de novo fatty acid and cholesterol, and hence lipid synthesis (Capuzzi et al., 1974), in a specific manner in mammalian liver.

THE PERMISSIVE EFFECT OF GLUCOCORTICOIDS ON THE BIOLOGICAL ACTIVITY OF cAMP

Adrenal glucocorticoids have been implicated in the control of many metabolic processes involving cAMP, such as in glycogen synthesis and degradation, gluconeogenesis, lipolysis, and protein synthesis; they may play a similar role in gastric acid secretion (Domschke et al., 1972). In general they exert their effect at a site beyond that of the synthesis of cAMP, but a glucocorticoid has in fact been found to be required to mediate the stimulation of adenyl cyclase by ACTH (but not by adrenaline, glucagon, or fluoride) in fat-cell membrane.

Moreover, the permissive effect of hydrocortisone on the regulatory activity of cAMP requires the synthesis of protein. However, the possibility that glucocorticoids cause the synthesis of proteins known to interact with cAMP, such as cAMP-stimulated protein kinases, has apparently not been tested (Jost and Rickenberg, 1971).

Fig. 4 presents a model for the interaction between glucocorticoids and cAMP. Evidently the model, particularly as regards the effect of cAMP on transcription, is tentative. It is assumed that glucocorticoids stimulate the synthesis of several proteins, including that of protein phosphokinases, and regulatory elements of membranal adenyl cyclases; that is, the effect of glucocorticoids would be twofold: an increase in the concentration of cAMP and of proteins that interact with cAMP. Cyclic AMP, in both the cytoplasm and the nucleus, enhances the activity of protein kinases and presumably also interacts directly with other proteins. The phosphorylation (or other cAMP-linked alteration) of a nuclear protein (acidic, histone?) may then lead to the depression of specific genes.

cAMP AND THE PERMEABILITY OF MEMBRANES

Water. ADH enhances the permeability of certain epithelial membranes, for example, in the kidney, to water, sodium, and other low molecular weight substances such as urea through the synthesis and accumulation of cAMP. The effects on osmotic flow and permeability to urea may be mediated by a single pool of cAMP. Delorenzo et al. (1973) suggest that the effect of cAMP on sodium and/or water transport in toad-bladder membrane might be mediated through the level of phosphorylation of a specific protein; ADH and cAMP decrease the phosphorylation of this specific protein, partially through the activation, in the presence of cAMP, of a membrane-bound phosphoprotein phosphatase.

Ca^{++} inhibited the basal level of adenyl cyclase activity in golden hamster kidney and ADH did not overcome this inhibition (Marumo

and Edelman, 1971). PGE_1, a less potent activator of adenyl cyclase than ADH, decreases ADH-mediated increases in renal medullary cAMP production by competing with ADH for the receptors which influence adenyl cyclase (Beck et al., 1971). Stoff et al. (1972) claim a permissive effect of aldosterone on the permeability responses to ADH mediated by a steroid-dependent increase in the accumulation of cAMP in the pertinent epithelial cells, probably as a consequence of a diminution in the rate of degradation of the intracellular nucleotide.

Catecholamines which stimulate adrenergic alpha-receptors inhibit the response to ADH in the toad-bladder. Goodman et al. (1972) reported that acute or sustained metabolic acidosis or alkalosis did not affect, in any significant way at least, the level of renal cortical cAMP; this also implies that cAMP does not mediate the effects of acidosis and alkalosis on renal ammoniagenesis (Goodman et al., 1972).

Sodium. ADH and cAMP consistently enhanced the short-circuit current and sodium transport across frog skin. It has been suggested that the increase in the sodium-dependent short-circuit current is related to the reduction in concentration of protein disulphide groups (through the action of cAMP) and possibly to a change in membrane structure, resulting in enhanced permeability to Na^+.

Potassium. Adrenaline, glucagon and cAMP cause an efflux of K^+ from the liver; that in response to glucagon precedes activation of glycogen phosphorylase. A variety of lipolytic agents such as adrenaline, ACTH, and cAMP increase the efflux of K^+ from isolated fat cells.

Calcium. Glucagon and cAMP cause an immediate efflux of Ca^{++}, preceding that of K^+, from liver. Dibutyryl cAMP caused mobilisation of Ca^{++} from bone, an effect blocked by thyrocalcitonin. Glucagon enhances Ca^{++} accumulation by the heart muscle during excitation, an effect mediated at least in part by cAMP. Transport of Ca^{++} in intestinal mucosa is also affected by cAMP and is apparently dependent on the presence of a factor induced by vitamin D. It has been suggested that $Ca++$ transport plays an important role in the regulation of gluconeogenesis and glycolysis. It has been speculated that shifts in the intracellular distribution of Ca^{++} are responsible for many, if not all, of the effects of cAMP.

Amino-acids. cAMP also appears to stimulate the uptake of amino-acids in a variety of tissues. Thus uptake of alpha-aminoisobutyric acid was stimulated in rat livers perfused with glucagon or cAMP. An enhancement of the transport of amino-acids requires a much higher concentration of exogenous cAMP than a stimulation of glycogenolysis.

cAMP AND SECRETION

Insulin release. It would appear that glucagon stimulates insulin release by activating adenyl cyclase; the mechanism by which cAMP might act to stimulate insulin release is unknown. Charles et al. (1973) obtained results suggesting a minor role for cAMP in directly stimulating insulin release but a prominent role in modulating glucose-induced release of insulin; such modulation may be achieved by an effect on the movement of granules in the beta-cell (Montague and Cook, 1971). It seems possible that the mode of action of cAMP in stimulating insulin release may be to promote microtubular function by increasing the phosphorylation of microtubular proteins (Lacy et al., 1968; Montague and Howell, 1972). Both diazoxide and imidazole inhibited insulin release from mammalian pancreas but diazoxide, unlike imidazole, was without significant effect on the activity of the cAMP-diesterase (Sams and Montague, 1972).

Growth hormone secretion. Evidence suggests that cAMP also mediates the release of growth hormone (GH) by an action requiring ionised calcium (Lockhart Ewart and Taylor, 1971; Cooper et al., 1972) and a source of metabolic energy (Lockhart Ewart and Taylor, 1971). The mechanism is independent of pituitary protein synthesis de novo, but the integrity of the glycolytic pathway of glucose metabolism appears to be essential (Lockhart Ewart and Taylor, 1971). A microfilamentous or microtubular protein may be involved (Cooper et al., 1972). It is now suggested that cAMP may be the specific trigger of the migration of storage granules to the cell periphery for discharge. The cyclic nucleotide has been invoked as an activator, together with Ca^{++}, of a contractile microtubular system, as seems to be involved also in the secretion of insulin from the pancreatic cells, of catecholamines from perfused adrenals and of thyroid hormones.

Gastric acid secretion. Results obtained by Bieck et al. (1973) indicate that hydrochloric acid secretion into the gastric juice is mediated by cAMP. Histamine, which stimulates gastric acid secretion, stimulates gastric mucosal adenylate cyclase via interaction with H_2 receptor without influencing cAMP breakdown (Dousa and Code, 1974). Domschke et al. (1972) claim that glucocorticoids may play a permissive role in gastric acid secretion via a permissive action on net cAMP production.

Pancreatic exocrine secretion. Case and Scratcherd (1972) claim that the action of secretin, but not that of pancreozymin, may be mediated through cAMP.

Salivary secretion. Amylase secretion from the parotid gland in response to catecholamines, which seems to be mediated via adrenergic beta-receptors, is mediated by increases in level of cAMP.

cAMP AND SYNAPTIC AND NEUROMUSCULAR TRANSMISSION

Synaptic transmission. According to a hypothesis advanced by Johnson et al. (1972) and supported by the results of other workers (McAfee and Greengard, 1972), cAMP, generated in postsynaptic neurons in response to transmitter released during synaptic transmission, activates a specific protein constituent of the postsynaptic plasma membrane; this process results in an alteration of the permeability of the membrane to inorganic ions, thereby bringing

about the hyperpolarisation of the membrane. It has also been proposed that the first step in neurosecretion is a cAMP-mediated phosphorylation of a neurotubular protein (Cooper et al., 1972).

Neuromuscular transmission. Facilitation of neuromuscular transmission by adrenaline seems to involve cAMP (Robison et al, 1968). Cyclic AMP levels increase in skeletal muscle in response to both adrenaline and high K^+, whose effects seems to be additive. The implication in the present case is that cAMP may play a role in the release of acetylcholine from nerve endings.

cAMP AND CARDIAC FUNCTION

Evidence supports the hypothesis that the positive inotropic effect of the catecholamines, of glucagon and possibly of histamine on cardiac muscle is mediated by cAMP. This positive inotropic response can be dissociated from the activation of cardiac phosphorylase. In fact whilst it has not been possible to dissociate the increased level of cAMP from the inotropic response, data suggest that the cAMP-dependent activity of phosphorylase b kinase might have to exceed a certain threshold before it becomes capable of catalysing the phosphorylase b-to-a reaction under the conditions prevailing within the myofibrils. Glucagon enhances Ca^{++} accumulation by heart muscle during excitation and the positive inotropic effect of the hormone, as also that of adrenaline, may result from an increase in the sarcotubular Ca^{++} pool of the heart muscle; the effect is mediated at least in part via cAMP. It has also been suggested that many cardioactive drugs affect the intracellular distribution and cellular concentration of Ca^{++} via cAMP.

cAMP AND ADRENERGIC ALPHA- AND BETA-RECEPTORS

Evidence indicates that in general adrenergic beta-receptor effects are mediated by an increase and alpha-receptor effects by a decrease in the intracellular level of cAMP. A puzzling fact, however, is that in intestinal smooth muscle a releasing action of the catecholamines has been produced both by stimulating adrenergic alpha- and beta-receptors; with adrenaline and noradrenaline a mixed alpha- and beta-receptor response has been obtained. The relaxation mediated by beta-receptors has been found to be preceded by and correlated with an increase in the cAMP content, whereas alpha-receptor relaxation after some delay is associated with a reduction of the cAMP content. Adrenergic beta-receptor stimulation is also combined with an increase of the phosphorylase a activity and a transient reduction of the concentration of the ATP and creatine phosphate contents of the muscle. Andersson and Nilsson (1972) reported that their findings indicated a relationship between relaxation of intestinal smooth muscle and an increased content of cAMP; they also found that cAMP stimulated the binding of Ca^{++} in a microsomal fraction of smooth muscle under utilisation of ATP and claimed that the relaxing action was probably dependent on a decrease of the free myoplasmic Ca^{++} concentration.

cAMP AND PHOTORECEPTOR PHYSIOLOGY

Studies by Miki et al. (1973) showed that illumination markedly diminishes the concentration of cyclic nucleotides in suspensions of photoreceptor membranes, but the locus of regulation is cyclic nucleotide phosphodiesterase (light-stimulated) and not adenylate cyclase. The process of activation of phosphodiesterase by light is in two steps, a light-dependent step followed by an ATP-dependent step. Illumination (in the absence of ATP) produces a trypsin-resistant, heat-labile, macromolocular stimulator. In the presence of ATP the stimulator increases the activity of photoreceptor phosphodiesterase. The light-produced stimulator appears unique to the photoreceptor membranes and does not activate phosphodiesterase in other tissues.

MODULATION OF INFLAMMATION AND IMMUNITY BY cAMP

From results of various in vitro studies, Bourne et al. (1974) have constructed a hypothesis by which certain hormones and mediators of inflammation act in vivo on neutrophils, mast cells and basophils to limit the intensity and extent of inflammatory, allergic or anaphylactic reactions, and to modify the function of immunologically-competent cells (lymphocytes) at several stages, from the recognition of an antigenic signal, through its amplification by clonal proliferation, to the expression of an immune response by differentiated T and B effector lymphocytes; this regulatory action is mediated by a general inhibitory action of cAMP on immunologic and inflammatory functions of leucocytes. This hypothesis suggests that certain vasoactive hormones, mediators of inflammation, and cAMP serve to protect the host from the dangerous consequences of an unregulated immune response. The hypothesis is based on the supposition that some or all of the in vitro observations that led to it reflect events that occur in vivo.

Such in vitro observations have yielded two main results. First, they have demonstrated receptors for a strikingly consistent array of vasodilating hormones — histamine, beta-adrenergic catecholamines, prostaglandins of the E series — in basophils, mast cells, neutrophils and T and B lymphocytes. It is beginning to appear that in the case of lymphocytes such specific and distinct receptors are not present in random fashion on all lymphocytes, but may in fact develop concomitantly with the commitment of a clone of immunologically-competent cells to expression of either cell-mediated or humoral immune responses.

Secondly, it has been shown that in contrast to cAMP's stimulation of secretion in other cells, the nucleotide consistently inhibits secretory events in leucocytes thought to be necessary for expression of immune responses. It inhibits the antigen-induced release of histamine from basophils, and of histamine and SRS-A ('slow reacting substance of anaphylaxis') from the primate lung (Orange and Austen, 1971). It also inhibits the cytolysis by sensitised T-lymphocytes of cells bearing the appropriate alloantigen, and prevents the secretion of interferon and possibly

even that a migratory inhibitory factor (MIF), thought to be responsible for the characteristic collection of mononuclear cells in delayed hypersensitivity skin reactions. The nucleotide also appears to inhibit either the production or the secretion of antibody by B lymphocytes following antigenic stimulation. Moreover, there is inconclusive evidence that neutrophil cAMP inhibits the phagocytosis-induced release of beta-glucuronidase and other lysosomal hydrolases by human neutrophils.

It is also possible that cAMP plays a role in the communication between different cell types (between T and B lymphocytes or between subpopulations of T cells) apparently occurring in the early stages of an immune response and determining either its amplification or its suppression; such a possibility has not yet, however, been carefully considered. Studies also suggest that cAMP may inhibit amplification of an immune response, whilst guanosine 3', 5'-monophosphate (cGMP) may enhance it (Watson et al., 1973). It is being suggested that cGMP and cAMP may act in a "push-pull" fashion to regulate functions of lymphocytes, neutrophils, and even mast cells: wherever cAMP appears to inhibit a reaction, cGMP may enhance it; similarly, wherever sympathetic neurohormones (catecholamines) appear to act through cAMP, the parasympathetic neurotransmitter acetylcholine (or its congeners) may act through cGMP. Cyclic GMP should therefore perhaps be included in the hypothesis of Bourne et al.

An essential feature of the above hypothesis concerns the nature of the hormones themselves, which originate either from neuroendocrine cells (the catecholamines) or from inflammatory reactions. In the first case the catecholamines provide a neuroendocrine mechanism allowing non-antigenic environmental influences to modify inflammatory or immune responses. In the latter case, the inflammatory mediators would be produced by reaction to tissue injury or by immunologic reactions per se, such as anaphylaxis; thus, the intensity or extent of a response to a specific stimulus could regulate subsequent responses to continued or repeated stimuli — the essential feature of feed-back circuits or servo mechanisms.

cAMP AND GROWTH AND MORPHOGENESIS

Cell growth and contact inhibition. Evidence points to an inhibition of mitotic activity by increased levels of cAMP (Marks and Grimm, 1971; Bronstad et al., 1971). Frank (1972) found that accumulation of cAMP within rat embryonic cells caused a strong decrease of thymidine incorporation and of cell proliferation; the cells were stopped in G1 phase of the cell cycle probably due to the interaction of cAMP with one or more metabolic pathways (Frank, 1972). Furthermore, many cells divide in logarithmic phase until they become confluent with other cells, at which time growth ceases or continues at a diminished rate (Burk, 1968; Otten et al., 1972). cAMP concentration remains low during logarithmic growth, increases when the cells approach confluency, and rises to even higher levels several days after the cells have stopped dividing; the contact-inhibited (Stoker and Rubin, 1967) cells are stopped in G1 phase. Washing away of the accumulated cAMP by serum reactivates 'resting' cells (Frank, 1972; Otten et al., 1972), probably through the activation of a cAMP-phosphodiesterase (Frank, 1972). Evidence therefore points to a common regulator mechanism for both contact inhibition and growth regulation of cell-cultures by serum (Frank, 1972); increases in cAMP levels could therefore be due to depletion of some serum factor (Otten et al., 1972).

Cell differentiation. Luin et al. (1973) observed that the morphology and histotypic pattern of some mammalian cells in culture can be changed from a less differentiated to a more differentiated state by agents raising intracellular cAMP. Tash and Mann (1973) found an immediate decrease in the level of cAMP in spermatozoa in response to agents that either depress the motility or shorten the life-span of spermatozoa; thus senescence of spermatozoa seems to be closely related to a decrease in cAMP levels.

cAMP and Turnover Tissue. Konnek et al. (1973) observed that cAMP incorporated in the growth media of either carcinoma or sarcoma cells in continuous culture causes not only a marked growth inhibition but also a dramatic alteration in cell morphology towards that of the normal differentiated cell. Apparently related to the morphology and growth inhibition are changes in the cell surface. These cell surface modifications induced by cAMP and apparently shared by normal cells require de novo mRNA synthesis which is associated with an increase in DNA-directed polymerase II activity. The facts that cell surface modifications induced by cAMP depend on mRNA transcription, are reversible and short-lived, and are closely related to the cell cycle of the normal cell, suggest that the universal property of cell division may be regulated by the relative transcriptional activity of one or more genes continuously producing mRNA, which govern properties of the cell surface.

Evidence moreover suggests that the properties of chalone, a cell-specific substance contained in a number of tissues and able to depress the mitotic activity of the corresponding cells in these tissues, may be related to the adenylate cyclase/cAMP system (Cooper and Smith, 1973). Both regulate cell kinetics by an inhibitory reaction; both are deficient in the tumour or transformed cell; both can restore controlled growth and contact inhibition to transformed cells; both can be influenced by the same classes of drug and naturally occurring molecules; and both chalone and adenylate cyclase are cell specific (Cooper and Smith, 1973).

Secondary Sexual characteristics. Singhal et al. (1971) claim that cAMP may be involved in triggering the known metabolic actions of androgens on secondary sexual tissue of the rat.

CONCLUSION

Research work is presently aimed toward hypotheses designed to provide a unitary molecular basis for the multiple effects of cAMP.

Various functions of adenyl cyclase have been discussed above. It has been pointed out that Ca++, rather than cAMP, may be the ultimate effector of certain regulatory sequences; Ca++ may be released from membrane ATP-Ca++ complexes by the action of adenyl cyclase, with formation of cAMP. The activation of various protein kinases by cAMP has also been referred to. Jost and Rickenburg (1971) propose that cAMP acts by affecting the interaction of the subunits of certain proteins, and that the multiple effects of cAMP may find their explanation on the basis of the function of the altered proteins; it also follows that cAMP may exert its effect at any metabolic level, provided that a protein (regulatory protein in the nucleus, enzyme, membranal protein, etc.) participates in the reaction.

The role of cAMP is primarily one of modulation. It appears certain that in many cases cAMP interacts with a number of proteins within the same cell; it may be summarised that proteins differ in their affinities for the cyclic nucleotide. Clearly such a hierarchy of affinities would provide a regulatory system of great subtlety. A hormone control (e.g. by glucocorticoids) of the synthesis of proteins that interact with cAMP would provide an additional dimension of both tissue specificity and flexibility.

Although the precise mode of action of cAMP at the molecular level is still within the realm of speculation, one major physiological function of the nucleotide appears to be the coordination of the mobilisation of potential reserves of carbon and energy when readily available sources, such as glucose, become limiting. This regulatory role of cAMP is exemplified by its stimulation of glycogenolysis, lipolysis, and the conversion of amino acids to their keto derivatives in the mammal and by its reversal of catabolite repression in bacteria.

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a few facts about the ebv

dr. t.j. bugeja. m.d.

INTRODUCTION: The EBV as it is now known is none else than the Epstein-Barr Virus. The name was derived from those of the two groups of workers who independently observed the virus under the electron microscope for the first time.

The story dates back to 1958 when Dr. Denis Burkitt described the chief characteristics of Burkitt's lymphoma as it is now known. Very significant was the observation that this was mostly confined to the lower, hotter areas of Africa where mosquitos were common so that a mosquito-borne virus was tentatively held as the causative agent. Subsequently the examination under the electron microscope of suspension cultures of biopsy material from these lymphomas revealed the herpes-type virus now known as the EBV. With the development of an indirect immunofluorescence test for the detection of antibody to this virus it was not only discovered that antibody was present in the sera of many African and American children but that high EBV antibody titres were seen in patients with nascpharyngeal carcinoma, Hodgkin's disease, sarcoid, S.L.E. and infectious mononucleosis. In the latter heterophile antibody can be detected temporarily usually in the first 10 days of the illness. On the other hand this EBV antibody was found to persist indefinitely.

Soon evidence was available that EBV infection is worldwide and is even found among Eskimos and Indian tribes. It appeared that as soon as maternal EBV antibody disappeared from the child's blood, infection with the virus is liable to occur. Whilst in the developing countries and amongst children in poor socio-economic levels infection occurs early in life from orphanages, day nurseries and big families it tends to appear later in more civilised parts of the world. In the child it is thought that EBV infection causes a mild atypical form of infectious mononucleosis (IM) which confers long lasting immunity to further infection. In the adult the picture is more typical of IM. These ideas were strengthened by the fact that a mononucleosis due to EBV occurs following transfusion of EBV antibody-free persons with EBV positive blood.

The EBV is known to be cell bound and not easily released from infected cells. This might explain the low contagiousness of infectious mononucleosis. It also implies that intimate and prolonged oral contact is required to transfer these infected cells to the new host. Though these ideas are consistent with epidemiologic evidence EBV isolation from the saliva or the throat has not as yet been accomplished. In the new host heterophile, antibodies may appear in titres of 1 in 40 or more and may transiently increase. As already mentioned EBV antibody is more permanent and a titre of 1 in 160 is suggestive of recent infection. It does not matter which is detectable first and neither has any relation to the clinical severity of the disease. In children not uncommonly one finds no heterophile antibodies in the presence of EBV antibodies; these are liable to show a milder form of infectious mononucleosis with less marked changes in the blood and hepatic function. The hospital stay in these cases would also be a short one. However, in all these cases where clinical and haematological pictures are those of infectious mononucleosis and heterophile antibodies are present, cytomegalic virus mononucleosis comes into the differential diagnosis. In fact this virus is held responsible for half these cases. These usually lack a sore throat and enlarged lymphnodes but have definite hepatosplenomegaly; fever may last anything between 2 and 3 weeks and the average age is higher than similar cases due to infectious mononucleosis. They are the "typhoidal variety" described years ago by Tidy.

Plenty of evidence derived using the election microscope and various antibody techniques is very suggestive of the EBV as the causal factor. There is still the possibility of its being a passenger virus multiplying in tumour-tissue. In addition malaria is thought to be an important co-factor in the production of lymphomas in Africa and New Guinea as the incidence is so much higher in holoendemic areas.

In nasopharyngeal cancer not only are antibodies detected in large titres but cultures cells derived from nasopharyngeal cancer also are known to contain the EBV. It is notwithstanding all this still possible that the EBV exists in the lymphoid elements in the tumour rather than the tumour cells themselves.

Antibodies to the EBV have been looked for in patients with Hodgkin's disease and figures where compared to a control group. The results were the following:

GROUPS	EBVA present	Titres = $\frac{1}{160}$
Hodgkin's	95%	47%
Control	89%	17%

An inverse relationship was also observed between the frequency of lymphocytes in the malignant lesions and the level of anti-EBV antibodies. Similar observations have been made in patients with sarcoidosis — especially the chronic and inactive forms of the disease and systemic lupus erythematosus. In the latter it is conjectured that the viruses may participate in the immune complexes that deposit in the kidney and skin.

DISCUSSION: Three questions arise out of necessity from what has gone before: Can the EBV be isolated from the throat or saliva and can infection be forstalled by the production and use

of an EBV vaccine. It is simply a matter of time before these things are done. The third is a more fundamental and perhaps more significant point and this is the relationship of the EBV to cancer, if any!

The experimental observation that tissue culture cells which underwent virus-induced malignant transformation can lose all signs of the abortive infection without changing their malignant potential points to the possibility that in humans too chronic viral infections might lead to the development of neoplastic cells which years later develop into infiltrative neoplasms. Thus if all trace of infection has ebbed from the neoplastic cells, the virus-induced tumours would be indistinguishable from neoplasms occurring "spontaneously" or as a result of carcinogens. With these ideas in mind it has been suggested that whilst infectious mononucleosis is a primary infection with EBV in an immunologically competent host, the chronic disease syndromes may be delayed host responses to EBV infection in immunologically incompetent hosts. The facts may be integrated with the theories in this discussion, as shown in Figure I (Bugeja Jan. 1972).

CONCLUSION: The existence of the EBV has been firmly established. Its relationship to infectious mononucleosis is real but that to Hodgkin's and Burkitt's lymphomas, systemic lupus, sarcoid and nasopharyngeal cancer is not definite yet. Further research will establish whether nasopharyngeal isolation of the EBV and a vaccine against infection by it are practical possibilities or not.

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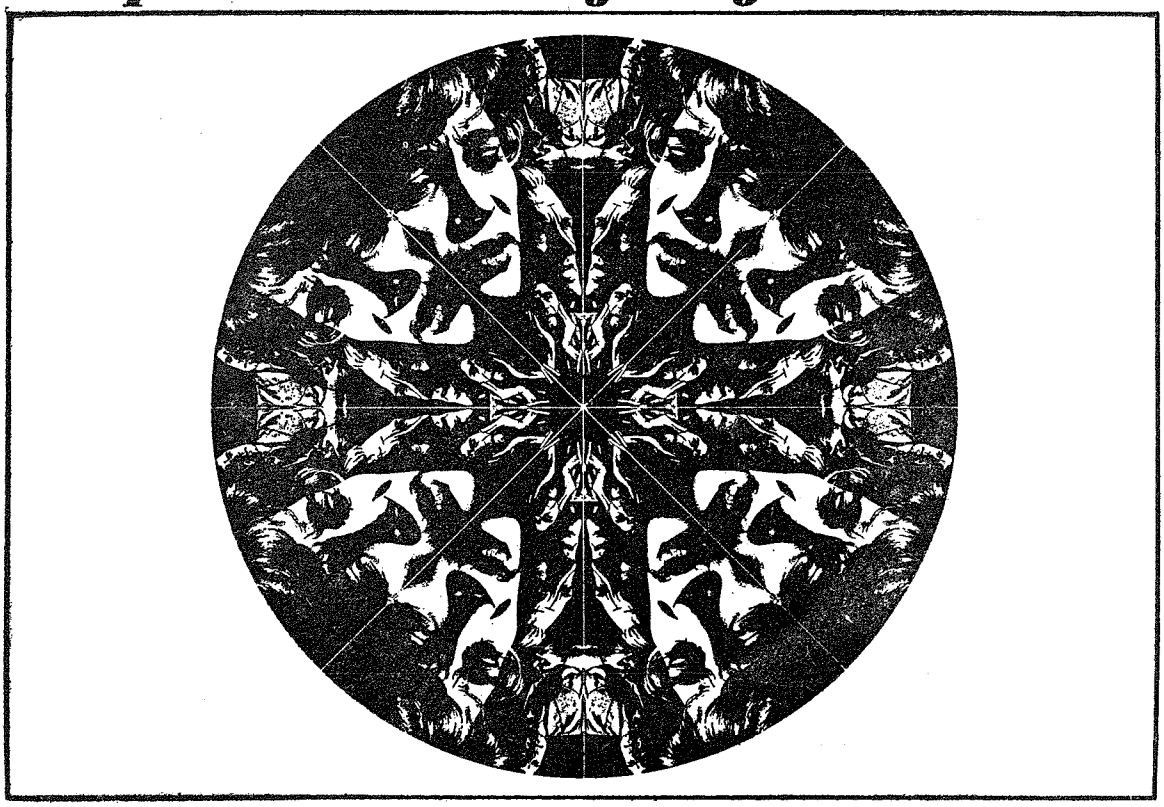

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meningiomas

dr. john gauci m.d. **dr. joe saliba m.d.** **dr. dorothy grech m.d.**

DEFINITION AND CYTOGENESIS

Harvey Cushing showed that these tumours are found at the sites of arachnoid granulations and on histological examination, there is so much resemblance between the structure of the tumour and that of normal granulation that the arachnoid cells are regarded as the origin of the majority of this group of neoplasms. They tend to be related to major venous sinuses and commonly arise parasagitally or on the base of the skull. Another common site is the sphenoid ridge. Rarely a meningioma may arise from the tela choroidea and appear as an intraventricular tumour.

INCIDENCE

Meningiomas account for about 15% of all primary intracranial tumours and for 25% of intraspinal tumours. Most cases occur between the ages of 20 and 60 years with a peak incidence at 45 years. In the cranial cavity, the female to male ratio is 2:1; in the spine it is 4:1.

PATHOLOGY

The meningioma is usually a well defined, smoothly lobulated firm mass attached to the dura by a broad base and indenting the brain. Less frequently it forms a thin, flat, dural plaque which may have a smooth or shaggy inner surface. Very rarely it forms an extensive sheet between the dura and the brain and cord — diffuse meningiomatosis. Most tumours are sharply delimited and non-invasive, but some show slow marginal invasion of the surrounding tissues — the dura, skull or brain. Those which invade the bone excite the formation of an externally projecting, dense, bony boss on the skull.

The cell type of these tumours is an oval cell with a large nucleus. These cells show a tendency to whorl formation. The centre of the whorl is liable to degeneration and calcification (psammoma bodies). The ratio between cells and stroma varies. Occasionally, the meningioma presents variability in its cellular picture and tissue structure; angioblastic meningiomas show a rich network of vascular spaces. In other tumours, the cells contain lipoidal substances and appear xanthomatous.

GROWTH AND BEHAVIOUR

Meningiomas grow slowly over a period of years — even 20-25; a fair average is five years. Because of their slow growth and because they cause gradual compression, there are fewer localizing symptoms than with other tumours.

As a rule, even when dural attachments are not removable, as along the longitudinal sinus, many of this group of tumours do not recur. However, some are malignant in that they grow more rapidly, invade the dura, bone or brain and occasionally produce metatases. These may be termed meningosarcomas.

SIGNS AND SYMPTOMS

A meningioma is on the whole much more likely to be silent than other types of tumours in the cerebral hemisphere. If not silent, it usually causes only focal seizures. Headaches, visual impairment and focal seizures are the most common complaints in that order. However, with a meningioma of the convex surface of either cerebral hemisphere, seizures are usually the first symptom.

Other signs and symptoms are mental changes such as loss of memory, apathy and indifference and carelessness in habits.

TREATMENT

Complete enucleation of the tumour is the only treatment. When possible, the dural attachment should be excised, but rather than run an undue risk, it is better to leave this undone. The removal may be difficult when the tumour is richly vascularised.

CLINICAL CASE

Mrs. E. Thomas **Aged 76 yrs.**
Admitted 23.6.73

The patient presented with a 6 month history of loss of grip in left hand and unsteadiness on legs.

The left hand felt dead and heavy and she occasionally had paraesthesiae in the whole of her hand. At the same time, her left foot also became weak and she found herself dragging her foot on walking. Prior to December 1972, she occasionally fell onto her left side for no apparent reason. There was never any loss of consciousness.

For the past two years, she has had occasional severe stabbing headaches, starting frontally and radiating to the occiput. They lasted 10 to 15 minutes, were not exacerbated by anything and went away spontaneously.

She has no difficulty with speech or vision and no right sided symptoms. There is no history of dizziness. She has never had any previous similar trouble.

Cardiovascular System:— No positive signs.
Respiratory System:— No positive signs.
Gastrointestinal Tract:— No positive signs. She has no vomiting. Appetite is good and her weight steady.
Genitourinary System:— No positive signs.

Past Medical History

Patient had a colostomy followed by reanastomosis for diverticulitis (1966).
No other serious illnesses.

Social History

The patient lives with her husband. She does not smoke and only drinks occasionally.

Family History

Father died of carcinoma bladder; Mother has heart trouble. Her four sisters and two brothers are all well.

On Examination the patient looks well. She is cheerful and co-operative. She is not clinically anaemic, cyanosed or jaundiced. There is no clubbing or lymphadenopathy. She is not in pain.

Thyroid and Breasts:— No abnormality detected.

Cardiovascular System:— Pulse — 80 per minute; regular.

Blood pressure — 150/80.

Jugular Venous Pressure — 0.

No oedema; apex beat not displaced; heart sounds normal.

Respiratory System:— Trachea central; lung expansion good; percussion note resonant; breath sounds vesicular. No adventitious sounds.

Gastrointestinal Tract:— Abdomen obese with scars and striae. No masses or tenderness.

Central Nervous System:— The cranial nerves were intact except for minimal weakness of the left orbicularis oculi and left cheek.

The fundi are normal — no papilloedema.

Motor System — There is no obvious wasting of limb muscles; no fasciculation or fibrillation. Tone may be slightly increased on the left side (difficult to demonstrate because the patient cannot relax her limbs). There is no ankle or patellar clonus. Power is markedly reduced on left side. The patient can raise her arm and flex her fingers but cannot grip. She cannot dorsiflex or plantarflex her left ankle. The patient cannot walk unaided and drags her left leg.

Reflexes	**R**	**L**
Biceps	+	+
Triceps	+	+ +
Supinators	+	+
Knee	+	+
Ankle	—	—

Sensory System — There is diminished sensation of light touch, pin-prick, hot and cold and vibration sense in left upper limb and left lower limb below knee. Proprioception is markedly reduced on the left side. There is sensory wandering of the left arm. Astereognosis in left hand is unreliable due to the diminished sensation. There are no signs of cerebellar dysfunction.

Gait — Patient can not walk on her own.

The Provisional diagnoses at this stage were

? cerebrovascular episode

? cerebral neoplasm

? sub-acute combined degeneration of cord

Investigations

The following investigations were done:

Full blood count

E.S.R.

Blood urea and electrolytes

B_{12} and folate levels

Wassermann reaction and Kahn Tests

Chest X-Ray

Skull X-Ray

On 3.7.73 a **lumbar puncture** was performed — Report: Easy entry; clear fluid, colourless; pressure — 160 mm. Laboratory results were normal.

On 7.7.73 an **E.E.G.** was done — Report: The record showed a 10 c/s alpha rhythm arising in the post central areas. Irregular slow waves of theta and delta frequencies occurred posteriorly in the right hemisphere leads with phase-reversals in the parietal region. This finding is abnormal and indicates a localized right parietal lesion.

A **brain scan** (showing technetium uptake on a gamma camera) was done. — Report: There is a well defined area of increased uptake based on the falx in the right parietal region. This is highly suggestive of a meningioma on the scan.

In view of the above report the differential diagnosis was reconsidered and a neurosurgeon's opinion was asked for.

Surgeon's Comment:

The dense uptake in the post-parietal region with the intact intellect and absence of raised pressure confirms the diagnosis of a meningioma which may be partly adherent to the falx; her body image projection of the right leg is not perfect so there may be a slight extension across the mid-line. I would avoid angiography, for at her age it has a definite morbidity. I will arrange craniotomy.

Mrs. Thomas was operated upon on 12.7.73.

OPERATION

Surgeon's Report:

On examination the patient was intellectually intact with evidence of a right parietal/post-parietal lesion. There was sensory wandering of the left hand and possibly position loss of the hand up to and including the wrist. There was some involvement of the left leg. There was a left facial assymmetry. Her body image projection of her right leg was not perfect either. The scan showed a large circumscribed lesion in the mid-line consistant with a falx meningioma.

Operation:

Craniotomy — removal of soft falx meningioma.

the patient was supine with the head turned over to the left.

A right parietal flap was cut between five burr holes and taken laterally. Intra-cranial tension was not increased; on opening the dura, the brain looked flattened in the post-parietal region and on needling through this area 2 cm. from the mid-line some soft, almost pink tumour tissue was aspirated. At this stage I was a little concerned in case I had made a mis-diagnosis but indeed, under the post-parietal region at $\frac{1}{2}$ cm. depth was a completely smooth plum coloured tumour with a well demarcated capsule which could be sucked out quite easily. It was clearly a meningioma the size of a large golf ball arising from the falx and lower border of the sagittal sinus. One or two large branches of the anterior cerebral artery were entering the under surface of the tumour but it was removed completely. Its

attachment to the falx was exposed over an area of 3 cm. by 2 cm.; there was no tumour on the other side. The dura was closed and the bone flat replaced.

PATHOLOGY

A. During operation — a biopsy was taken for frozen section — Report: Fragments of meningioma of fibrous type. It appears to be benign.
B. Specimens sent after operation — Report:
Specimen 1 — Tumour. Sections show a cellular fibroblastic meningioma.
Mitoses are not evident.
Specimen 2 — Dura. Sections show normal dura. No tumour is seen.

Post-operative Course

The patient's post-operative recovery was uneventful. There was no change in the patient's neurological condition but the stabbing pain in head disappeared. On recovering consciousness the patient complained of right sided head and neck pain. This lasted for about ten days. Slight constipation and anorexia were the only other post-operative complaints and these subsided regularly.

She was discharged on 30.7.73.

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answers to clinical problem

1. Salt Craving.
2. Physiological in certain races. Not in Euro-Epeans.
Peutz Jegher's Syndrome.
Hemochromatosis.
Addison's Disease.
Metallic Poisoning especially occupational i.e. lead, bismuth. arsenic.
Fordyce's Disease.
3. In cases of high sustained venous pressure, as found in constrictive pericarditis, congestive splenomegaly may be sufficiently pronounced to make the spleen palpable. In the absence of evidence of bacterial endocarditis or of tricuspid valve disease, splenomegly in a patient with congestive heart failure, should arouse suspicion of constrictive pericarditis.
4. Addison's Disease.
Malabsorption Syndrome.
Cirrhosis of the liver.
Infiltrative Diseases — Amyloidosis and Haemochromatosis.
Constrictive pericarditis
Tricuspid Stenosis.
Renal Disease eg: Salt loosing Nephritis
Cardiomyopathies.
5. The fact that the patient had a contact with T.B.
6. The probable diagnosis is a chronic adrenel insufficiency combined with constrictive pericarditis.
7. Scars that have been present before the onset of the adrenal failure remain unpigmented (appendicectomy scar) in contrast to those that are acquired after the onset of the adrenal failure (cholecystectomy scar).
8. An Addisonian is prone to hypoglycaemic symptoms due to increased insulin sensitivity (tiredness, lethargy, feeling of faintness) especially following extended fasting or following carbohydrate ingestion. Reactive hypoglycaemia after meals may occur, cortisol being one of the physiological antagonists of insulin. These patients are also especially hypoglycaemic after a night's rest and have more than usual difficulty in getting up in the morning.
9. Lethargy, tiredness, exertional dyspnoes and syncope are signs of contrictive pericarditis. However the lethargy and tiredness are more pronounced in this patient due to the superimposition of Addison's Disease. One C.V.S. effect of Addison's is hypotension. So although hypotension can probably give rise to a lessening of the signs of contrictive pericarditis e.g. venous distension, hepatomegaly, ascites, etc., the hypotension itself will predispose to and make the patient more susceptible to syncopal attacks.
10. A chest X-Ray may show calcification in the pericardium indicative of constructive pericarditis whilt a plain abdominal X-Ray may show calcification in the adrenal glands. Both these findings indicate a granulomatous process, in this case due to T.B.

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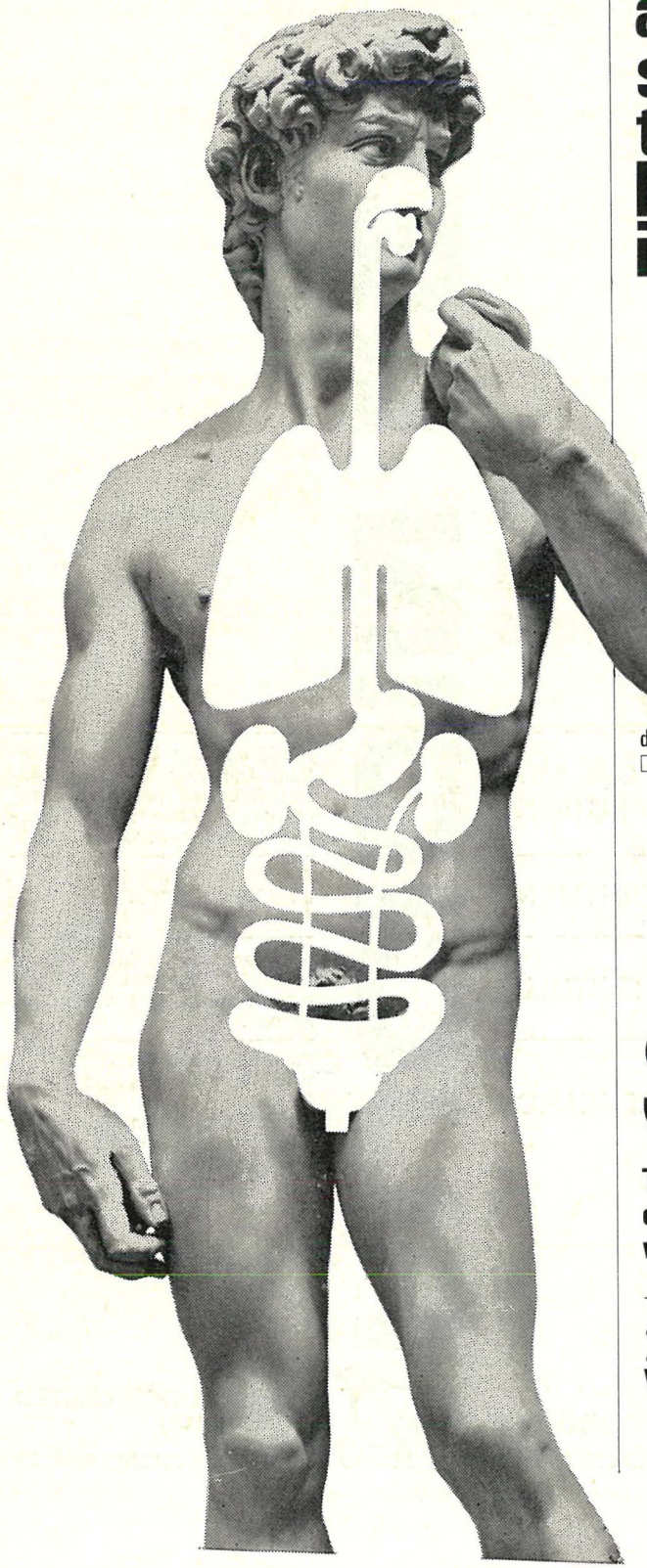

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