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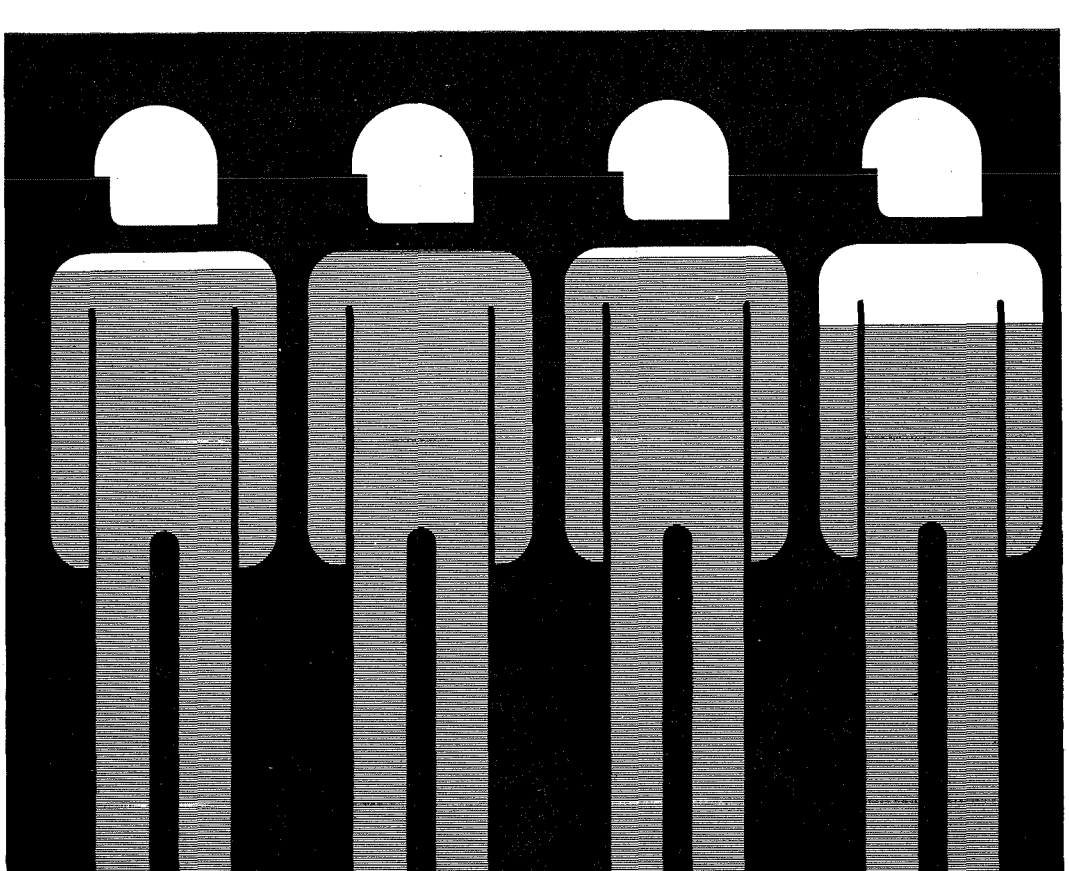
NOBRIUM: TOWARDS TRUE PRECISION IN THE CONTROL OF EXCESSIVE ANXIETY



1 Anxiety, tension and agitation* 81.0%

2 Phobias* 83.1%

3 Cardiac symptoms with anxiety* 81.2%

4 Respiratory symptoms with anxiety* 73.5%

Nobrium acts mainly on the amygdala and has a smaller, complementary action on the hypothalamus, curbing both the emotional and physical manifestations of anxiety

In over 50 clinical trials, involving more than 5,000 patients, Nobrium relieved more than 80% of the individual symptoms detailed in the trial reports

It has been shown that Nobrium exerts its major effect on the amygdala and has a smaller, complementary, action on the hypothalamus.[19] This suggests that Nobrium should control both the emotional and physical symptoms of anxiety without interfering with other functions

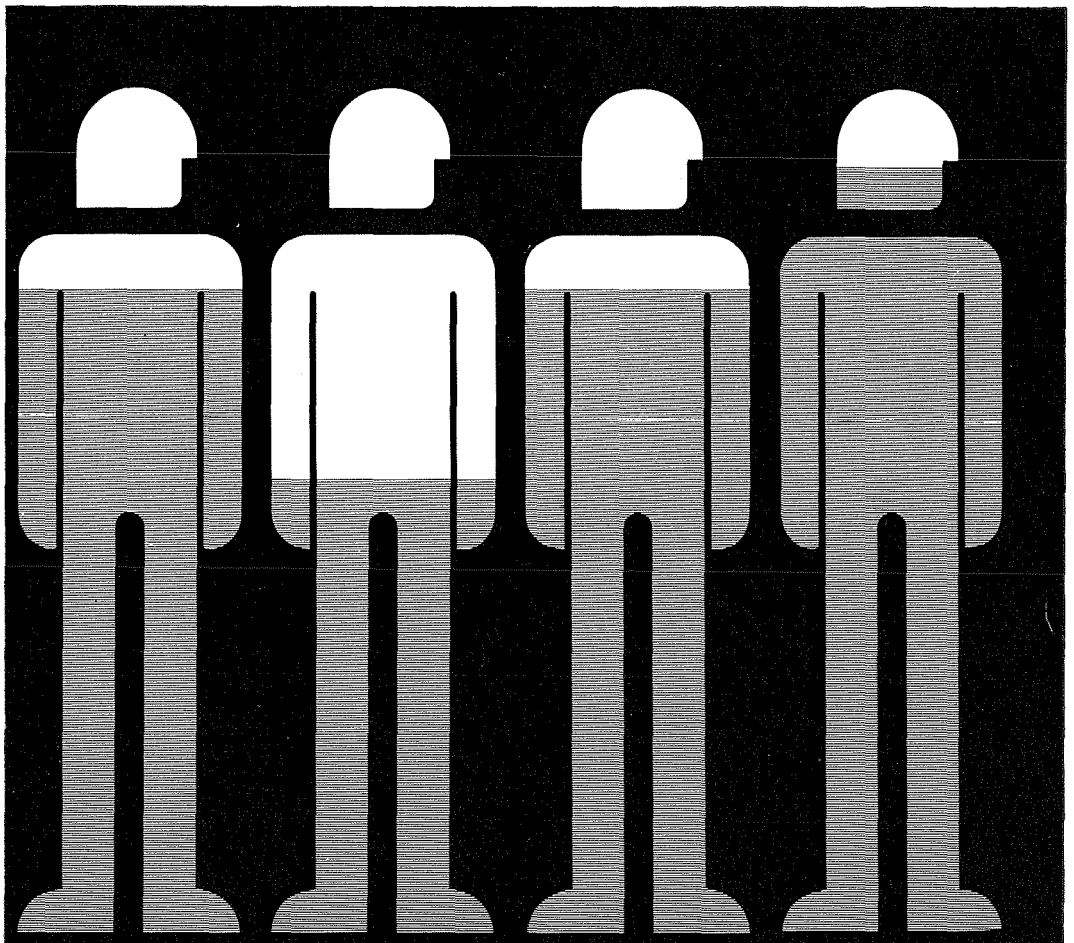
Nobrium: Good to excellent response in over 80% of anxiety symptoms and associated disorders

In over 50 published reports of clinical trials with Nobrium, involving more than 5,000 patients, details of 3,443 individual symptoms or associated disorders were reported. A good to excellent response was achieved in 2,781 (80.8%) of those symptoms. In no group, other than headache, did the good to excellent response drop below 73%

Nobrium: Thirteen double-blind trials

Thirteen of the published clinical trials were double-blind studies comparing Nobrium with either placebo, phenothiazine, barbiturate or chlordiazepoxide[20-32]

* Good to excellent symptom responses



5 Gastro-intestinal symptoms with anxiety * 75.9%

6 Headache of emotional origin * 53.6%

7 Alcoholism * 75.9%

8 Depression associated with anxiety * 88.75%

In every case Nobrium was clearly better than the placebo and this was frequently confirmed by statistical analysis. In a trial against a phenothiazine[20] Nobrium produces 64% good to very good responses, double that produced by the other treatment. Against phenobarbitone[21] Nobrium produced a 76% good to excellent response initially, compared with an initial response of 29% to phenobarbitone. Compared with chlordiazepoxide, both were effective but Nobrium seemed to have a better effect in somatic anxiety, as opposed to the 'free floating' variety

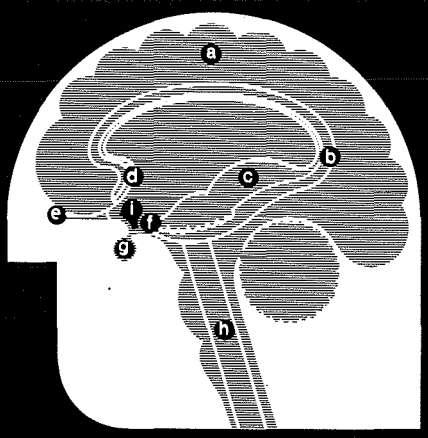
Nobrium and motor performance

In one double-blind study Nobrium was compared with a placebo with regard to its interaction with alcohol. The conclusion was that Nobrium '... in general, did not affect human mental or motor performance either alone or in combination with alcohol'[24] (Despite the findings of this trial patients should be instructed to avoid alcohol while under treatment with Nobrium). A study in which 75 trolley bus drivers were treated while they went on working as usual tends to confirm this. No significant difference could be found in alertness between subjects treated with Nobrium and those given a placebo[25]

Nobrium and anxiety in the body

Particular attention was paid in a number of reports to patients suffering from specific physical symptoms and disorders in association with anxiety. Details of 563 such cases could be extracted from the literature. Of the group 406 (72.1%) showed a good to excellent response to treatment

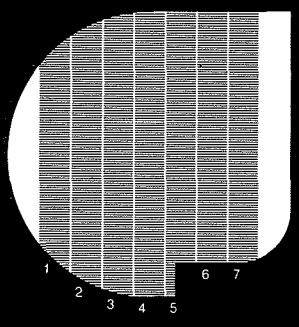
NOBRIUM

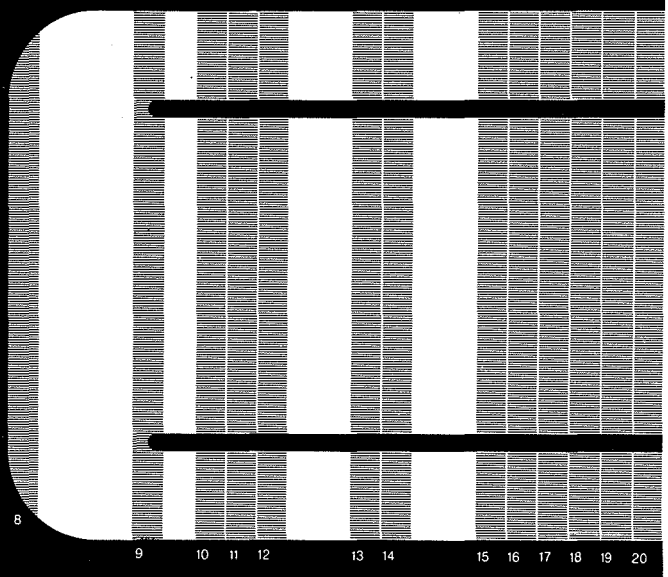


a Cortex
b Cingulate gyrus
c Hippocampus and induseum griseum
d Septum
e Olfactory bulb
f Amygdala
g Pituitary gland
h Brain stem reticular formation
i Hypothalamus

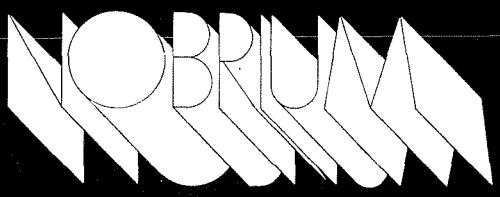
1 Migraine
2 Sweating
3 Dilated pupils
4 Psychosomatic skin disorders
5 Pallor
6 Dry mouth
7 Vomiting
8 Hyperthyroidism
9 Asthma
10 Heightened muscle tone
11 Hypertension
12 Tachycardia
13 Peptic ulceration/nervous dyspepsia
14 Nausea
15 Obesity or Anorexia nervosa
16 Ulcerative colitis
17 Menstrual difficulties
18 Diarrhoea
19 Spontaneous orgasms
20 Neurodermatitis
21 Angioneurotic oedema
22 Sweating
23 Tremor
24 Heightened muscle tone
25 Heightened muscle tone
26 Angioneurotic oedema

Structures of the brain





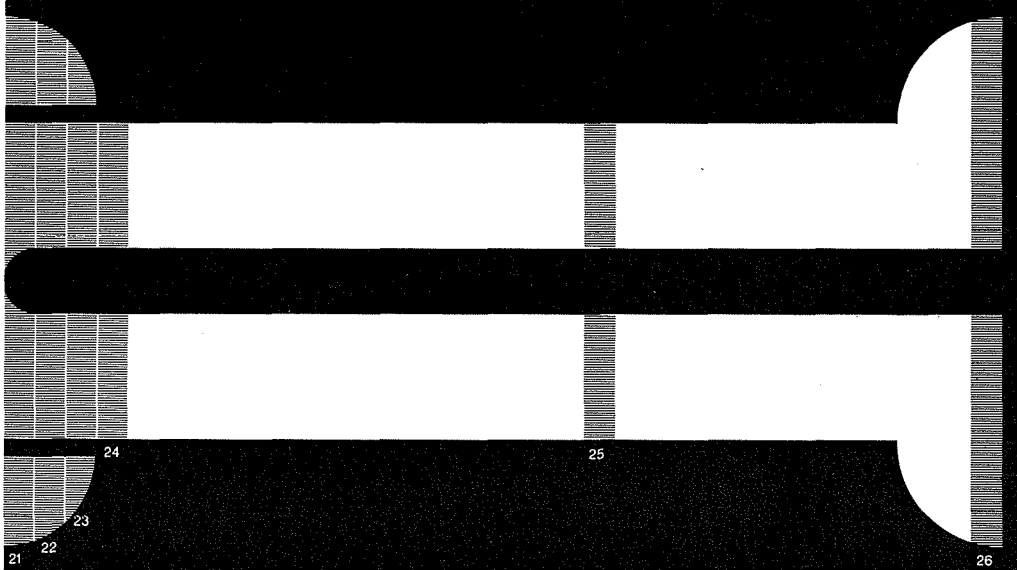
Somatic and psychosomatic disorders of the body



The amygdala in the limbic system plays the crucial part in the generation and transmission of anxiety

When sensory stimuli reverberate through the cortex it evaluates those stimuli and decides, in a flat, uninflected way, the response to make. In 1937, it was suggested[1] that the limbic system was the anatomical source of the emotions which intensified the individual's response

Later research work[2] suggested the amygdala as the source of aggression and anxiety. This was confirmed by experiments[2,3] in which removal of the amygdala produced a tranquillizing or taming effect on previously wild animals and others where electrical stimulation produced a whole spectrum of emotions from anxiety, through panic to extreme rage [4]



In excessive anxiety the hypothalamus constantly prepares the body for a violent physical challenge which never materializes, producing a long list of anxiety symptoms and psychosomatic disorders

Close to the amygdala - and with many connections to it - is the hypothalamus, the structure which acts, through the autonomic nervous system,[5] the neuro-endocrine structure[6] and neuro-secretory mechanisms[7] to produce an appropriate level of physical arousal

This physical arousal can be produced in circumstances where it can serve no useful purpose, during academic examinations, for example[8,9] and even when watching anxiety-provoking films.[10] If such changes are too frequent or too prolonged they may permanently damage the heart or circulation[11,12]

The physical changes produced by anxiety are many: the electrical resistance of the skin changes,[13] so does muscle tone,[14] secretion of saliva[15] respiration[16] and respiratory efficiency.[17] A specific study on soldiers subjected to experimental stress recounted changes in the blood picture and concluded that such changes could '. . . trigger or otherwise promote psychosomatic and psychiatric disease'[18]

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Nobrium is a trade mark for pharmaceutical preparations containing medazepam

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JANUARY '72

chestpiece

Journal of the
Malta Medical Students' Association

Editor: Albert Fenech
Assistant Editor: Andrew Castillo
Cover Design: Thomas Brundin

Editorial

Maltese Medics are renowned for their profound knowledge of Medicine — a fact attributed mostly to the excellent Student/Teacher ratio, and to the high standard of our Teachers. However, one undeniable fact is that most of us students hardly ever step aside from the path of Stethoscopes and Sphygmos in order to indulge in any other cultural interest. The Student who can hum the second movement of Beethoven's Choral Symphony No. 9 in D Minor or tell you the name of the calf's fourth stomach(!) happens to be a rarity in our circle. This disinterest (Apathy seems too common a word nowadays) amplifies the difficulties of publishing a journal such as the CHESTPIECE. The whole point of a Student Journal is to bring to the surface any matters concerning the students' academic life. We are lucky inasmuch as we have our OWN journal — why don't we make the most of it? Letters to the Editor haven't been received for AGES. Attempts to bribe the students in order to get some of their articles have failed dismally. With the increasing difficulty in finding adverts, on which the CHESTPIECE entirely depends, good issues are imperative for the life of the Journal. The only person who commented on the fact that the last issue came out a year ago was a doctor — NOT a Student. It is at times like these that one wonders whether all the trouble is worth the while. Surely we can spare a small fraction of our free time to scribble a few crumbs of wisdom.

Talking of free time, a recent change in Universities abroad has been a drastic cut down of superfluous 'Chalk and Talk' which we call lectures. All students admit that a good percentage of the lectures are a waste of time. The custom here is to write down very diligently every syllable uttered by the Lecturer — even the occasional(!) unintentional mistake — which in itself is contrary to the aims of a lecture.

Our Examiners have recently turned 'progressive' and the principles of 'Continuous Assessment' (the famous twenty letter word) are slowly creeping into our system. The whole point of this system, which is to ensure better Doctors, is entirely missed since for all the work this system entails, its bearing on the Finals is ridiculously minimal.

We congratulate the M.M.S.A. on the successful outcome of the International Federation of Medical Student Associations' Winter Meeting held here between December 28'th. and January 6'th. All the foreign delegates were impressed by the organisation and smooth running of all the activities, and enjoyed their stay on this Island.

We would be very grateful for any comments or criticisms sent in by any of our readers. Such letters should be addressed to:

The Editor
Chestpiece
R.U.M. Medical School
Gwardamangia.

As you may have noticed, our cover design reads "Autumn '71" as it was primarily planned for the October issue. Since that issue didn't materialise, and since we liked the cover so much (three cheers for Tom) we decided to use it for this issue. We hope you don't object to it.

A word of thanks go to our printers at St. Joseph's Home, and to all the advertisers who use our journal.

Osteoclastoma of the Femur

Case report by Charles A. Gauci M.D.

Osteoclastoma or giant cell tumour of bone is a relatively infrequent neoplasm. It is generally regarded as being benign, in the sense that as a rule it does not metastasize; however, there is no doubt that a malignant variant which metastasizes does exist. It is claimed that as many as 15-20% of all osteoclastomas are malignant (1). The tumour usually arises at the end of a long bone, invariably the epiphyses with secondary involvement of the methaphyseal area. It is typically an osteolytic lesion that produces some expansion of the bone end.

The most common sites of origin are depicted in Fig. 1. which is based upon a survey of 97 cases carried out by Dahlin (2). The age incidence is usually between 20-55 years, with a predominance of cases in the third decade. Young children and the elderly are seldom affected. Males are affected as frequently as females.

PATHOLOGY

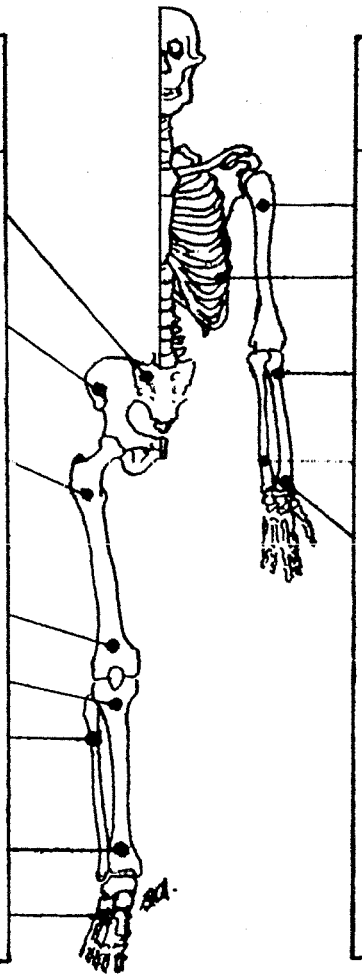
Macroscopic; Osteoclastomas are usually eccentrically located in the epiphyseo-metaphyseal area and have sharp borders delineating them from the normal bone. They are composed of a vascular greyish-red tissue with some zones of necrosis, yellowish streaks and areas of trabeculation extending across cystic cavities; commonly the cortex is thinned and it is not rare to find evidence of tumour tissue extending through cortex into the adjacent soft tissue, as occured in the case reported below. There may be secondary joint involvement.

Microscopic; The tumour tissue consists of two characteristic components viz. (a) spindle shaped cells and (b) multinucleated giant cells (morphologically similar to osteoclasts) the nuclei of which are centrally situated and which have numerous radiating processes that appear to anastomose with those of the spindle cells. It is generally agreed that these giant cells are derived from the spindle cells by fusion of the latter.

The histological appearance of the spindle cells is generally accepted as giving the best indication of malignancy (3). Important features here include: hypercellularity, presence of large hyperchromatic nuclei and abundant mitotic figures; invasion of blood vessels by tumour cells is an ominous sign. However, Jaffe stresses that many a metastasizing tumour has a benign appearance and yet may cause the death of the patient (4). Metastasis occurs usually in the lungs via the bloodstream.

Fig. 1

NUMBER OF CASES	SITE
9	SACRUM
5	ILEUM
1	PROXIMAL END OF FEMUR
32	DISTAL END OF FEMUR
22	PROXIMAL END OF TIBIA
6	PROXIMAL END OF FIBULA
3	DISTAL END OF TIBIA
1	SMALL BONES OF FOOT



SITE	NUMBER OF CASES
PROXIMAL END OF HUMERUS	2
RIBS	1
PROXIMAL END OF RADIUS	1
DISTAL END OF ULNA	4
DISTAL END OF RADIUS	10

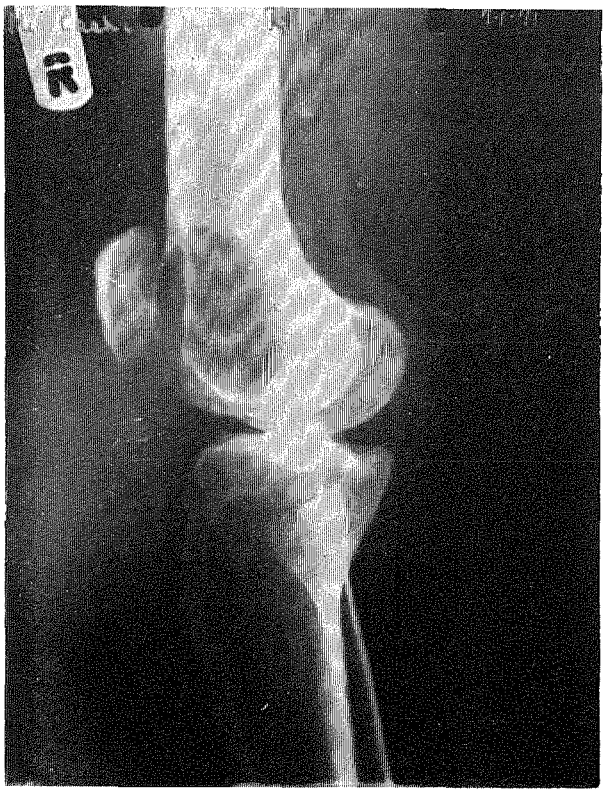


Fig. 2

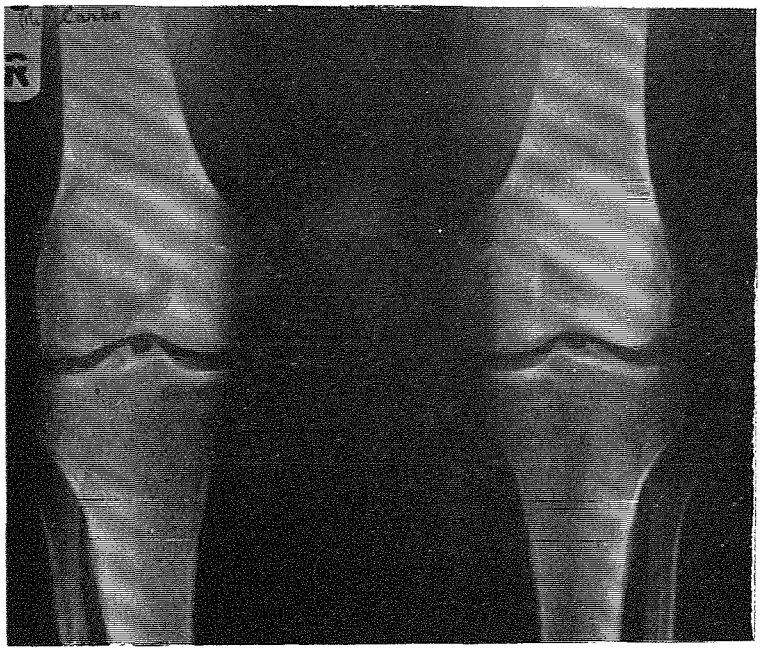


Fig. 3

Fig. 2 and 3: radiographs of right knee showing well defined cystic space in lower end of right Femur.

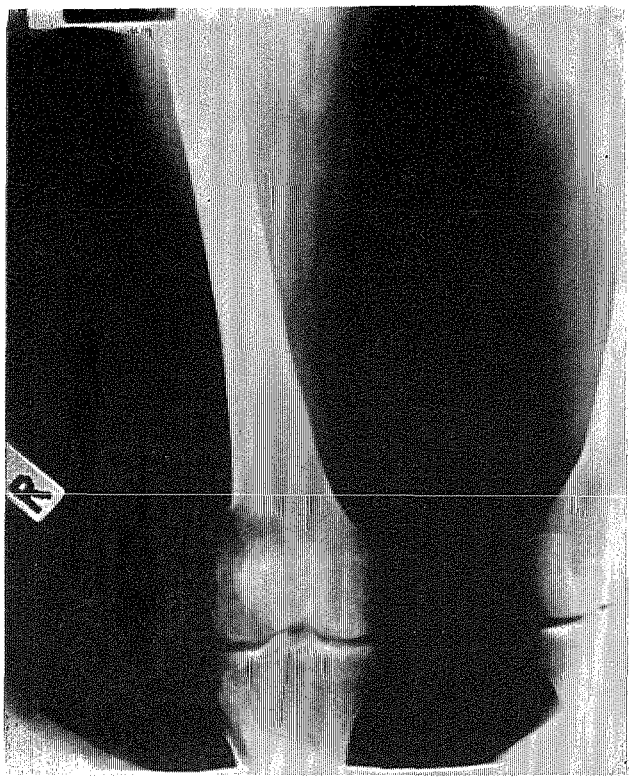


Fig. 4 (2/4/71)

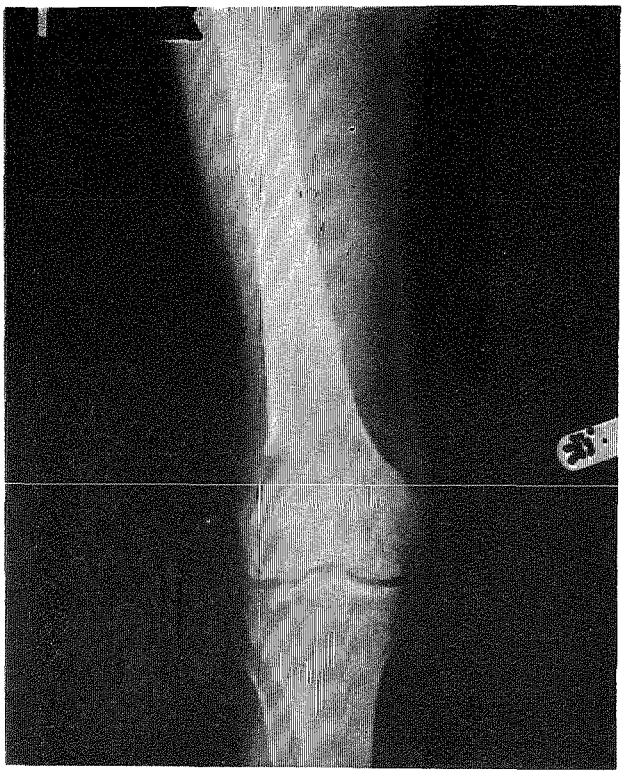


Fig. 5 (13/7/71)

Figs. 4, 5 and 6: Post operative check radiographs showing progressive filling up of space left by Surgeon in lower end of right Femur.

CLINICAL FEATURES

The patient usually presents because of bone pain and loss of function of the adjacent joint. Often we can obtain a history of injury. There may be visible swelling of the involved bone, usually of an asymmetrical nature and "Egg shell crackling" may be demonstrated in some cases. An occasional mode of presentation is pathological fracture.

The radiographic appearances are as would be expected from an osteolytic lesion. The bone end is usually enlarged and occupied by a cyst-like space; close inspection shows local bone destruction with no new bone formation and the bony cortex is thinned out. Typical as these radiographic findings may be, the diagnosis must be ultimately made by biopsy.

CASE REPORT

C.C. a 59 year old male (mechanic by trade) was admitted to M.O.D. on 25/1/71.

On admission patient stated that the previous July he had hit his right knee against a car. The event was followed by some pain and swelling in the joint which subsided within a few days. About three months later he began to experience pain in his right knee. This pain was of a deep boring nature and it started insidiously and progressed steadily until the patient was crippled by it and was unable to attend work. This pain was not relieved by anything but was exacerbated by walking. Accompanying this pain there was also a progressively increasing swelling of the joint and markedly impaired movements. Patient said that he did not lose welght.

He was given poultices by his G.P. all to no avail. Finally he was submitted to a radiological examination which showed the presence of a well defined cyst in the lower end of the right femur (Figs. 2, 3.). He was then referred to the Consultant Orthopaedic Surgeon who advised hospitalisation.

There were no other symptoms; patient was a heavy smoker and drinker. On examination the patient's general condition was satisfactory and the relevant features were marked pain and tenderness especially on the lateral aspect of the right knee joint. Flexion of the right knee joint was full but extension was limited and painful. The right thigh and calf were wasted and weak.

On 28/1/71 under general anaesthesia and utilising a tourniquet, the surgeon opened the lower end of the right femur and found a large cavity full of tumour tissue which he scraped out, including in the procedure healthy tissue all round the cyst wall. The curettings were submitted for histological examination.

Histology showed Osteoclastoma with tumour cells within a venule. The multinucleated tumour cells are compactly arranged; in areas were there is stroma this is densely cellular.

Diagnosis:— osteoclastoma femur, venous emboli. Following pathological confirmation of the diagnosis the patient was submitted to a course of radiotherapy. The most important feature in the pathologist's report was the presence of venous emboli—a presumptive indication of malignancy. With this thought in mind, the patient was submitted to a chest X-ray on 26/2/71; this did not show any abnormality.

The patient responded favourably to radiotherapy; he was fitted with a caliper pending consolidation of the lower end of the femur, and discharged from M.O.D. on 16/4/71.

Follow up was of course mandatory, and the patient was seen frequently at the out-patient department where a close watch was kept for any possible secondaries especially in the lungs. The patient complained of pain and stiffness in the right knee joint initially, but the pain gradually diminished although a certain degree of stiffness persisted.

Check radiographs of the operated area were taken on 2/4/71, 13/7/71 and 5/10/71 and showed that there was progressive calcification and consolidation of the bony trabeculae at the site of operation. (Figs. 4,5,6.).

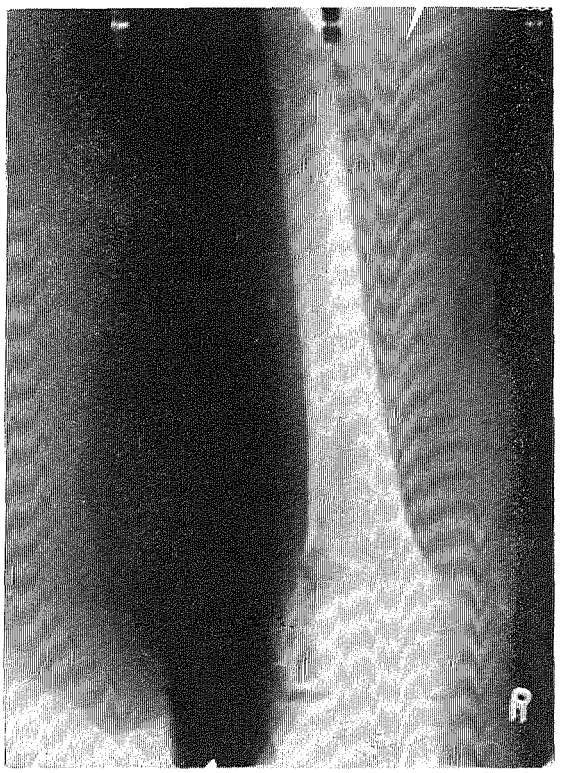


Fig. 6 (5/10/71)

ACKNOWLEDGMENTS

I am grateful to Dr. A. Bartolo, Consultant Orthopaedic Surgeon at St. Luke's Hospital, for permission to publish this case.

I thank Mr. J .Scerri, medical photographer at the R.U.M. Medical School, for reproducing the radiographs of the case.

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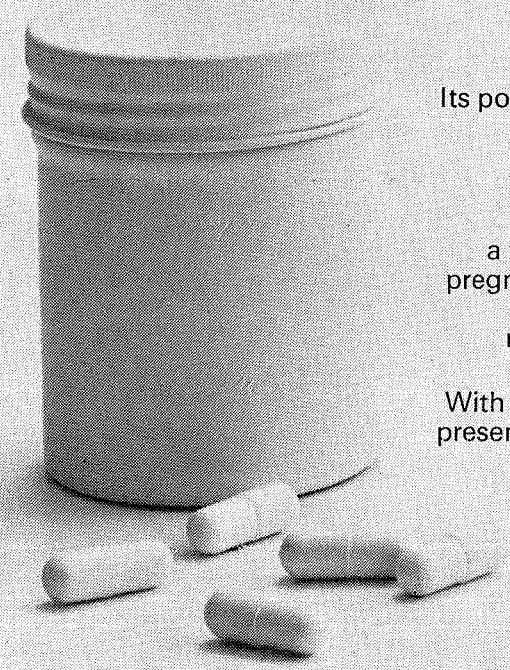

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A Study of Tonsillitis in Childhood

A.J. Psaila M.D., D.C.H. (Lond.), M.R.C.P. (U.K.) M.R.C.P. (Edin.)

Acute tonsillitis is one of the commonest infections of childhood. The infection itself responds readily to Penicillin Therapy as it is often caused by a Penicillin sensitive Streptococcus; but very often the infection is either missed or not treated properly and serious complications, namely acute glomerulonephritis and acute rheumatic fever, can occur.

It is difficult to miss the diagnosis in a child over 6 who presents with sore throat, difficulty in swallowing and pyrexia, but in younger children the infection can present in other ways and unless the throat is well examined the diagnosis may be missed.

In young infants acute tonsillitis can present with hyperpyrexia and febrile convulsions. It can present with vomiting and diarrhoea and also with anorexia and coughing. In older children the presentation might be otalgia, anorexia or pyrexia without any symptoms referred to the throat. (See Tables 1 & 2).

Table 1 shows the mode of presentation of acute tonsillitis in a personal series of 100 children aged between 6-12 seen from January 1970 to June 1971.

Sore Throat	72
Pyrexia	16
Otalgia	4
Cough	6
Anorexia	2

Table 2 shows mode of presentation in another series of 100 children aged between 4 months and 6 years in the same period.

Pyrexia	42
Fits	5
Sore throat	20
Vomiting and diarrhoea	10
Anorexia	3
Cough	20

In children who are prone to asthmatic bronchitis, shortness of breath, cough and wheezing might be the immediate sequel to acute tonsillitis and very often the presenting sympton.

In all these circumstances, unless examination of the throat is carried out, the tonsillar infection can be missed and treatment is directed to symptons such as ear drops for otalgia, salicylicates for pyrexia and bronchodilators and expectorant mixtures for wheezing and coughing.

I must therefore emphasise that examination of the throat should be the fundamental part of the examination of children. The tongue should be well depressed by a tongue depressor (several disposable ones on the market). In this way the fauces can be well scrutinised. Good light is very important for proper examination. Two practical hints are appropriate in this context — first of all, a child naturally dislikes having his throat looked at and therefore it is wise to defer it until other systems have been examined. Secondly, it is very important to have the mother holding the child properly for good examination. The best technique is to have the child sitting on the mother's lap. With one hand the mother holds both the child's arms and with the other hand on the child's forehead, she fixes his head against her chest.

Sometimes acute tonsillitis is associated with acute infection of the adenoids. The adenoids and tonsils are part of Waldeyer's ring of lymphoid tissue and they can easily be infected together. Acute adenoiditis presents with nasal discharge and obstruction. Only the adenoids might be infected and the diagnosis of acute adenoiditis should always be a positive diagnosis. It is made by means of a small mirror and a tongue depressor. The adenoids will be seen to be inflamed, with small yellow spots of pus exuding from the spaces in them.

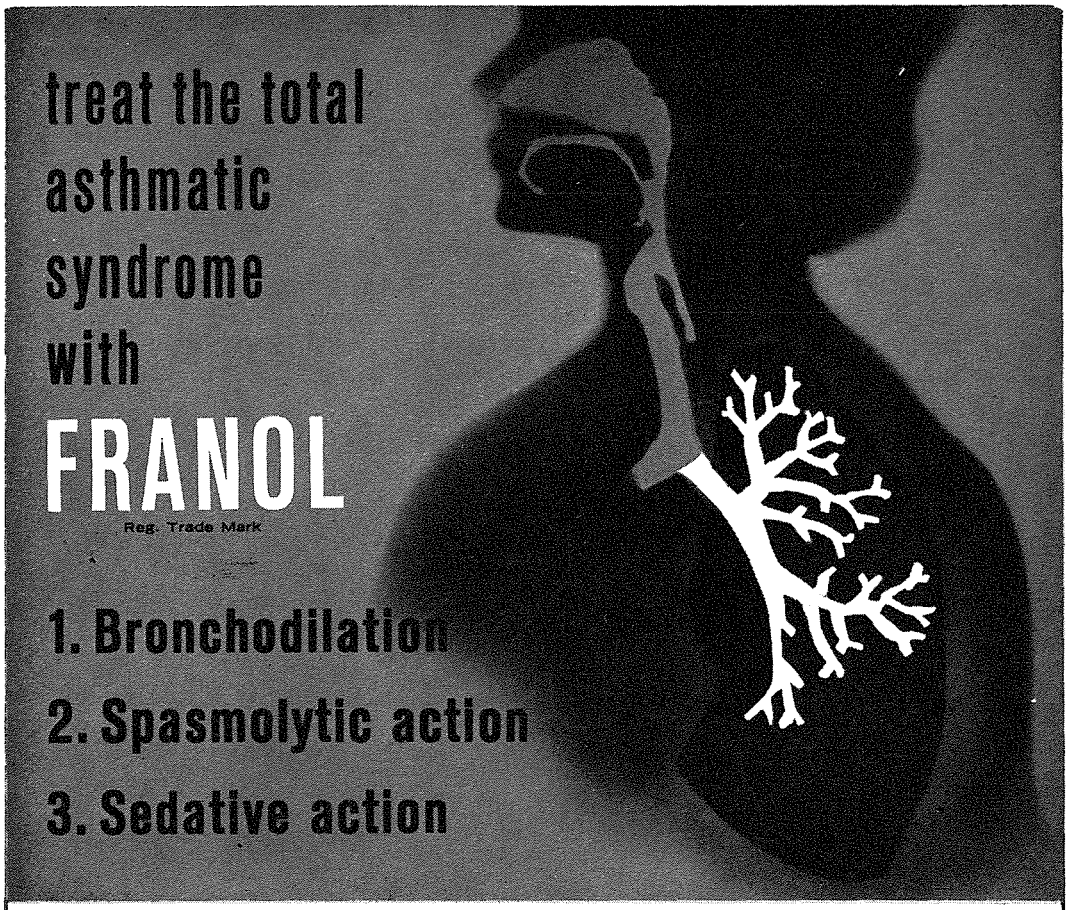
Once the diagnosis of acute tonsillitis and/or adenoiditis is made, treatment should be started immediately with Penicillin; in young children better Intramuscularly. Treatment should last for a minimum of five days.

Although acute tonsillitis is very often caused by haemolytic streptococci there are various viruses and other bacteria which can cause the infection. Amongst the viruses, the virus of glandular fever (infective mononucleosis) is one of the known agents. Amongst other bacteria, the pneumococci, diphtheria, diphtheroids, and Vincent's Organisms are also occasionally responsible agents. However, it is very rare that one has to resort to throat swabs and antibiotic sensitivity tests. One is always safe with Penicillin.

Once treatment with Penicillin is started, the temperature subsides within 3 days. If this does not happen it is probable that a complication is brewing and complications can arise not only if acute tonsillitis is overlooked but also if Penicillin is administered in inadequate doses and over a short period.

Complications may arise as a result of direct spread of the infection such as otitis media, suppurative cervical adenitis and chest infections.

Other complications may occur in distant parts of the body after an interval varying from a few days and up to three weeks. I here include rheumatic fever, glomerulonephritis, Henoch-Schonlein's purpura and erythema nodosum. These latter complications are not caused by the streptococcus itself but by immunological reactions incited by the streptococcus. Of these immunological reactions the most serious is rheumatic fever with



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its associated rheumatic carditis which very often results in chronic valvular heart disease. Kaplan & Mayeserian (1962) found that in rheumatic carditis an antigenic component of Group A streptococcus may be capable of inducing an antibody response which gives a cross reaction with heart muscle and smooth muscle.

Rheumatic fever and acute glomerulonephritis can lead to chronic illnes of the heart and kidneys respectively which in turn lead to death at an early age. Proper and prompt treatment of acute tonsillitis can prevent this.

Acute tonsillitis confers very little immunity, and it not infrequently happens that a child has several attacks in the course of a year. The infection is highly contagious and in places where children are together, as in schools or crowded homes, small epidemics are not uncommon. Some children have sore throats so frequently that, partly because of the frequent infections and partly because of several drugs administered over a long period, they lose their appetite and weight and become quite lethargic.

When the tonsils have become chronically diseased, a mild fever is often present, albuminuria might be present, and continuous swallowing of mucopus from the throat often leads to chronic gastritis. Mesenteric adenitis might follow. This is due to swelling of the mesenteric glands and might give rise to sharp attacks of abdominal pain of a colicky nature accompanied by vomiting and localised tenderness in the region of the umbilicus. These attacks closely simulate appendicitis and sometimes a laparotomy is performed which could have been prevented if a thorough examination of the throat had been carried out. Chronic infection of the trachea and bronchi are also common in such cases.

These cases of frequent tonsillitis leading to chronic tonsillitis should be treated by tonsillectomy. If the adenoids are infected as well they should be removed at the same time. Mere enlargement of the tonsils is no indication for tonsillectomy, unless they are so large that there is a gradual obstruction of the patient's breathing. Tonsillectomy by itself may make the child an easier prey to catarrhal infections, so it is not to be taken haphazardly as the patient may be worse off after the operation. Repeated tonsillitis means, of course, that the tonsils are no longer capable to resist infection. Before the operation the child's health is to be improved by correcting associated anaemia, vitamin deficiency and controlling chronic sepsis by antibiotics.

SUMMARY

In infants and young children tonsillitis may be missed unless examination of the throat is done routinely in all sick children.

Treatment with adequate does of Penicillin for a minimum of 5 days is sufficient for streptococcal sore throats. Missed diagnosis and inadequate therapy can lead to serious complications.

Frequent sore throats may lead to chronic tonsillitis resulting in debility and ill health. These cases should be treated by tonsillectomy.

REFERENCES

Kaplan, M.H. & Meyeserian M (1962) Lancet 1, 706.

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The Medical Defence Union Limited is again this year offering prizes in two essay competitions, one for Medical students and one for Dental students. First prizes will be £100 and second prizes will be £50.

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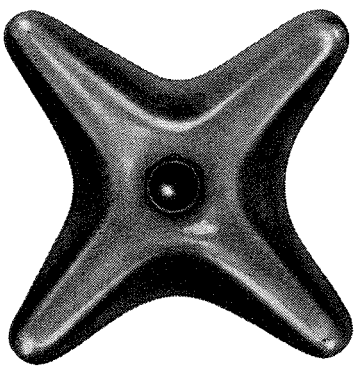

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Clerking in Cardiff ..... Summer '71

Joe DeGiovanni and Robert Carachi

This summer we clerked at the Welsh National School of Medicine in Cardiff during the months of July and August. The first part of our clerking took us to the Clinical Haematology department of Prof. A. Jacobs. This department run by pathologists and physicians has its own wards and its own out-patients sessions specifically for people with haematological conditions. We went on daily ward rounds with the professor and his staff and followed up the treatment regimes and the laboratory investigations with his registrars. These investigations are carried out by a highly skilled staff of technlclans, and Include blood counts, bone-marrow smears, immunoelectrophoresis, coagulation assays, and whole body counting. The out-patients sessions were a very profitable exprience, as we saw a variety of haematological conditions which were very instructive indeed. Our experience during our short stay in the Clincal haematology department helped us to correlate for the first time haematology and medicine on the clinical side, and the rehabilitation of the patient by the social worker attached to the department on the sociological side. Most of our work was done at the Cardiff Royal Infirmary.

The rest of our stay was spent in the Pathology department run by Prof. Williams. The mornings were passed in the post-mortem room, studying biopsy material, and visiting the fine pathology museum in the hospital. We also attended clinical meetings with the surgeons and dermatologists and occasionally we had tutorial sessions in the afternoon. The bulk of the post-mortems were cases of pneumoconiosis which needed to be assessed by the board before compensation was granted to the dependants. The post-mortem of hospital cases is a thorough investigation which is very instructive.

We were living in a newly built ten storey hostel in Heath Park where the new hospital was being built. The hostel is fully equipped with a games room and coloured television. There is also a bar which is frequented daily by all the students. The board was very good unlike that which is served in the quarters at St. Luke's which leaves much to be desired.

We were shown around by different doctors who took us to the outlying hospitals which form part of the United Cardiff complex of hospitals.

We made the most of our stay at the Infirmiry by visiting other units like the highly specialised Renal and Spina Bifida Units. During our spare time we toured the beautiful Welsh countryside with the great number of friends we made during our stay or on our own bicycles (bought at a police sale by auction for a pound each!) It was very quiet during a certain period of our stay when most of the students were on holidays, however we had an opportunity to join in the social life of the students before they left. There is so much to see both in and around the Infirmiry that one needs to spend at least a period of two months to get the full benefit of such a visit.

Finally we would like to thank Prof. G.P. Xuereb, and Dr. Kilpatrick for making our visit possible, and Prof. Jacobs, and Prof. Williams for the interest they showed in us.

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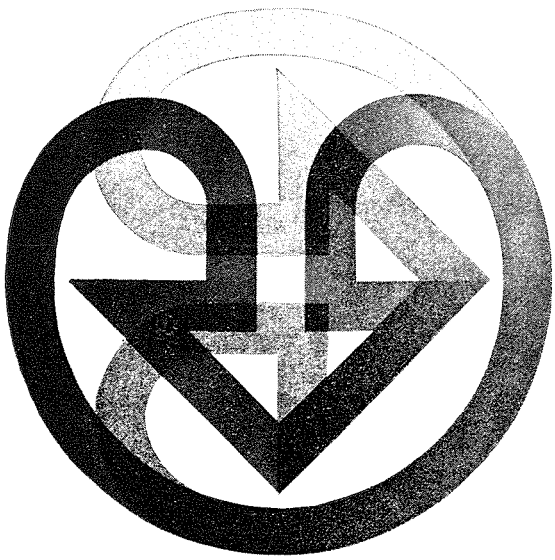

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Treatment of Acute Lymphoblastic Leukaemia

Joe DeGiovanni and Robert Carachi

Case history: P.T. was an 8 year old child complaining of lassitude, tiredness, anorexia and loss of weight. Admitted on 2/4/69.
Past history: Chicken pox, mumps and measles.
Family history: Nothing relevant.

On examination the patient was anaemic, and had scattered non-tender glands in the axillae and small haemorrhages on the hard palate. Pulse 90 regular. JVP:O. B.P. 120/80. Soft systolic ejection murmur maximal at the apex. Chest clinically clear. Firm hepatic enlargement (2 fingers) and palpable spleen. C.N.S. : N.A.D.

Marrow punture revealed acute lymphoblastic leukemia; 50% of the cells were blasts.

Blood: Hb. 6.2 gm., platelets 206,000, WBC 4,900.

He was started on the MRC regime for acute lymphoblastic leukaemia using Prednisone, Vincristine, 6-Mercaptopurine, Methotrexate, Asparaginase and Folinic acid. These were given according to a planned pattern and stopped 21 weeks after immunotherapy by BCG was started; the BCG was given weekly and the patient has remained in remission for 2 years.

In acute leukaemia there is an accumulation of malignant colonies of abnormal blast cells in the bone marrow and other tissues resulting in poor red cell, platelet and granulocyte production and leading to a fatal result if left untreated.

Management:

Originally treatment was merely supportive together with irradiation of local infiltration. The results were very disappointing but they have been markedly improved with the introduction of Cytotoxic drugs. The best results have been obtained with Intensive Combination Drug Therapy (Fig 1.). Increasing the dose of a chemo therapeutic agent above a certain limit merely increases the toxicity without altering the remission rate. The use of a drug combination with different side effects may allow the same dose of each agent to be given with no added toxic effects.

Figure 1

	Mean survival
No specific treatment	5 Months
Folic acid antagonists + Steroids.	9 Months
Purine Antagonists	12 Months
VCR + Endoxan	14 Months
Intensive Combination therapy	Over 3 years

The use of combination therapy has not only increased the mean survival but the quality of life has also been improved considerably.

Treatment of acute leukaemia is more limited than that of solid tumours because of dissemination which rules out the use of Surgery and Radio-therapy, and so one has to resort to chemotherapy. Besides the treatment of the actual disease one has to prevent complications by giving supportive therapy such as platelet transfusion, prophylactic antibiotics, prevention of meningeal leukaemia and hyperuricaemia together with the use of Barrier Nursing.

The modern approach in the treatment of acute lymphoblastic leukaemia involves 3 steps:

1. Remission induction.
2. Cytoreduction of residual leukaemic cells.
3. Maintenance.

1. Remission induction.

Remission induction involves treatment with chemotherapy until the patient becomes clinically free from disease. This can be achieved by using Vincristine and Prednisone with a remission in 85% of cases. If this fails Daunorubicin can be added and there can be a remission in 90% of cases or else Rubidomycin and the remission occurs in 100% of cases but there is an increase in toxicity with the last two agents. Other cytotoxic drugs have been used such as L-Asparaginase, Methotrexate, 6-Mercaptopurine, Cyclophosphamide and Cytosine Arabinoside.

With remission induction one does not eradicate all the malignant cells and up to 10^9 leukaemic cells may still remain undetected.

2. Cytoreduction chemotherapy.

The number of residual leukaemic cells can be reduced to a minimum by cytoreductive chemotherapy using different drugs from those used to induce the original remission.

Continuing the chemotherapy with a single agent during periods of remission intermittently results in prolongation of remission. However, combination chemotherapy is more effective. Drugs commonly used for this purpose are Prednisone, Vincristine, Methotrexate, 6-Mercaptopurine and L-Asparaginase.

The logic behind this step is that leukaemic cells are not rapidly dividing cells as was previously thought. In some malignant diseases the cell doubling time may be even longer than normal cells. The intermittent use of antimitotic drugs enables the normal cells to recover more rapidly than malignant cells between the doses of the drug. Thus it can be given in larger doses and is more effective in prolonging remissions.

The management of the patient in complete remission and the elimination of the residual disease is the main difficulty in the treatment of acute leukaemia. The problem is further complicated by the fact that the treatment is given blindly at this time because it is not known how much leukaemic cells are still present. What

is required is a marker that can give an estimate of the amount of tumour left. The discovery of such a marker whether it be a circulating tumour antigen, enzyme, hormone or other metabolite would revolutionize the treatment of acute leukaemia.

3. Maintenance.

This can be achieved by any of these 3 methods: (i) Chemotherapy (ii) Immunotherapy (iii) Immunotherapy + Chemotherapy

Immunotherapy

This increases the resistance to tumour growth by stimulating an immunological response. Theoretically it can be achieved in various ways, but in practice only some are effective.

a) Passive immunotherapy. This consists of the administration of horse antilymphocytic serum but it has not proved to be effective; moreover, it can be dangerous because the serum has cytotoxic and enhancement antibodies and these cannot be separated.

b) Active immunotherapy. For this to be effective the number of tumour cells must be very small — less than 10^5 in the case of mouse leukaemia L1210. Active immunotherapy is only justified if the leukaemic cells carry a specific antigen. It has been found by Dore' that a third of patients with leukaemia have antibodies in their sera against their own leukaemic cells and those of other leukaemic patients; therefore, part of the resistance offered by the host against leukaemia is immunological.

Active immunotherapy can be specific or non-specific. These can be used concurrently. Specific immunotherapy consists of injecting irradiated leukaemic cells which still carry antigenic properties or by injecting the antigen directly. Non-specific immunotherapy consists in the stimulation of the lympho-reticular system by non-specific antigens such as B.C.G. With the exception of one study by Prof. Mathe' other experimenters have not come up with any good results in this field.

c) 'Adoptive' immunotherapy is based on the antileukaemic effect of the lymphocytes transfused or produced by bone marrow grafts. Remissions with transfused lymphocytes are short while with Bone Marrow grafts they can be much longer. Remissions with the latter are induced by the reactions of the lymphocytes against the leukaemic cells and correspond to a cure if all the leukaemic patients' haemopoietic tissue is destroyed. However the graft affects normal antigens and may induce a severe lethal disease, 'Secondary disease'. Because of these dangers in acute lymphoblastic leukaemia, adoptive immunotherapy must be reserved for patients refractory to chemotherapy.

Conclusion:

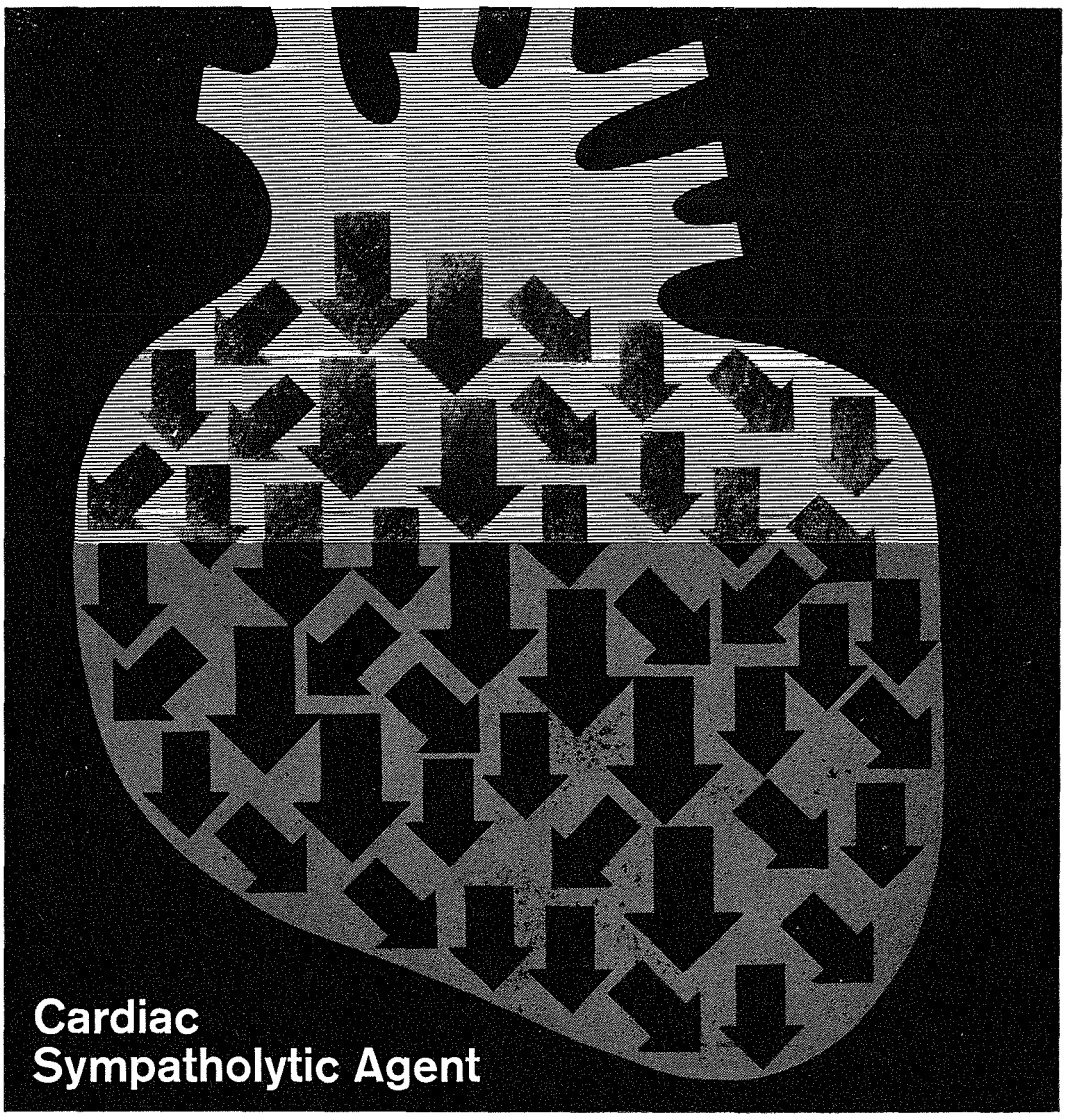
The case presented was one of Acute Lymphoblastic Leukaemia which has been in remission for 2 years during which period P.T. was on Non-Specific Immunotherapy by giving B.C.G. with the Multiple Puncture Technique (Heaf). Whether this long remission is due to the immunotherapy or not has yet to be proved.

Penicillin — The present for the man who has everything.

You can always tell the difference between a University, a polytechnic and a Technical College by the way the students react in the morning.

In a Technical College, the lecturer walks in, says, "Good morning," and the students ignore him.

In a Polytechnic they say, "Good morning", back and in a University half of them write it down and half of them go to sleep and someone at the back puts his hand up and says "Why?"



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Natural Childbirth

A. Leigh Bennett Dick-Read

Natural Childbirth occurs when a woman has her baby without the need for outside intervention. It therefore follows that any discomfort or pain she experiences will be below the level at which she would find it intolerable. Many women claim to have had no pain at all.

It is often said that Natural Childbirth does not work. This is not true for hundreds of thousands of Western women, notably in North America and West Germany, and millions of Primitive, or Non — Literate women who have had little or no contact with Western Civilisation. Natural Childbirth is the rule rather than the exception. A 98% success rate has been demonstrated with Western women(1) and with Non — Literate women the figure is probably higher.(2)

Many have tried Natural Childbirth. Some have failed. Consistent failure is due ONLY to an incomplete understanding of Natural Childbirth Techniques.

The theory and practice of Natural Childbirth were developed during the first quarter of this century by Grantly Dick-Read, an Englishman.(3) Dick-Read was a highly qualfied physiologist, anatomist and Accoucheur who developed his theory both empirically at the bedside and from his researches into the neuro-physiology of parturition.

Before we discuss the theory and practice of Natural Childbirth I refer you to the words of Dick-Read:

"The importance of my theory is that its implementation in obstetric practice shows that "it works" with considerable success".(4)

First we shall outline the structure and function of the uterus. (Here I must acknowledge the patient help of a medical student.) Then we shall discuss Natural Labour. (here I must thank the physician who read and criticised my manuscript.)

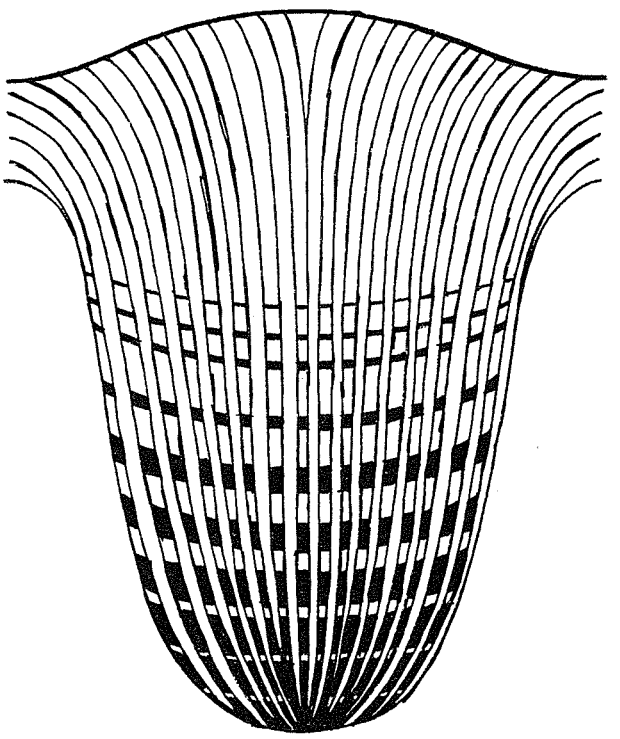
THE UTERUS

In a non-pregnant woman the uterus is a small pear shaped organ about three inches long and two inches wide at its widest point. During pregnancy it expands upward and outward within the abdomen to accommodate foetus, placenta and amniotic fluid. Its ultimate size may vary considerably from woman to woman.

The uterus consists of three muscle layers. (Diagram A) The inner muscles are circular and their density increases towards the cervical or lower and of the organ. The middle layer consists of muscle fibers which run in all directions and infiltrate the outer and inner layers. The most important of these central muscles are found to encircle the large blood vessels of the uterus. The outer layer consists of longitudinal muscles running upwards and outwards over the fundus and down the posterior wall.

The innervation of the uterus is of vital importance in understanding the mechanics of labour.

Diagram A.



Showing diagrammatically the relative distribution of longitudinal and circular muscle fibres in the uterus at full term.

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The circular muscles are supplied by the sympathetic nervous system. The central muscle is also innervated by the sympathetic nervous system. The longitudinal muscles are innervated by both parasympathetic nerves and a local innervation from ganglia within the uterine muscle itself. This local innervation is in no way associated with the spinal cord or the sympathetic nervous system.

Thus, the local innervation within the longitudinal muscles maintains the expulsive contractions of birth. The parasympathetic nervous supply stimulates these expulsive contractions. The circular muscles, innervated by the sympathetic nervous system tend to inhibit expulsion during pregnancy. The central muscles, when contracted under the influence of the sympathetic nervous system, tend to constrict the large blood vessels of the uterus. This prevents haemorrhage after birth.

LABOUR

When the system is functioning naturally, (I would say normally — but "natural" and "normal" are not, I fear, synonymous,) the outer and inner uterine muscles act such that each complements the other. The circular muscles prior to labour are firm and tend to constrict

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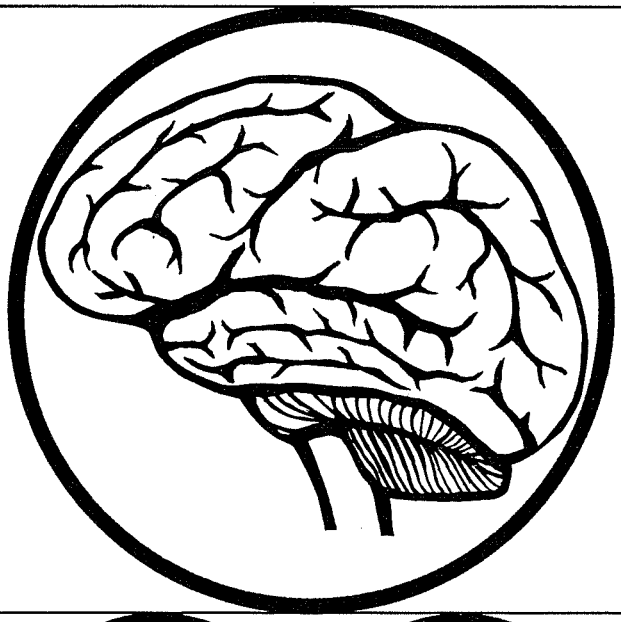

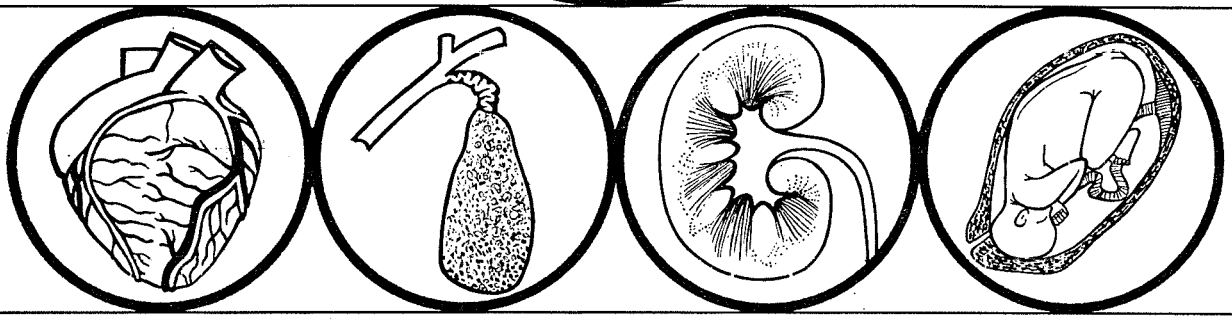

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the cervix, whilst the longitudinal muscles are flaccid and relaxed. However, with the onset of labour, the longitudinal muscles begin to contract at ever decreasing intervals and in ever increasing strength, while the circular muscles relax to allow the gradual dilation of the outlet. This continues until the cervix is sufficiently dilated to allow the foetus to pass into the vagina.

However, for reasons we shall not discuss here, such conditions have not been normal for Western women since the middle ages.(5)

Let us consider the other two systems of the lower abdomen. Sufficient faeces in the rectum or urine in the bladder stimulates the urge to defecate or micturate. When conditions are right, the sphincters in the neck of the bladder and the anus relax in response to pressure and allow the expulsion of the urine or the faeces. Should abnormal conditions such as inflammation of the urethra or fissure of the anus be present, the relevant sphincter muscle may well develop a spasm. This spasm is very painful and could have a certain inhibiting effect. The mechanism of painful labour is similar.

NORMAL LABOUR AND PAIN

Fortunate is the physically normal woman who understands and does not fear childbirth for she will have little or no pain in labour. Usually Western woman is not lucky. Nanna or Ommi, married friends or the girls at school, have all combined to ensure that she knows the full measure of her coming ordeal. If she ever heard anyone say: "It wasn't that bad, really," she has probably forgotten. Why?

The first stage of labour announces itself in one of three ways. Either the bag of waters leaks, or possibly bursts; or the "show" may appear — that is a slight haemorrhage along with the mucous plug from the inside of the cervix; or thirdly, and this is the most reliable indication, the first contractions will be felt as abdominal tightness recurring at intervals of fifteen or twenty minutes.

Since many women are likely to experience contractions for as much as a fortnight before the onset of labour the medical adviser must, of course, try to ascertain that the contractions are recurring at regular, decreasing intervals before recommending a hasty migration to the hospital or maternity home!

You will notice that I referred to CONTRACTIONS — not PAINS; because contractions do not hurt.

You will remember that the longitudinal muscles are innervated by the parasympathetic nervous system, which stimulates its contractions, and the local innervation, which maintains contractions. Once labour has begun there is no mechanism by which the mother can cause the longitudinal muscles — of their own accord — to reverse the progress of labour, because, as we have seen, the local innervation operates independently of the Central Nervous System.

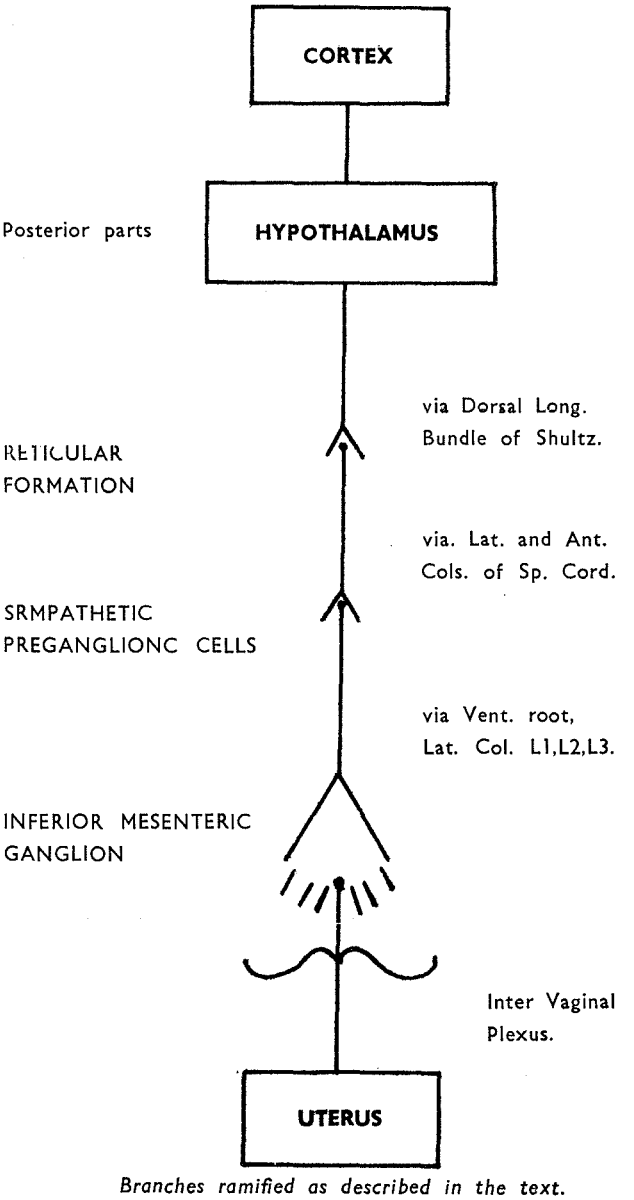
However, as we have seen, the circular and central muscles are innervated by the symapthetic nervous system. If the woman expects and is afraid of pain, she will anticipate pain with each contraction.(6) Now the *interpretation* of sensations arising within the uterus are profoundly influenced by the mental state of the woman.(7) If a woman thinks a contraction (a new experience associated exclusively with childbirth) ought to be painful she will be frightened.

THE FEAR-TENSION-PAIN SYNDROME.

Now when we are afraid the Thalamus, in conjunction with the Cortex, sets into operation the best means of reducing the need to fear. If you meet a thug intent on "braining" you, you will rapidly decide whether you should face him bravely — or run like the devil. The stimulus is received by the eyes and passed to the cortex.

Diagram B.

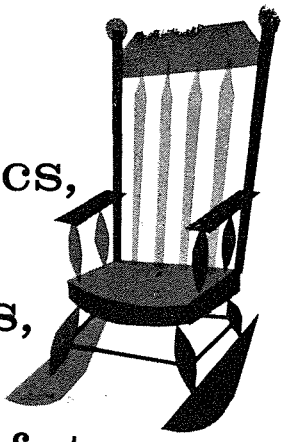
Outlining the course taken by a Sympathetic nervous impulse between the Cortex and the Uterus.



Branches ramified as described in the text.

FEAR: Innibitory action on Hypothalamus broken.
TENSION: Contraction of Central and Circular Muscles.

from
pediatrics,
to
geriatrics,
when
speed and safety
are desired



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Here the strength of the stimulus is assesed. Here, through the intervention of the Thalamus, the *judged* significance of the incoming stimulus is interpreted — *relative to the current emotional state of the individual.* The cortex then makes the decision of fight or flight. Instruction to the relevant effector organs is transmitted via the sympathetic nervous system which over-rides all the other activities in the areas stimulated.

The path followed by impulses in the sympathetic nerves is shown in Diagram B. Fear, already present in the cortex, tends to encourage a "Pain" interpretation of stimuli received from the contracting longitudinal muscles. Fear, a form of stress, tends to reduce the inhibitory influence of the cortex over the Hypothalamus. This can lead to panic and an increase in the "Pain" interpretation of the stimuli being received from the uterus. In soldiers the tendency for Fear to reduce the inhibitory effect of the cortex on the Hypothalamus may be minimised by training.

A frightened woman cannot cause her longitudinal muscles to stop contracting of their own accord. She can, however, cause her circular and central muscles to contract. When this happens her longitudinal and circular muscles act so as to oppose each other.

The upper arm muscles are another example of a complementary muscle system. To bend the elbow we contract the biceps and relax the triceps. To straighten the arm we relax the biceps and contract the triceps. If we contract both together, each opposes the action of the other. If we contract both strongly, the arm begins to vibrate and shortly both muscles begin to ache. Excessive Tension is painful!

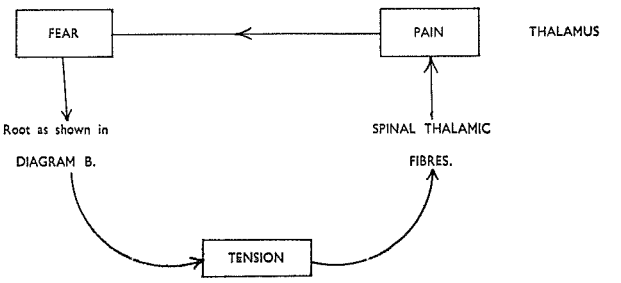
Similarly, the uterus muscles, when in opposition, are in a state of tension — and the greater the tension the greater the pain. The degree of pain felt depends not only on the strength of the stimulus but also on the emotional interpretation of the stimulus.

The mechanism functions in accordance with a law postulated by Dick-Read which states that: "A stimulus of fixed magnitude applied to any specific sensory receptor produces a motor response commensurate with the integrity of its interpretation."

The degree of pain felt during the first stage of labour is directly proportional to the degree of fear experienced by the woman. Fear gives rise to pain. Pain re-enforces Fear (of Paln), and we have a vlclous clrcle! This is known as the Fear-Tension-Pain Syndrome. Diagram C.

Diagram C.

The FEAR-TENSION-PAIN SYNDROME



UTERUS

BREAKING THE SYNDROME.

"There is no physiological function which gives rise to pain in the normal course of health," for, Professor Julius Welf bluntly stated: "Structure is adapted to Function," and Pain's purpose is to warn us of an abnormal condition! Nociceptors or pain receivers are specific for the type of stimuli to which they will respond.(8) The only type of nociceptors found in uterine and intestinal tissue (tissue which may otherwise be burned, cauterised or physically moved without pain) are those specific for excessive tension or laceration.

If a healthy woman experiences great discomfort or pain during labour its prime is almost certainly tension of the uterine muscle. Excessive tension causes the central and circular muscles to contract. This inhibits the blood supply to the uterus and therefore the foetus. The extreme form of this condition is called white or ischaemic uterus, and can lead to a Caesarian Section.(9)

Thus, in order to achieve Natural Labour most women — Western and therefore Maltese women — must receive Antenatal Training. This should consist of an elementary explanation of the Mechanics of childbirth and why it should not hurt. Mothers who need exercises to keep them fit should do them and, as will be seen, all mothers should be taught to relax.(10) Obstetricians and Midwives also need to become familiar with the techniques of Natural Childbirth.

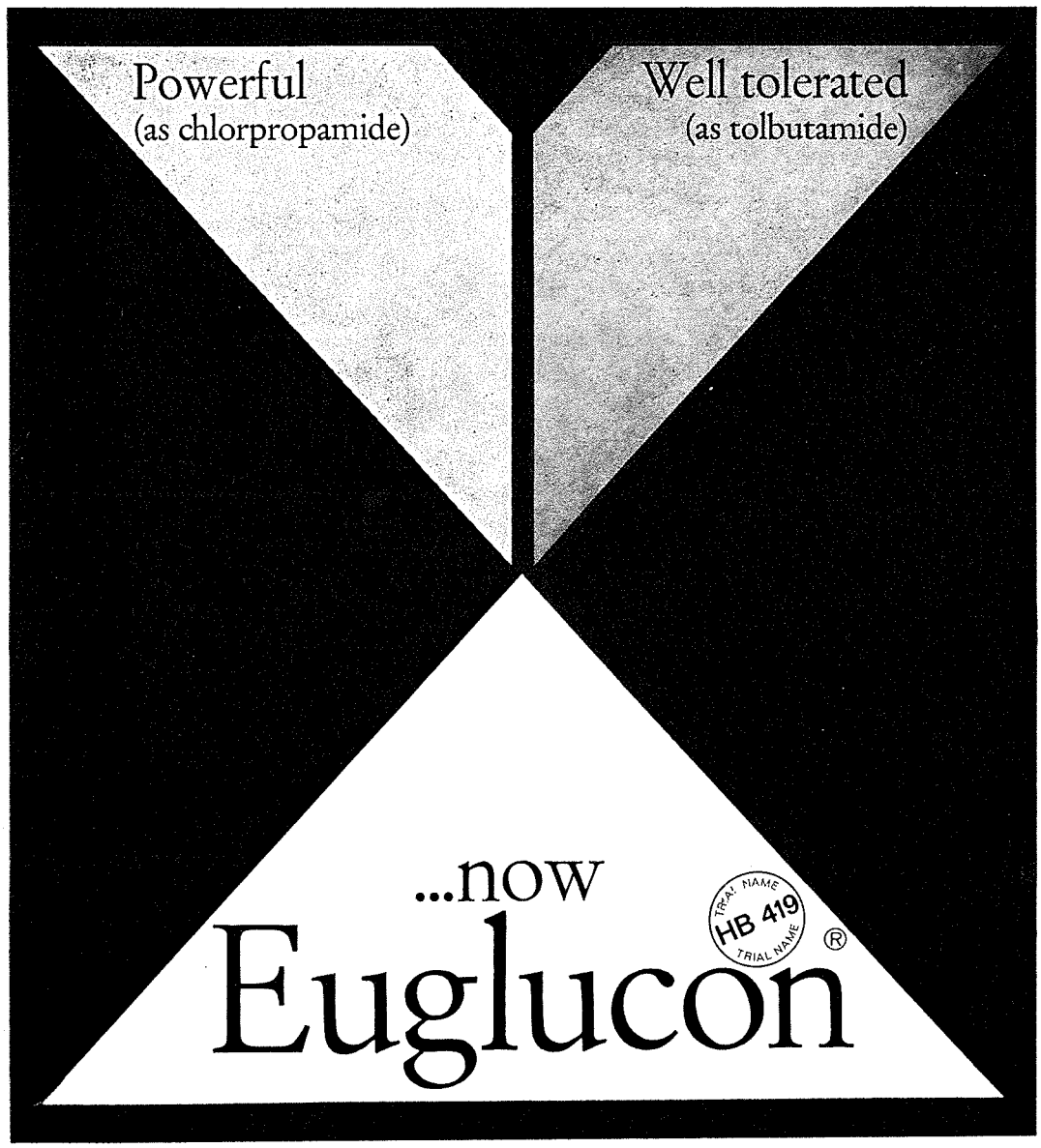
A much respected Maltese Medical Officer of Health once told me that it was impossible to teach Maltese Mothers to have their babies naturally because of the "Maltese Mentality". I profoundly disagree. Women are women be they from Lusotho or L'Isla and Natural Childbirth is precisely the same phenomenon in women of all physical types and cultures (11) In Hamburg, West Germany, Doctor Rudolph Hellmann is the leader of a growing band of doctors who use these techniques. In the United States Natural Childbirth is known to most people and practised by more obstetricians every year. Indeed, the faculty at Duke Universtiy, North Carolina, teaches it under their Dean Professor Bayard Carter. In South Africa, where Dick-Read practised between 1949 and 1952, his principles are practised by his former partner Doctor Costa Halamandres. Natural Childbirth is NOT the priviledge of Non-Literate alone.

NATURAL CHILDBIRTH.

In his lectures Dick-Read used to refer to the three P's and the three C's which can help those who attend women in labour to achieve or approach *Perfect Confinement.*

PATIENCE: No woman should ever be left alone in labour unless she asks to be. If possible, and he is likely to prove an asset, her husband should be present. Not only to hold her hand, rub her back (when during the first stage, the cervix is nearing full dilation) and tell

The best of both worlds



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her how marvellous she is, but share with his wife the joy of welcoming their child into the world together. The first stage, especially in the primapara, can seem like an age. If the mother lets the contractions come and go of their own accord, the cervix will dilate in its own good time. Impatience can result in "bearing down" too soon and this may lead to overtiring of the mother and to unnecessary laceration in a later stage. Furthermore, a fully dilated cervix will suffer minimum discomfort when it stretches as the baby passes through.

PEACEFULNESS: Women in labour are acutely senstive to sound in general and talk in particular. Anything less than an atmosphere of peaceful purposefulness in the labour room is likely to disturb a woman who is anxious — who, inspite of her instruction, is too influenced by her former fears or too little instructed to be completely confident and relaxed.

Conscious relaxation assists in the relaxation of the Levator ani muscle — which is influenced by the spinal nerves and may contract around the vagina in such conditions of stress (Fear). Such practised relaxation — necessary if a woman is afraid — originating in the cortex, results in the efficient support of the inhibitory effect of the cortex on the hypothalamus.

PERSONAL INTEREST: A great Medical Technician is of inestimable value to a woman who requires his intervention, but those who attend women in Natural Labour must consider every aspect of the labour from the point of view of the mother. Without deep personal concern it is not possible to maintain the stamina required of a woman who needs constant encouragement and guidance. No man can deceive a woman in labour with false confidence or hallow enthuslasm.

A Gynaecologist usually expects demands on his skill . An Obstetrician is more likely to experince great demands on his emotions.

CONFIDENCE:..... requires competence. A confident woman must be well instructed and have faith in her obstetrician.

CONCENTRATED OBSERVATION: Without Personal Interest it is not possible to maintain the Concentrated Observation necessary to keep one step ahead of a woman in labour!

CHEERFULNESS: Natural Childbirth IS a Happy Event. However, Dick-Read wrote: "...I once heard a Medical man greet his patient: "Ha, ha! Cheer up, old girl. You've got to go through Hell, but I'll go anywhere with you — so keep smiling. Ha! ha!". I said that we would hate to detain him if he would like to go on ahead."(4)

See the film "Childbirth Without Fear". See the expressions on the faces of the ladies at crowning. They answer the question: "Does Natural Childbirth work?".

Before I am shouted down for being unqualified and out of step, I ask you to bear with me. Although the ideas I have expressed may be contrary to your experience and your schooling, I am not naïve enough to think that you are naïve enough to accept anything I have said without questions closely. I merely suggest that you verify this information for yourselves.I am sure not one of your professors would think much of you if you soaked up his words like a sponge and squeezed out the same water unconsidered and unenriched. I ask you to give what I have said at least a little consideration.

I hope that in the not too distant future you will be able to visit Obstetricians in Germany, the United States and elsewhere to see for yourselves how they achieve the results they do. Then, one day, I hope you too will join the growing army of Obstetricians whose patients have proved that Childbirth is Glorious.

On the 8th January 1956, His Holiness Pope Pius XII, addressing a group of Doctors of the International Secretariat of Catholic Doctors and the A.M.C.I., on Painless Childbirth, referred specifically to Doctor Grantly Dick-Read and his work. Discussing "Painless Childbirth Techniques" in general he said: "Scripture does not forbid it.... If the new technique spares her the sufferings of childbirth, the mother can accept it without any scruples of conscience...." (12)

On the 25th October 1956 Doctor and Mrs. Dick-Read visited Castel Gandolfo for a private audience at which His Holiness personally presented Doctor Dick-Read with the Silver Papal Medal. He also presented Mrs. Dick-Read with a Rosary.

REFERENCES

1. Vide Grantly Dick-Read.
2. See "No Time For Fear" — Grantly Dick-Read, 1955.
3. See "Doctor Courageous" — A. Noyes Thomas, a Biography, 1957.
4. See "Childbirth Without Fear" — Grantly Dick-Read. (The second Revised American Edition, 1959 is in the R.U.M. Medical School Library.) Royal University of Malta.
5. See "Childbirth Without Fear" Chapter IX.; "Childbirth and the Christian Family" (1962) — Helen Wersel.
6. Definitions of Pain are questionable! If a pain stimulus does not tend to distract a woman from the job of having a baby, does she FEEL pain? If a runner were to be stopped suddenly about three quarters of the way through a long distance race and asked, "does it hurt?", he would probably reply "of course!" But if, at the end of the race, (having not been stopped) he is asked the same question the answer is "of course *not* — I was too busy!" Unless of course, he was unfit when he started; What is Pain?

   See "Pain" — Richard Behan, 1915.

   And "Pain" — Sir Thomas Lewis, 1946 Edition in R.U.M. Medical School Library.
7. Vide Sir Henry Head (eg. reference to B.M.J.)
8. Vide Pavlov, Sherrington and Dick-Read.
9. See Sir Thomas Lewis — Archives of Internal Medicine, Vol. XIIV, page 713, May 1932.
10. See "Antenatal Illustrated" — Grantly Dick-Read, 1955.

    And "Introduction to Motherhood" — Grantly Dick-Read 1950.

    And "What Every Woman Should Know About Childbirth" — Jessica Dick-Read and Prunella Briance, 1965.

    And "Antenatal and Postnatal Care" — F.J. Browne 1935, Dick-Read contributed a chapter.
11. The concept that "Racial Differences" are significantly responsible for the actual — variable — incidence of intervention of any form is, I suggest, erroneous;

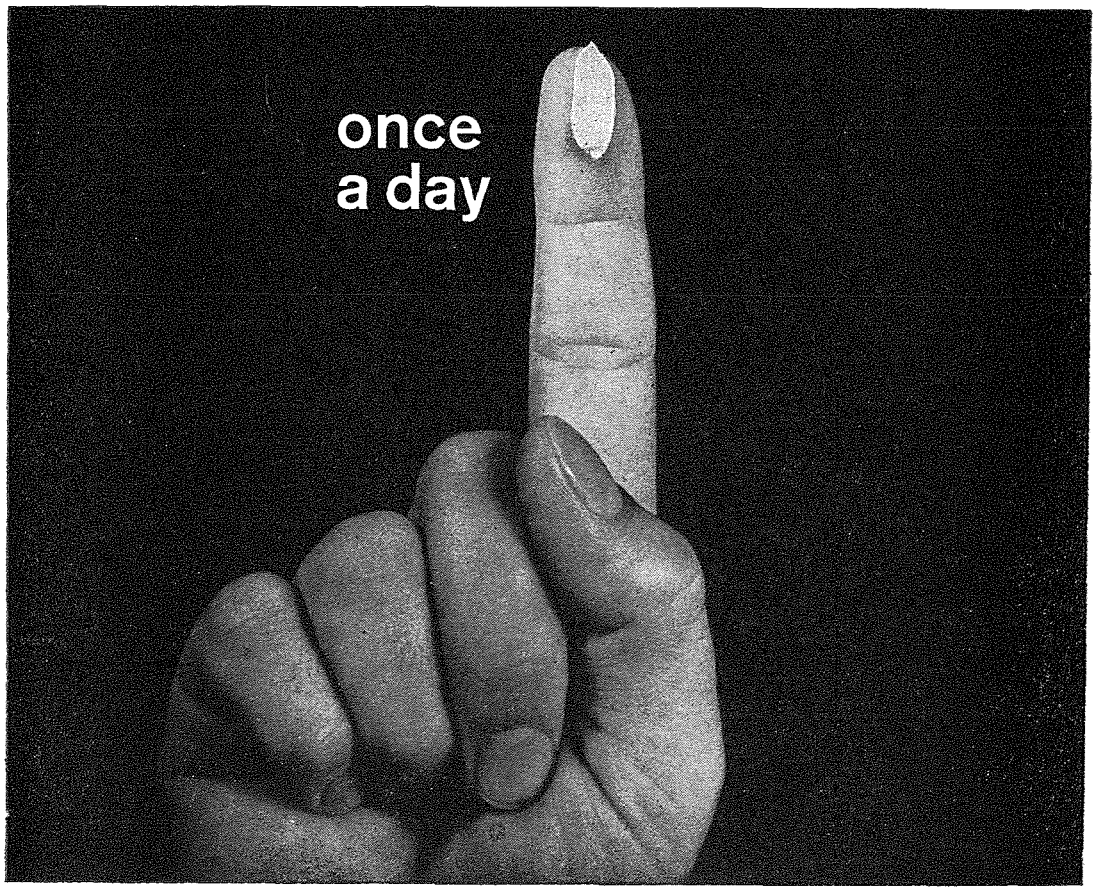
    a) because intra ethnic group (racial differences of morphology are demonstrably more pronounced than inter ethnic group differences,

    b) because what differences there are that may be due to genetic or enviromental (Physical) conditions do not of themselves cause the number of individuals who require intervention to be in any way great enough to relate to the actual incidents of intervention in most Western countries. Since the incidents of intervention can vary dramatically from area and from practise to practise within one ethnic group, I am persuaded that, for the most part, the incidents of intervention are related to enviromental (Social) factors.

    In addition to "Childbirth Without Fear" see also "No Time For Fear", on researches in Africa;

    The writings of Ashley Montagu, (an Anthropologist) Dunn and Dobshanksky (Geneticists) on the incidence of Morphological differences;

    The writings of Stuart Chase and Alfred Koraybski on how fact and fiction are confused when the ability to think critically and impartially is limited and on the problems of being accurate and clear *to others* when using Indo-European languages (eg. English and Italian).
12. Address "Nous Avons Recu...." — 8th January 1956.



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Book Reviews

Lecture Notes on Neurology
Ivan. T. Draper. M.B., Ch.B., F.R.C.P.E.
Third Edition
£1.50. 5"x7½", 231 pages.
Blackwell Scientific Publications

Nearly half of this book serves as an introduction; the rest is a broad account of diseases of the nervous system. It is the former which deserves greatest merit, and it is precisely this section which will be of most use to the student. Anyone starting with a ludicrous knowledge of neurophysiology and anatomy, will, with the aid of this book, learn and appreciate the clinico-pathology of some aspects of neurological disease. The style is simple, clear and concise. The sections on the cranial nerves, although incomplete in parts, are admirably written.

Less persuasive are the chapters on neurological disease. Treatment is briefly dealt with — for instance cerebrovascular disorders deserve more detailed information on the specific care of such patients, although two pages on the care of the paraplegic may be found at the end of the book.

Some sections of this small book are unique. A small chapter only three pages long on the differential diagnosis of disease of the spinal cord is excellent and concise. Likewise exceptional are the two pages on facial palsy.

In conclusion this book is for the student who tries to learn to evaluate the signs and symptoms he sees in the wards — it may on occasion be found wanting to some who are faced with the task of treating these interesting disorders.

J.V.P.

A DICTIONARY OF IMMUNOLOGY
Edited by W.J. Herbert and P.C. Wilkinson (Blackwell Scientific Publications 45/- net)

Immunology being so much in the limelight nowadays, much recently published works in Medicine, Biochemistry and Biology employ the use of terms with an immunological bearing. Unfortunately the place allotted for the teaching of Immunology in most medical curricula at present is still somewhat limited, and consequently many immunological terms have an air of mystery to many students and doctors. The aim of this book is to supply definitions of Immunological terms which can be understood by anyone having a background of Biological knowledge. It is quite amazing to see what a large number of new words have been carved in the past few years, necessitated by such a rapidly expanding science. The layout of this dictionary is admirable. It is useful as a work of reference, or on its own, as well as a supplement to a proper text on Immunology. The only drawback is its price; in paperback fares, this could probably be reduced to a few shillings.

A.G.S.

Lecture Notes on Pharmacology
J.H. Burn M.B., F.R.S.
Tenth Edition
£1.25 5"x7½", 158 pages.
Blackwell Scientific Publications

Pharmacology is the basis of medicine, and a thorough grasp of drugs, their indication, dosage and side-effects will be of unlimited value to the student who will later practice medicine. In reality, however, most will discover that their knowledge of pharmacology is "resuscitated" only when and where necessary, and that a sound clinical acquaintance with a few important groups of drugs is more gratifying than an encyclopaediac store of information on the pharmacology of drugs.

Unfortunately, this book fails to achieve either aim. Instead, one finds a rather sketchy account of a limited number of drugs. The "important drugs" such as antibiotics, digitalis, diuretics and analgesics — are too lightly dealt with to be of sufficient use for the practical minded. One cannot conscientiously be satisfied with six pages on antibiotics (including a few lines on tetracyclines and streptomycin). Dosage is sadly neglected — even in the important cases such as digitalis. In other respects, this edition is aware of the realities of clinical pharmacology; for instance, L-dopa is "mentioned" in Parkinson's disease, which is more than one can say for other contempory textbooks.

I fail to see the exact scope of this book. Its only value lies in affording a quick summary of drugs and their use. It is unsatisfactory for our examination purposes, and perhaps more important, for practical use.

J.V.P.

20th GENERAL ASSEMBLY OF I.F.M.S.A.

The M.M.S.A. was represented at the 20th G.A. of I.F.M.S.A. by Mr. Joseph M. De Giovanni. The G.A. was held in Paris from the 16th to the 30th August 1971.

The Assembly discussed matters related to Medical Education and Social Medicine. Topic discussions were held on:—

1. Student participation in decision making bodies concerning Medical Education Systems and Curricula.
2. Health care Systems with regard to Rehabilitation.
3. The place of physical Medicine and Rehabilitation in Medical Education.
4. Health Care systems with regard to Medical Manpower.
5. The legislation of abortion.

The Assembly agreed to hold the Winter Meetingof IFMSA in Malta later that year. The M.M.S.A. is to publish an international student journal on Medical Education together with the Students' Scientific Society of the United Arab Republic.

Why Cancer?

Tonio J. Bugeja

INTRODUCTION: One requires very few words to justify writing such an article as this: no one can afford not to be at least curious as to the "Why" and "How" of the most dreaded, almost invariably fatal ailment of the twentieth century. While the "How" is of the utmost interest to the clinician there is much to be said in favour of educating the layman as to the possible "Why" of cancer and hence its prevention. To people in the medical field this can prove a most provoking and thought-stimulating question.

It has long been held that "a substance or an activity" is the cause of cancer. Lately the trend has been that of talking about "carcinogenic compounds". Both these views are extreme attitudes and it is more likely that "cancer" comprises a large group of apparently diverse pathological conditions, all, however, being just different manifestations of a simple basic process. Histopathologically, hyperchromatism, aneuploidy, increased nucleus to cytoplasm ratio, increased nuclear mass and increased number of mitoses, characterizes cancerous cells. Physiologically, cancer cells possess in common a loss of contact inhibition, a lack of normal cohesiveness, increased amoeboid motility, lowered calcium content, increased membrane permeability and an increase in cytolytic effects; they all possess the capacity to invade and destroy surrounding normal tissue. In general, tissues are more susceptible to neoplastic conversion, the younger and the more actively dividing they are. A further similarity among cancers appears in the precancerous stages, well-described by many in cervix, breast, mouth, lung, skin, bladder and vulva, and resembling each other very much. Once more cancers are all focal and localized at inception (though clinically this cannot always be confirmed due to the advanced stage of the lesion when seen). This seems to indicate that the initial steps in the carcinogenic sequence always takes place in a local area, one cell or a single group of cells. Finally, **Greenstein** has shown that the enzyme patterns of malignant tumours from different tissues with different normal patterns tend to converge towards a common cancer system. In fact, cancer appears to be a tissue response to a very complex mixture of circumstances that coincide and interrelate in a specific manner; it is common to all living tissue and any cell capable of division is subject to it. The immediate implication of these statements is that not only can we not implicate just one cause, but that in addition no carcinogenic threshold dose or dose-result relationship can be stated as this varies with other types and amounts of carcinogens acting at the same site.

The production of cancer basically requires three conditions:

(a) the presence and adequate dosage of an external agent or **initiator,**

(b) an internal predisposition or **promoting factor,**

(c) the passage of relatively long periods of time i.e. **a phase of initiation.**

In fact **Berenblum** states that some initiators though responsible for the start of the cancer process, require, at low dosage, a promoting factor to complete it. Most initiators do not need promoters but all promoters need initiators. The value of this statement appears later with a consideration of the possible agents in each classification.

With these basic ideas in hand we can build a simple formula to guide our thoughts; this, however, will essentially be an extreme over-simplification and take the following form:

One prefers the use of the term "neoplastic conversion" rather than "neoplasm" (new growth or cancer) as this bears out the exact microscopical nature of cancer i.e. that of an an irreversible change in tumour cells. By neoplasm or new growth we often have in mind, unfortunately, a more advanced stage — that of cellular proliferation with tumour expansion, infiltration and spread. I say "unfortunately" because the prognosis then is always much nearer to zero and this is where the question "Why cancer?" is so important: the possibility of effective prevention of cancer will only be in sight when the answer to this question is truly found.

The final common pathway of most cancer theories consists of a genetic change in the developing cancer cell, a somatic mutation. Whether somatic mutation is cause or consequence, it is generally a prominent feature of the neoplastic conversion. On the other hand germ-cell mutation, which is hereditary from generation to generation, plays an important role in the development of certain rare human cancers such as retinoblastoma of infants and familial multiple polyposis of the colon, where so strongly does the genetic ability favour cancer in these families that other external and internal factors never alter the emersion of the tumour trait to any significant degree. Thus, it seems now generally accepted by workers in this field that malignancy is a change in the normal process governing "information and data" within every cell. This is usually part of the genetic constitution of each cell unit and interference with it can clearly lead to such abnormal behaviour as direct stimulation of proliferation, or proliferation as a result of release from controls inside or outside the cell. It has also become conspicuous that viruses (by replacing or redirecting activity of genetic material), chemical carcinogens (by combining with DNA) and ionizing radiations (by causing chromosomal breaks) are all capable of causing

changes in the genetic material, the DNA or information centre of the cell.

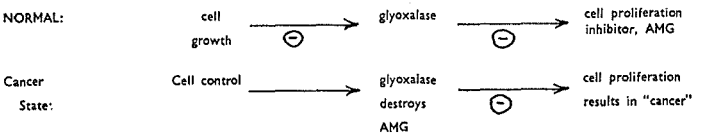
A cursory look at a list of theories (which makes no attempt at being exhaustive but rather is a cross-section of old and modern theories) indicates well the complexity of multiple factor interaction that is possible and the ingenuity needed for integration of all major factors into a coherent single theory; none of these theories can be grouped into the biochemical ones, those based on immunology and a miscellaneous third set.

BIOCHEMICAL THEORIES: Somatic mutation has been explained simply on the basis of an interaction between an external chemical compound and the DNA of the cell. It has also been theorised that latent viruses may be activated as a result of deletion of repressor or controlling factors by the foreign chemical substance. Others have suggested that it is an alteration in the structure of *chalones* (specific chemical messengers controlling cell division) which leads to the cancerous state. Abell and Heidelberger have postulated a deletion of enzymatic growth control factors by such chemical binding between carcinogenic hydrocarbons and these enzymes, the deleted factors possibly being an RNA molecule. **Szent-Györgyi** *et al* claim that a cell proliferation inhibitor, probably an aldoketone methyl glyoxal (AMG), exists; its action can be stopped by a glyoxalase, so that if the cell loses the ability to control the glyoxalase, uncontrolled cell growth could result (see fig. 1).

The cell contact inhibition theory is similar in that here cancer cells lose this mutual restraint and abnormal tissue accumulation occurs once more due to loss of the normal inhibition. On a different note some workers have postulated an abnormal response to altered hormonal activity. However, this theory appears to be limited to the hormone dependant ones like, for example, cancer of the breast. To summarise these six or seven theories in one sentence: a change in the biochemical activities of the cancerous cell is held responsible for the ensuing proliferation. This has been experimentally confirmed but one must now find out whether the change is the cause or the result of the abnormality.

IMMUNOLOGICAL THEORIES: **Cohnheim** suggested that "rests" derived from tissues misplaced during embryonic development proliferated to tumour later. This may explain teratomas but not their malignancy, nor why not all become malignant. **Tyler** has drawn an analogy between transplant rejection and cancer. He postulated that parallel to the application of the clonal selection theory of acquired immunity to lymphocytes, tumour specific antigens (formed possibly by a combination of chemical compounds and cell protein) form in regional lymph nodes which enlarge and "tumour graft" rejection occurs. The graft takes in the event that continued primary tumour growth throws off excessive tumour antigen which overwhelms the sensitized clones of antigens. This theory deals almost exclusively with metastasis. Metastasis of normal and benign tumours probably does not occur

Fig. I.



(except for the phenomenon of endometriosis) because of cell contact inhibition, a property characteristic of normal but not of cancerous cells. Thus the possibility exists that clinical cancer only develops when the tumour can overwhelm the immune defences of the host, which by the present evidence seems to be generally weak. The long latent period in most (clinically detectable) cancers may result from antibody production during the preclinical stages.

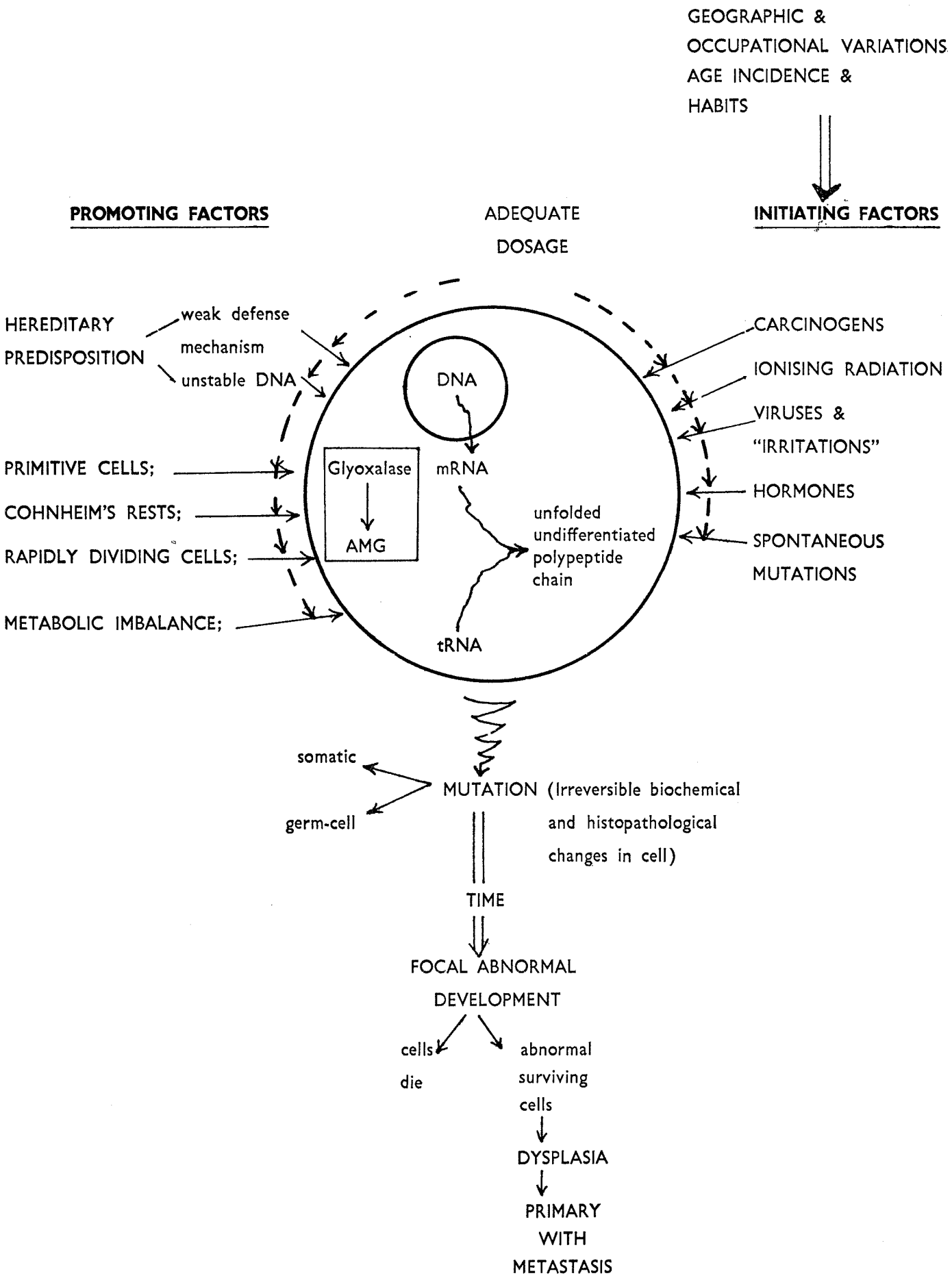
OTHERS: Chronic irritation, though often held responsible for cancerous change, is not always implicated; when it is, the primary factor may still be the irritant chemical substance itself rather than the mechanical irritation. Cellular infection by carcinogenic viruses (a form of chronic irritation, if you like) leading to abnormal multiplication, is the basis of the infective theory. The experimental observation that tissue culture cells which under-went virus-induced 'malignant" transformation can lose all signs of the abortive infection without changing their malignant potential, points to the possibility that viruses might induce neoplasms in humans by a "hit and run" effect: chronic viral infection (e.g. with **herpes** virus) might lead to the development of cancerous cell growth indistinguishable from neoplasms occurring through the agency of chemical carcinogens.

No epidemiological or statistical evidence has as yet confirmed the view that there can be an inborn genetically transmitted tendency for an individual's cells to become cancerous. This evidence must be hard to come by though, since this tendency may alone be just the promoting factor, and so (according to **Berenblum**) not capable of bringing about cancerous change.

Thiersch suggested that a balance between epithelial and connective tissue elements existing normally is lost when cancerous change occurs. Still he makes no attempt to state whether this is the cause or consequence of cancer. **Mendelsohn** in the field of cell population dynamics suggests that in any tissue a fraction of cells are actively proliferating while the other portion consists of cells in the resting stage; the result is that the rate of growth depends on the fraction of proliferating ones of the whole population. The latter fraction is usually small, varies from tissue to tissue, and increases substantially with injury and repair. In neoplasms a higher fraction results with overgrowth of the normal tissue bed by the dividing tumour cells.

Promising unorthodox information has very recently been obtained by **Clarence D. Cone, Jnr.,** head of the molecular biophysics laboratory at Langley Research Centre, in Vinginia. Mr. Cone has found that normal cells divide at a slow healthy rate when electrical charge on

Fig. II.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COHNHEIM'S RESTS;
RAPIDLY DIVIDING CELLS;
METABOLIC IMBALANCE;
DNA
Glyoxalase
AMG
mRNA
tRNA
unfolded
undifferentiated
polypeptide
chain
CARCINOGENS
IONISING RADIATION
VIRUSES &
"IRRITATIONS"
HORMONES
SPONTANEOUS
MUTATIONS
somatic
germ-cell
MUTATION (Irreversible biochemical
and histopathological
changes in cell)
TIME
FOCAL ABNORMAL
DEVELOPMENT
cells
die
abnormal
surviving
cells
DYSPLASIA
PRIMARY
WITH
METASTASIS

their surface (produced by the continual removal of salts across the membranes) is high; they divide at a much faster (cancerous) rate when this is low. In addition, the living cells tend to adhere strongly to one another when the surface voltage is high and vice versa. Mr Cone therefore proposed that electrical activity is the central mechanism for control of cell division.

It seems also possible that chemical and other carcinogens, instead of inducing abnormal cancerous changes, act by allowing the survival and proliferation of spontaneous mutants while suppressing proliferation of normal cells, or may in general interfere in the interests of some of these mutants. From a teleological point of view it has been suggested that cancerous change is just a form of local defence, mechanical and immunological, after a more general defence mechanism has failed against the particular carcinogen. This view must be correlated with the observation that a neoplasm always grows away from the site of application of the carcinogen.

So much for theories; we are now in a good position to try and integrate all the various possible factors which may act at various sites in the cell to produce the clinical cancer (see fig II). In the normal way of events the messenger RNA takes a mirror image of the DNA in the nucleus to the transfer RNA which carries the amino acids. The transfer RNA in the cytoplasm forms a mirror image of the messenger RNA and the amino acids are then "zipped up" into polypeptides which are then folded into proteins. Hence, carcinogenic action may be directed against the DNA, the RNA or the as yet unfolded, undifferentiated ploypeptide chain. Of special mention is the possibility of "loss of cell control over the glyoxalase", postulated by **Szent-Györgyi.**

The promoting factors include a hereditary predisposition due to a weak circulating defence mechanism or an unstable DNA; rapidly dividing or primitive cells (including Cohnheim's Rests); and a general metabolic imbalance in the form of hormones, temperature regulation, pH, gaseous transport and exchange and electrolyte transport.

The initiating factors may take the form of chemical or physical carcinogens, ionising radiation, viruses and inflammatory chronic conditions or hormones; these factors admit of geographic and occupational variations, age incidences and variation with social habits. Finally gene mutations may occur spontaneously. This may be an initiator or a promoter initiated by a combination with a promoter; there must be in each case an adequate dosage of each factor. When all these requirements are met, the stage is set for a mutation to occur (be it somatic or germ-cell). After a variable latent period (required for the abnormal cells to overcome local general defence mechanism, or according to the teleological view: the time required for this form of defence mechanism to "build up") a focal abnormality appears starting as a dysplasia and passing on to a "primary with metastasis".

CONCLUSION: A study of the various interrelated ways leading to the inception of cancer should point out the high risk persons and so facilitate early diagnosis, explain the increasing incidence of some types of cancer and shed considerable light on its eventual prevention.

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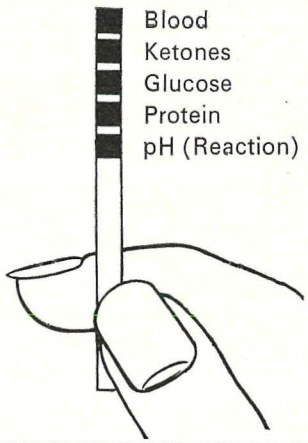
Labstix*

reagent strips for urinary pH, and the presence or absence of protein, glucose, ketones and blood in urine.



Blood	Read at 30 seconds after wetting
Ketones	Read at 15 seconds after wetting
Glucose	Read at 10 seconds after wetting
Protein	Read immediately
pH (Reaction)	Read immediately

Reference:
1. Jameson, R.M., Lancet, June 7th 1969, p. 1164.

Ames Company
Division of Miles Laboratories Ltd.
Stoke Court, Stoke Poges, Slough, Bucks.

Sole agent in Malta: Louis Vella Ltd., 168-170, Britannia Street, Valletta, Malta G.C.

*Trade mark

Non modo plus Alphosyl psoriasis curiae praescribitur quam quidquid aliud medicamentum...

Sed ecce Alphosyl capillare!

It's a fact. Alphosyl is the most widely prescribed product used specifically for the treatment of psoriasis.

Alphosyl Lotion. Alphosyl Cream. Alphosyl Shampoo.

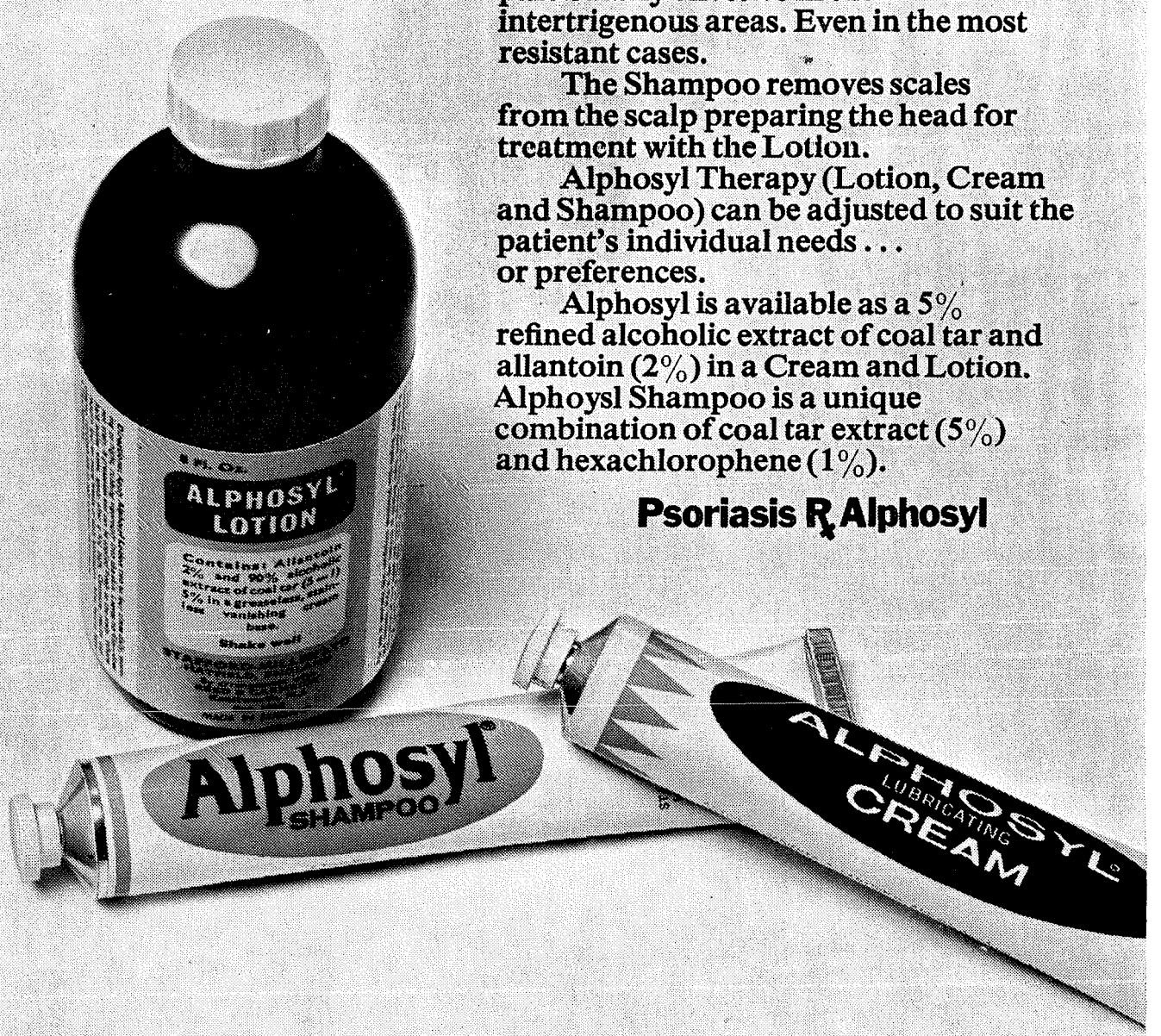
The Cream and the Shampoo are recent additions. Alphosyl Cream is particularly effective in the intertrigenous areas. Even in the most resistant cases.

The Shampoo removes scales from the scalp preparing the head for treatment with the Lotion.

Alphosyl Therapy (Lotion, Cream and Shampoo) can be adjusted to suit the patient's individual needs . . . or preferences.

Alphosyl is available as a 5% refined alcoholic extract of coal tar and allantoin (2%) in a Cream and Lotion. Alphoysl Shampoo is a unique combination of coal tar extract (5%) and hexachlorophene (1%).

Psoriasis $\mathbb{R}_x$ Alphosyl



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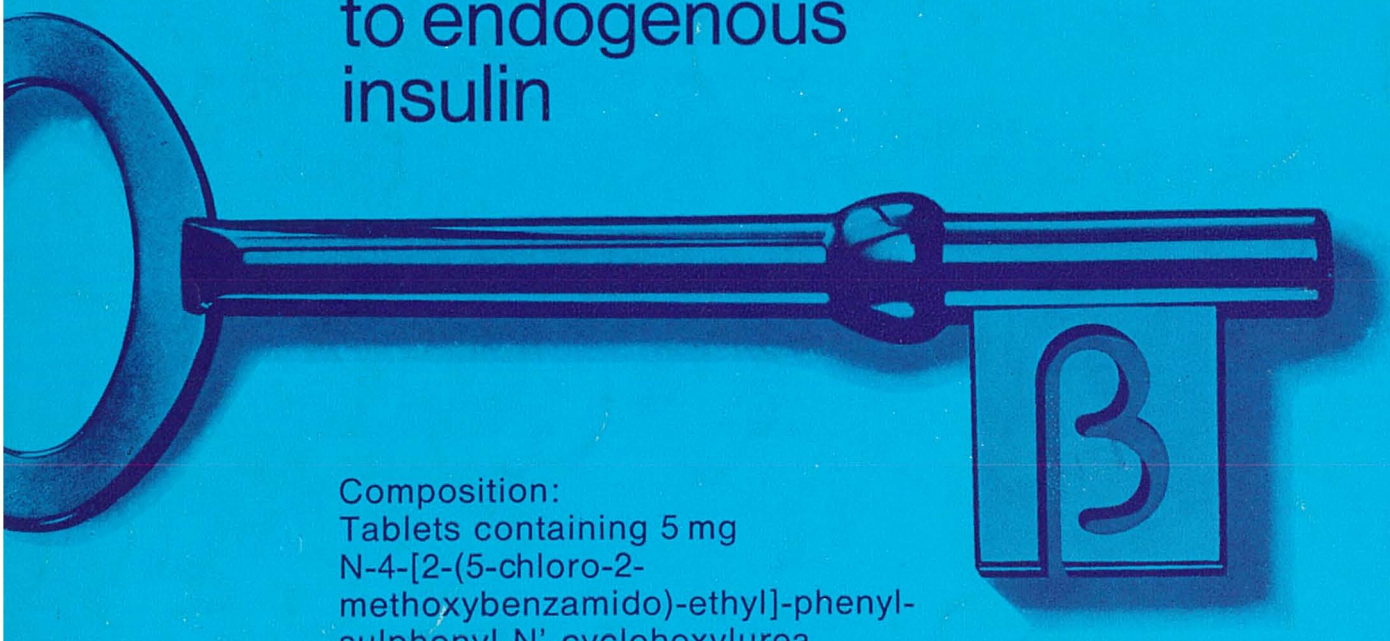
The new key to endogenous insulin



Composition:
Tablets containing 5 mg
N-4-[2-(5-chloro-2-methoxybenzamido)-ethyl]-phenyl-sulphonyl-N'-cyclohexylurea

HOECHST – a pioneer in diabetes therapy

Farbwerke Hoechst AG
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