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Medi-Scope

THE MEDICAL JOURNAL FOR STUDENTS OF MEDICINE AND SURGERY IN MALTA

DEVELOPMENT OF A HEALTH INFORMATION SYSTEM

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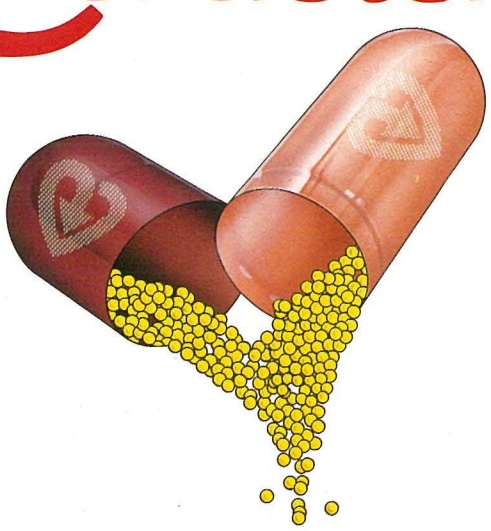

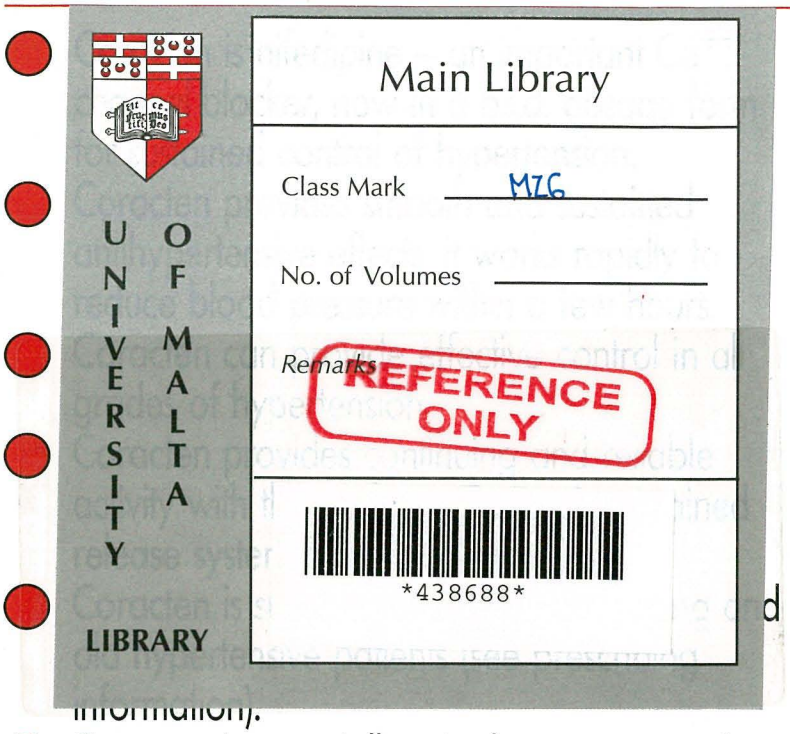

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Contra-indications, warnings etc.
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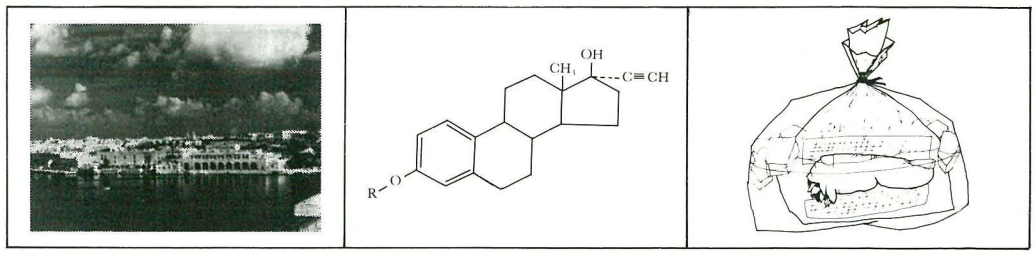

Editor's Letter

The second issue of Medi-Scope in its new format has now been published, and after our initial success, the editorial board is planning improvements to be made in coming issues.

Already the size of the journal has been increased, with more articles and advertisements. This has been done in preparation for issue 14, which will be published in 1500 copies and posted to dental students and dentists, as well as to veterinary surgeons.

Our principal goal, to rekindle interest in this journal, has been achieved, but there is still a paucity of articles and study aids, especially from medical students. I hope that our efforts to change this situation will be as successful as our efforts to improve this journal.

The Editor
15th October 1989

Cover Photo:
Computers in Clinical Practice
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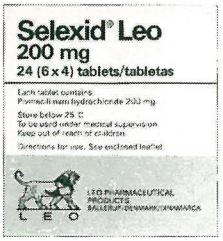

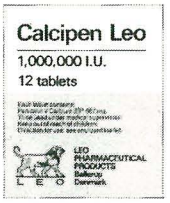

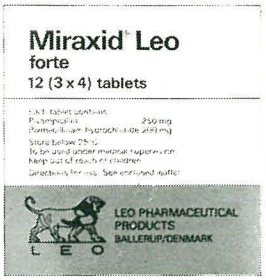

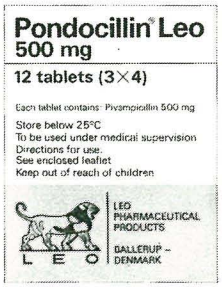

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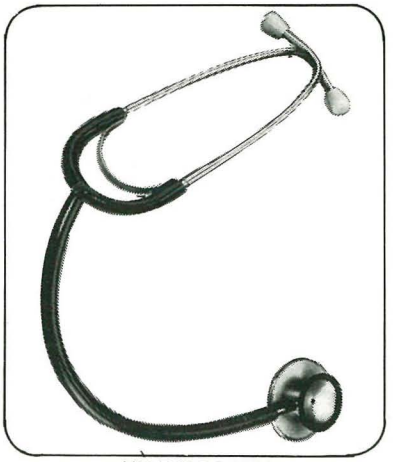

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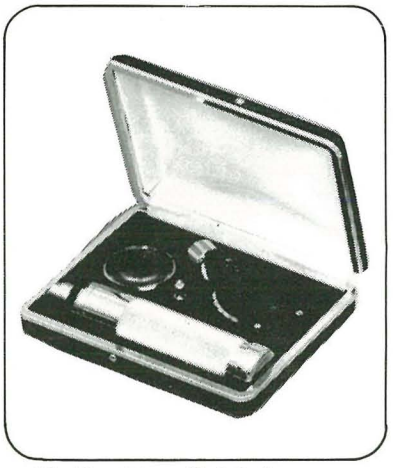

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DEVELOPMENT OF A HEALTH INFORMATION SYSTEM FOR THE MALTESE ISLANDS

Status quo and future plans for the Health Services Information Unit

JULIAN MAMO MD MSC (EPIDEMIOLOGY)
HUGO AGIUS MUSCAT MD
MIRIAM ELLUL MD
REINHARD LENICKER

Introduction

Among the 38 regional targets laid down by the World Health Organization for attaining the goal of "Health for all by the year 2000" is one entirely dedicated to the setting up of a Health Information System. Target 35 states that:

"Before 1990, Member States should have health information systems capable of supporting their national strategies for health for all."

So it was that in May 1983 a Health Services Information Unit (H.S.I.U.) was established with the following objectives:

(i) To provide a systematic and analytical basic source of information fundamental to health services and their development;

(ii) To ensure a critical evaluation of the development and implementation of health programmes in the light of predetermined health indicators;

(iii) To provide a computerised register containing comprehensive medical data on all persons coming into contact with the health services (this will eventually cover the entire population) with the aim of providing readily available clinical information to medical practitioners on the patients they are treating, of scheduling appointments and follow up procedures, of managing immunisation and the preventive programmes and of conducting surveys and research.

The original site of this Unit was at 6, Harper Lane, Floriana — the building now housing the Health Education and Nutrition Units. Since then the H.S.I.U. was moved to premises at the boundary wall of St. Luke's hospital which were opened in May of 1985.

Although the premises remain the same to-day, many of the original staff members and some of the priorities of this Unit have changed. The W.H.O. aims for information systems in providing support for the planning, monitoring and evaluation of health development and services; the assessment of national progress towards health for all; and the dissemination of relevant scientific information remain the terms of reference for this Unit. While medically qualified personnel now direct the progress of the Unit there has been a gradual replacement of staff by the technical grades whose training is dedicated to this line of work.

Functions presently carried out or in the process of being implemented by the Unit include:

(a) Vital Statistics Record Keeping

This involves the registration of data pertaining to Mortality (from Death certificates), Cancer registration/ notification, various infectious diseases (where notifiable) as well as a Non-Communicable Disease component consisting principally of the ongoing MONICA register of myocardial infarction.

(b) Services Information

Data relating to hospital admissions are presently stored for a limited period and used at the Hospital reception.

It is planned to start collecting limited data on hospital discharges similar to a system used in other countries. In addition, staff registers are kept including lists of registered doctors, pharmacists and so on.

(c) Health Care Systems

These include the main clinical data systems stored at the HSIU through the COSTAR (Computer Stored Ambulatory Record) system. The collection of data from Health Centres is a prime example. At the present time this is collected only from the Floriana Centre although plans are underway to have all Health Centres included in this scheme by 1990.

Also some data is stored on COSTAR from St. Luke's Hospital. This includes data from the Diabetes Clinic at which data is input directly on terminals placed at the clinic; and the Obstetrics and Gynaecology department where data is collected on forms and sent for 'capturing' to HSIU.

(d) Health Care Support Systems

These include a number of ancillary services to offer enhanced administrative support for the health services. A "Master Index" of all hospital files is kept and maintained in collaboration with the records section of St. Luke's

Hospital. Appointments are also scheduled through a system utilized by the hospital reception. There is also a separate system at the Diabetes Clinic for retaining and utilizing data pertaining to "Blue Cards" i.e. anti-diabetic free drugs.

(e) Surveys

Each year support is offered for individuals or groups undergoing large scale surveys. These include the MONICA project which undertakes 5-yearly large sample surveys of the Maltese population for cardiovascular risk factors. The Diabetes Program had also been supported in its various stages in previous years. For 1989 much support was given to the Eye Disease Survey, largely related to Glaucoma studies.

Other smaller studies were undertaken or supported such as the Smoking Survey on attitudes and habits of Health Personnel presently being analysed.

(f) Surveillance

Other forms of surveillance (ongoing data collecting and monitoring) besides the above have been supported or proposed for the future. These include the formulation of a questionnaire for monitoring patients at the Coronary Care Unit and detailing of a plan for its computerization. Plans are also underway to support the Emergency and Admission Department of St. Luke's Hospital in a similar endeavour.

With regard to infectious diseases, besides the collection and reporting of statistics, notifications are also processed for the co-ordination of community control.

As can be seen an ambitious plan is underway for the provision of a better system for the collection and utilization of medical and related data. A configuration of the proposed plan for the computerization and linkage of data is represented in Figure 1 and a sub-unit of any one peripheral section e.g. a health centre or a hospital department in Figure 2.

Two important facts must be borne in mind when considering the implementation of any computerization system:

1. A computer only stores whatever is collected and captured.
2. The extraction of data from computers is not always a straightforward process. It is often limited by the software provided and the

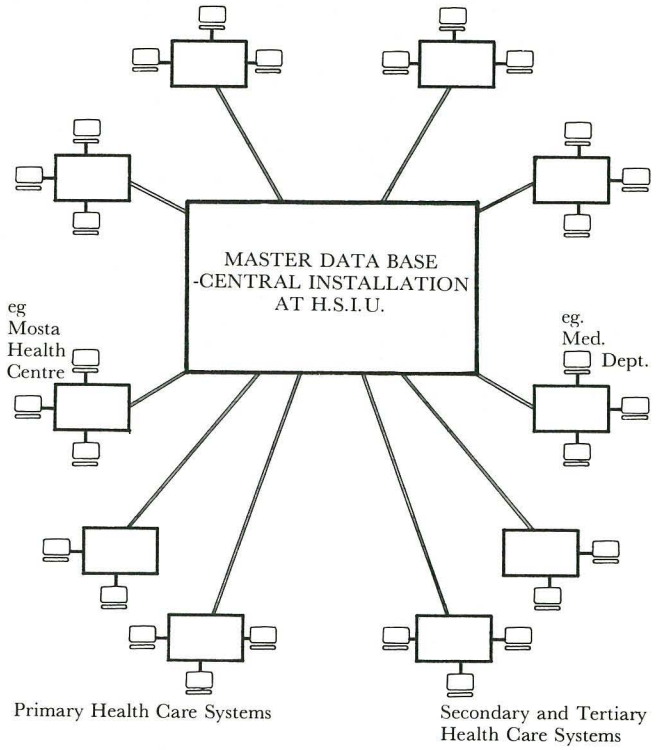

Figure 1: Computerized set-up and record linkage Digramatic representation.

Note: While the central installation would act as a main data base with "back ups" of all sub databases, many independent processes would be carried out at the peripheries.

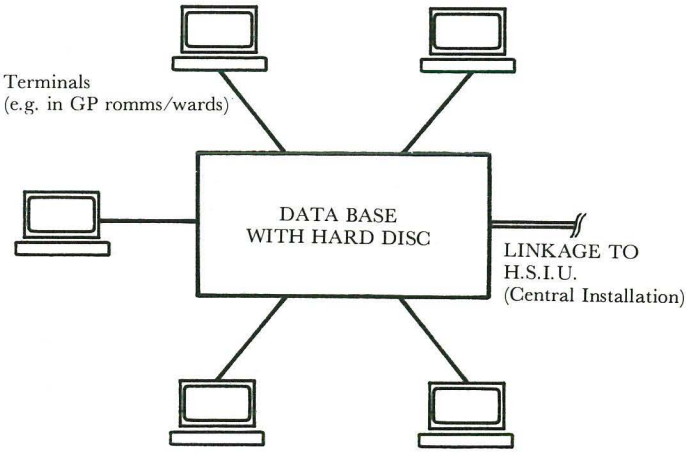

Figure 2: Computer set-up and linkage in a Peripheral Unit e.g. Health Centre/ Hospital Dept.

Note: Data capture, updating, searches and analysis on the peripheral data base could be carried out at the peripheral Unit.

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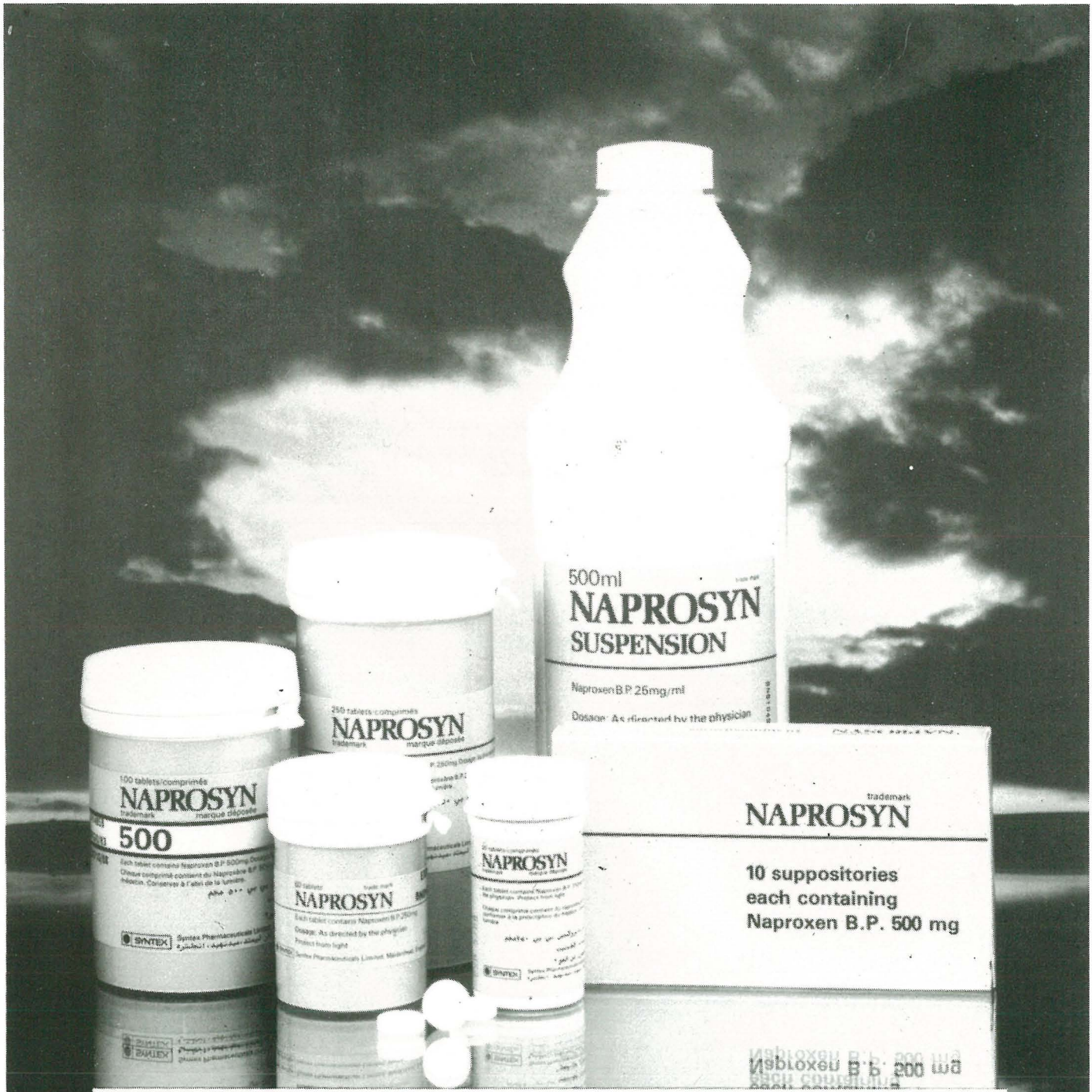

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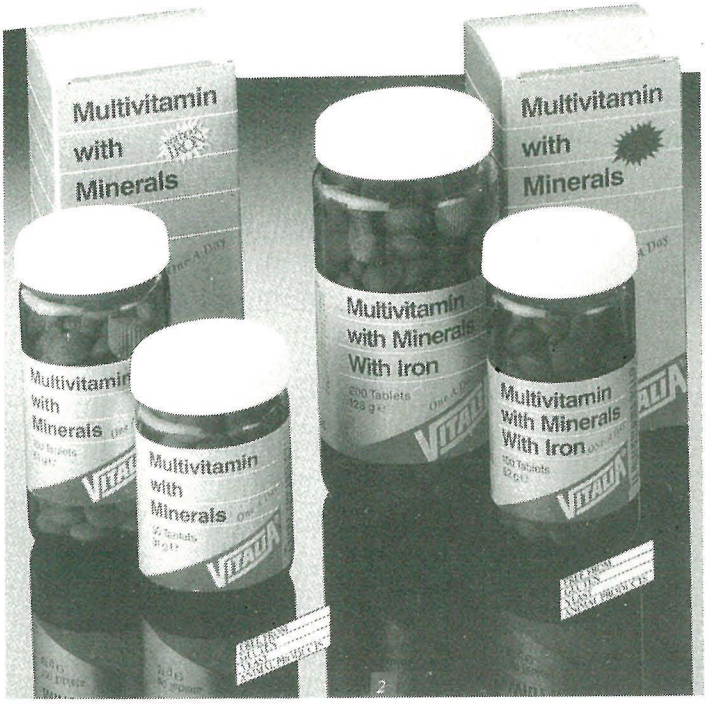

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Vitamin B12	3 mcg	Iodine	0.15 mg
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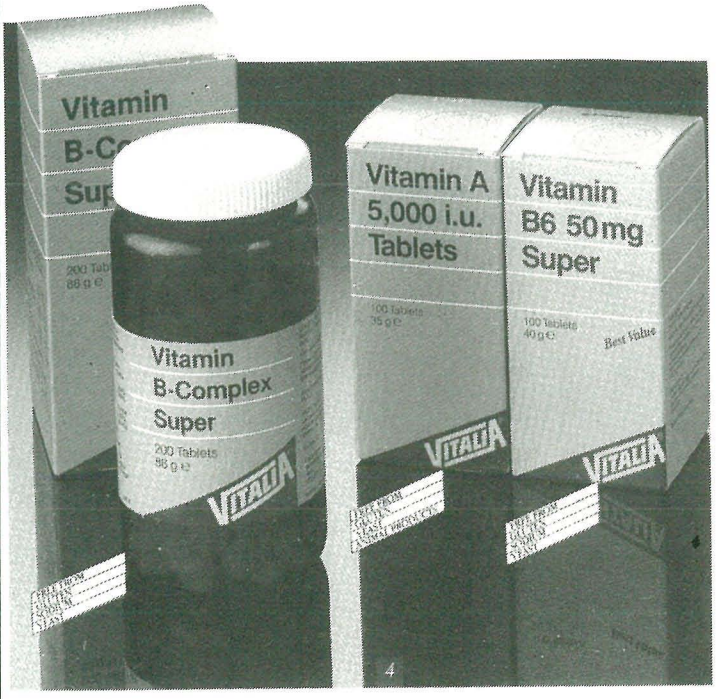

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TWO PATIENTS PRESENTING WITH RAYNAUD'S PHENOMENON & THE DEMONSTRATION OF CRYOGLOBULINAEMIA

A.P. AQUILINA MD DCP

Department of Pathology

Various tests in pathological conditions make use of an abnormal precipitation of proteins. Hence Bence Jones proteins which precipitate from heated urine are relevant in multiple myeloma. Precipitation of monoclonal macroglobulin forms the basis of the SIA Test. However most of these techniques have been replaced by electrophoretic and immunological methods. There remains a heterogenous group of conditions characterized by the presence of cryoglobulin where the demonstration of limited solubility remains a cornerstone in diagnosis.

The cryoglobulin precipitation tests was first described over 50 years ago[1]; it remains an essential investigation in the recognition of cryoglobulinaemia and is also useful in the detection of immune complexes in general.

Two patients both presenting with Raynaud's phenomenon in whom pathological quantities of cyroglobulin were present will be briefly discussed.

Case I

A 54 year old gentleman presented with a two month history of severe acrocyanosis and gangrene of four fingertips (three on right hand, one on left hand). He also complained of severe pain and tenderness over the middle and terminal phalanges. He was a Type I diabetic since 14 years of age. Apart from his presenting complaint, physical examination was unremarkable and peripheral pulses were normal. Relevant investigations showed:

Blood count and differential	— *Normal*
ESR	— *15 mm/hr*
Serum Creatinine	— *166 umol/l (80-124)*
Creatinine Clearance	— *25 ml/min*
ANF (latex aggl.)	— *Negative*
RA test	— *Positive 1:320 (N 1:20)*
Bence Jones Proteins	— *Negative*
S.P.E.: Alb	— *40 g/l (30-45)*
Gamma globulin	— *26.1 g/l (7-13)*
Immunoelectrophoresis	
	IgG 2800 mg/dl (710-1540)
	IgA 681 mg/dl (60-490)
	IgM 270 mg/dl (37-204)
B.M. aspirate	— *Normal findings*
CXR	— *Normal*
Abdominal C/T Scan	— *Normal*
Cryoglobulin	— *96 mg/dl*
Immunoelectrophoresis of purified cryoglobulins	— *IgM & IgG*

Case II

A 21 year old lady presented with a 6 month history of acrocyanosis involving the digits of both hands and feet. The only other relevant point on examination was the presence of livido reticularis of both lower limbs. There was nothing else of relevance in her history.

Investigations:

Blood count and differential	— *Normal*
Serum creatinine, U&E	— *Normal*
ESR	— *5 mm/hr*
ANF (latex aggl.)	— *Negative*
RA	— *Negative*
Cryoglobulin	— *36 mg/dl*

Detection and Analysis of Cryoglobulin

It is important to adhere strictly to an optimal technique in detection of cryoglobulins. This is because the temperature at which cryoglobulins begin to precipitate from serum varies considerably and may be as high as 35°C in some patients.

The syringe and blood container should be preheated to 37°C. Blood is collected and kept at 37°C for 4-6 hours, allowing a clot to form and retract. The serum is then collected in a graduated pipette and stored at 4°C for a period of seven days. If cryoglobulins are present, floccula are seen to develop and a deposit may form at the bottom. The next steps involve quantitative and qualitative analysis of the cryoglobulins. The pipette is centrifuged and the precipitate washed, redissolved and reprecipitated four times in saline at 37°C and 4°C respectively. The precipitate is then finally dissolved in acetate buffer at pH 4 at room temperature. Failure to detect a cryoglobulin (false negative result) may be due to loss of the protein due to adsorption on erythrocytes membranes if clotting of blood occurs below 37°C. Cryoglobulin may also become adsorbed to serum lipids and remain suspended as floccules. (Normal subjects are occasionally observed to have cryoglobulins in the range of 80-100 ug/ml, but such trace amounts are not apparent on gross inspection).

The extent to which a purified cryoglobulin is further analysed immunochemically depends on what information is sought and on what facilities are available. For routine characterization, electrophoresis and immunoelectrophoresis using antisera to whole human serum, to γ, μ and α chains and to κ and λ chains will suffice. This will enable cryoglobulins to be classified into single components or mixed types.

Classification of Cryoglobulins

Brouet et al, have developed a practical scheme for classifying cryoglobulins. This is based on immunochemical characterization of immunoglobulins as monoclonal or polyclonal.

TYPE I: Type I cryoglobulins are composed of monoclonal immunoglobulin usually IGM or IgG, rarely IgA. Usually the immunoglobulin is present in the serum in high concentrations (more than 5 mg/ml). These patients often have

multiple myeloma, Waldenstrom's macroglobulinaemia and other lymphoproliferative diseases.

TYPE II: This type of cyroglobulinaemia consists of a monoclonal component which has Rheumatoid Factor Activity (usually IgM) and a polyclonal IgG which behaves as an antigen for the IgM rheumatoid factor. This type also occurs in lymphoproliferative and autoimmune diseases but is characteristic of Essential Mixed Cryoglobulinaemia.

TYPE III: This is the most common type and consists of a polyclonal immunoglobulin (usually IgM) with rheumatoid factor activity and a polyclonal immunoglobulin (usually IgG) which again behaves as the antigen for the rheumatoid factor. Type III cryoglobulinaemia is associated with autoimmune disorders and persistent infection e.g. bacterial endocarditis. Unlike Type I and Type II, the amount of cryoglobulin is usually low (less than 1 mg/ml).

Clinical Correlations of Cryoglobulinaemia

The most common clinical features are related to cutaneous manifestations, usually vascular purpura and Raynaud's phenomenon. Acrocyanosis occurs only in a minority of patients.

In a review of available literature the following manifestations were found in decreasing frequency: arthritic pains, evidence of glomerulonephritis, neurological disorders (usually peripheral neuropathy), coagulation abnormalities (predominantly haemorrhage) and unexplained abdominal pain (Ref. Table 1).

Comments

Digital gangrene and cold or exercise-induced purpura have been closely associated with cold insoluble immunoglobulin, especially mixed cryoglobulins with antiglobulin activity. However, the 'in vivo' role of cold agglutination and precipitation as regards pathogenesis of the illness has not been confirmed. It is also possible that vascular injury and cryoprecipitation are both manifestations of circulating immune complexes and are coincidentally found together.

The management of cryoglobulinaemia obviously lies with this cause. In mixed essential cryoglobulinaemia (which is a classical example of an immune complex disease), plasmapheresis is the treatment of choice.

Concluding, it is worth stressing that demonstration of proteins with inherently limited solubility remains a valuable diagnostic measure in these syndromes as well as a useful guide to prognosis and therapy.

TABLE 1.
Review of literature (296 patients) with the incidence of signs and symptoms and indicating symptomatology of the two patients presented.

Manifestations	*Incidence*	*Patient 1*	*Patient 2*
Cutaneous	86%	x	x
Arthritis	34%		
Nephritis	36%	x	
Neurological	20%	x	
Haemorrhage/Thrombosis	5%		
Abdominal pain	2%		

Acknowledgements

Professor A.J. Psaila M.D. D.C.H., F.R.C.P. and Mr D. Gatt L.R.C.P. F.R.C.S. allowed me to study their patients.

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hardware on which it is run. Faults and breakdowns of systems are not rare.

Conclusion

The need for the provision of an enhanced system for information for health has long been felt. Efforts are underway for establishing a manageable system of capturing and recording such data which could prove useful in various clinical, epidemiological and administrative functions. It now rests with all concerned individuals to play their part and dedicate more time and effort towards proper record keeping, which is essential for informed decision taking.

The HSIU acknowledges the efforts of the Health Department, and particularly the persisting support of Dr. Alfred Grech in this project. The progress made on the project so far is largely due to the tireless work of all past and present staff at the HSIU. We are also grateful to the expertise and support of the World Health Organisation. Special mention must be made of Sir Henry Yellowless, Mr. K. Floisand and Mr. M. Subramanian of the Regional Office for Europe.

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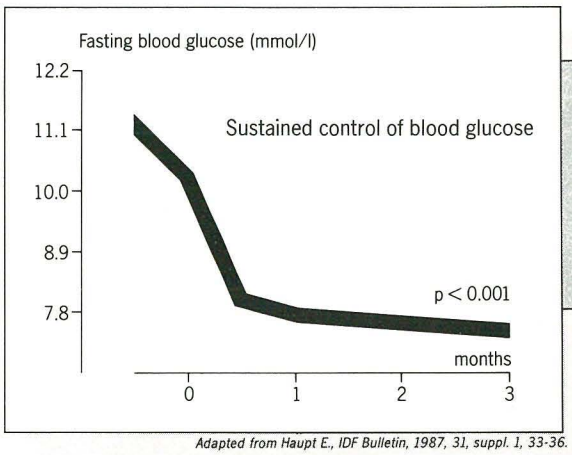
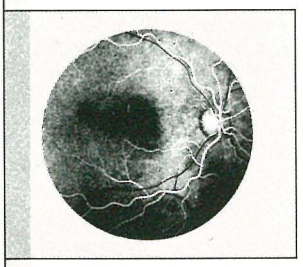


Adapted from Haupt E., IDF Bulletin, 1987, 31, suppl. 1, 33-36.



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(6) : Ponari O. et al., Thromb. Res., 1979, 16 : 191-203. (7) : Daver J. et al., Sem. Hôp. Paris, 1973, 49 : 279-82. (8) : Almer L.O., Thromb. Res., 1984, 35 : 19-25. (9) : Duhault J. et al., Ophtalmologica, Basel, 1975, 170 : 345-52.

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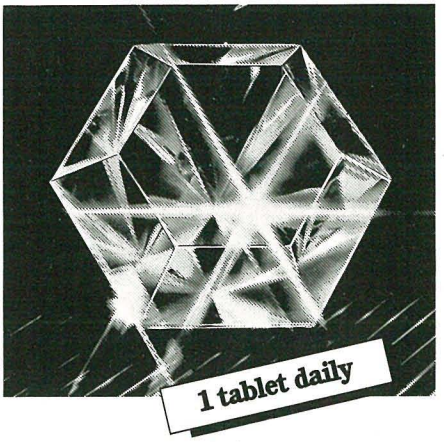

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CLINICAL CASE HISTORIES AND POST MORTEM REPORTS FROM THE MALTA LAZZARETTO IN THE 18TH CENTURY

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Hon. Fellow of the University of Malta

The theme of this paper derives from the unpublished manuscript records of the Registers of Ships arriving in Maltese ports and held in quarantine from 1739 to 1801[1].

Clinical case histories from other contemporary hospitals — the Holy Infirmary and the Women's Hospital at Valletta, Santo Spirito Hospital at Rabat (Malta) and the Gozo Hospital — have not been met with. The Lazzaretto case histories are the only ones that have reached us and, wanting as they are in details of their contents, they constitute the only means of improving our knowledge of the pattern of disease in Malta two hundred years ago.

They occur in the form of entries written by the *attuario dell'Officio della Sanità di Malta* or Registrar of the Sanitary Commissioners whose office was at the *Barriera* at Valletta[2]. The *attuario* was a layman and it is likely that what he wrote was dictated to him by the *barberotto* (barber-surgeon) or by the physician attending the case; or, occasionally, by the *protomedico* or Chief Government Physician examining the patient.

The text is cast in the Italian language of the period with misspellings, at times, of the names of the organs and pathological findings. The entries are here reproduced in English but an attempt has been made to preserve as much as possible the flavour of the Italian original by giving, in some instances, an *ad litteram* translation.

Ascribing a retrospective diagnosis has created some difficulty as the clinical information contained in the records is not always sufficient and clear enough to allow identification of a specific disease. However, a tentative diagnosis has been attempted for the purpose of grouping and classifying the various case histories.

Injuries

Skull

1. On the 28 March 1781 a soldier on a French warship fell and hit his head. He sustained a contusion of the right temporal muscle without any external wound or fracture; but the concussion of the brain and the resulting extravasation of blood in its substance caused his death — and this (diagnosis) is confirmed by the extrusion of a quantity of blood from the corresponding ear[3].

2. Following a fist fight on 9 November 1782 among five Turks undergoing quarantine at the Lazzaretto one of them, aged thirty years, died from the blows received. Observation of the cadaver showed the discharge of a substantial quantity of blood from the right ear and from the nose — from which one necessarily infers that the victim had been hit on the head though there were no signs of an external lesion; in fact a contusion of the brain substance is enough to produce an internal extravasation of blood as confirmed by the exit of blood from the parts mentioned[4].

3. On 1 November 1783 a Moslem captive of twenty years of age was admitted to the Lazzaretto with a fracture of the skull in the left parietal region caused by a ball shot from a fusil (light musket). This caused a "natural trephine" opening (of the cranium) with exposure of the *dura mater*. An abscess formed under the *dura* and when this was incised there was a discharge of pus and cortical substance of the brain with fragments of bone. He died nine days after[5].

4. A seaman of thirty years fell from a tall mast on 10 February 1798. He hit the deck and with the impact went overboard. On being recovered from the sea he was deeply unconscious. He sustained two wounds in the occipital region — one on the left side and the other on the posterior aspect of the bone. Death was due to haemorrhage in the substance of the brain as confirmed by the issue of blood from the nostrils, the left ear and also from the mouth[6].

Face

On 1 November 1783 a French seaman aged thirty years was admitted to the Lazzaretto with a fracture of the face caused by a fire-arm. The missile traversed the lower jaw, fractured its two joints, amputated the tongue from its roots and tore the mastoid muscles rendering him unable to chew. He survived for thirty-nine days dying on the 9 December 1783[7].

Multiple fractures

A captive Turk, thirty years of age, died on the 22 February 1794 from three wounds, received during a combat at sea twelve days previously, caused by a blunt instrument. The first was a "simple wound" on the left side of the sternum; the second involved the left hand with fractures of the index, middle and ring fingers; the third was a "complete" wound of the left thigh complicated by a comminuted fracture of the upper end of the femur near the (hip) joint. This was accompanied by bleeding from a severed arterial trunk. It ended in gangrene — a sufficient cause for his death[8].

Note: Nearly all those recoreded as having had open and comminuted fractures produced by gunshot died of gangrene.

Internal organs

1. A Maltese sailor of a corsairing vessel aged forty years committed suicide by shooting himself with a pistol on 25 August 1781. The projectile entered the left thoracic region between the third and fourth ribs near the sternum. It penetrated the lobe of the lung obliquely and got lodged beneath the lower end of the scapula[9].

Note: Presumably a *post mortem* was performed in this case since the tract or trajectory of the projectile has been so well followed.

2. On 7 August 1780 a captive Turk aged forty-five years died at the Lazzaretto from a wound caused by a cutting instrument. It was situated in the lateral side of the left knee-joint involving the ligaments and tendons of the articulation. It was followed by swelling and inflammation (of the leg) extending to the tip of the foot. He finally died of gangrene[10].

Cancer

Lip

On 4 August 1776 a French sea-captain asked to be admitted to the Lazzaretto to be treated for a cancer of the lower lip that was still in the initial stages[11].

Tongue

The Consul of Sweden in Tripoli came to Malta on 4 August 1778 suffering from cancer of

the tongue. After undergoing the prescribed period of quarantine at the Lazzaretto, he took lodgings at the Falcon Hotel to be treated for his condition by the *protomedico* Dr. Lorenzo Theij (or Thein). However, it was found to be too diffused and the patient died soon after. He was buried *in pratique* in the external ditch of the Lazzaretto[12].

Upper maxilla

A Greek seaman, aged fifty years, was landed at the Lazzaretto on 10 April 1781 with a scirrhous tumour on the right cheek and upper maxilla from which he had been suffering for the previous three years. The growth eventually "degenerated into a true carcinoma. As the carcinous virus (*sic*) spread, the affected part became inflamed with recurrent bleedings from the mouth. In the end fever supervened and carried him off"[13].

Note: It is not recorded what kind of treatment was carried out for the lip cancer and what was the outcome. In the case of the tongue cancer, it does not appear that any surgery was intended as Dr. Lorenzo Theij was a physician and no physician, in those days, would do any surgery. As regards the place of the patient's burial, it is known that there were no less than six graveyards at the Lazzaretto one of them being reserved for Protestants and Lutherans and called the *cimiterio esteriore*.

Concerning the third case, the word *virus* is not used in the modern connotation of an infective agent but in the literal Latin meaning of "poison".

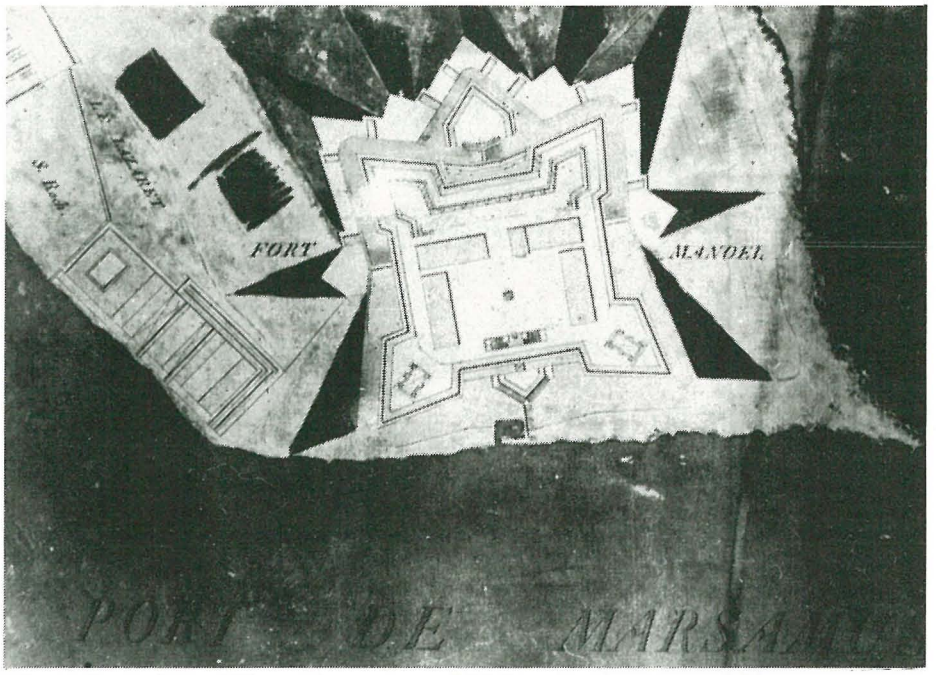
Medical Illnesses

Scurvy

1. On 26 May 1782 a Venetian ship arrived from Bergen (Norway) which it left four months earlier on 16 January. It was carrying a cargo of lead for Venice. It landed seven seamen out of a complement of twelve to perform quarantine at the Lazzaretto and at the same time receive treatment for the scurvy[14].

2. A Venetian warship brought a sailor of forty years to the Lazzaretto on 18 February 1784 suffering from long-standing scurvy but having become worse during the past two months. He had diarrhoea, tenesmus, bloody stools, continuous fever, emaciation and a cachetic habitus. He died[15].

Note: Though these two cases were diagnosed as scurvy in the *attuario's* entries, the clinical picture is not convincing. Admittedly the diet of seamen, consisting mainly of biscuits and salted meat without fresh vegetables and fruits, was likely to produce a state of sub-clinical scurvy; but in the two cases under review there is no mention of such common signs of scurvy as joint symptoms from bleeding around or into the joints, ecchymoses into the skin of the lower limbs, spongy and bleeding gums, etc. Indeed the vagueness of the clinical picture raises the possibility that the first case was lead poisoning from contamination of the food and water on board the ship; and that the second case was one of chronic bacillary dysentery with secondary malnutrition and vitamin deficienty



A section of an 18th century map of Malta showing part of Marsamxett or Quarantine Harbour with Fort Manoel and the Lazzaretto (left). *(Courtesy National Archaelogical Museum, Valletta).*

Typhus

On 26 January 1786 a Venetian warship with a crew of two hundred and ten men came from Corfu and landed thirty-four sailors at the Lazzaretto suffering from putrid and malignant fever with petechiae. Only eleven of them were subsequently discharged recovered[16].

Note: There is mention of an earlier patient with "malignant fever with petechiae" being admitted to the Lazzaretto in August 1762.

Since the 16th century typhus was known as the "petechial disease" and was ascribed to "corruption of the air and the breath by filth" from men crowded in small enclosed places.

Were the Maltese cases louse-borne? It is of interest to read in the *attuario's* register that in February 1755 a Moor of sixty years died on board a caique. When "viewed" by the *protomedico* he was found to be "a mere skeleton ... eaten up by lice"[17].

Plague

1. On 14 May 1785 a seaman from a Maltese corsairing galiot sickened with fever, headache and vomiting. He had a sticky tongue. A bubo appeared in the right inguinal region but subsided after two days. Another bubo developed in the left groin but this, too, disappeared after seven days and he became symptom-free. However, after a respite of eight days the fever recurred with the bubo in the right groin. The bubo was incised but although its pus was evacuated the tissue passed into a state of necrosis. A copious diarrhoea supervened and he died of true plague. His body was burned and the ashes thrown into the sea[18].

2. The captain of a Venetian polacre arrived in Malta on 18 May 1786 complaining of having fallen sick during the voyage from Tripoli (in Barbary) where there was the plague. He had severe headaches. On examination there was a carbuncle in the carpal region of the left hand which eventually became gangrenous; a swelling in the right parotid; and gangrenous blotches over the entire skin surface of the body — "all evident signs of true plague from which he died as certified by the *protomedico*". His corpse was burned and the ashes thrown into the sea[19].

3. A thirty-year old sailor was landed at the Lazzaretto from a Ragusean ketch on 18 November 1787. He had been suffering from a "continuous malignant fever" for the previous eighteen days with bouts of delirium, a sticky tongue, violet coloured petechiae on his trunk and convulsive movements. On the ninth day of his illness there appeared swellings of the parotid glands and, although one of them was incised, the swelling involved the internal structures (of the neck) and "injected its poison as far as the vital region (the heart) causing stertorous breathing which carried him off".

Although no signs of plague were observed, wrote the *attuario*, the case was regarded as one of plague and, with the aim of protecting the public health, the cadaver, bedding and clothing were disposed of by burning"[20].

4. A sailor, aged forty, arriving on a French warship from Constantinople on 11 April 1788 died at the Lazzaretto on the seventh day of an illness characterised by fever, headache, dry tongue, an insatiable thirst, the eruption of a bubo in the right inguinal region and the appearance of violet blotches in the skin. He finally passed into a marked delirium and died within a few hours.

His corpse was burned and the ashes thrown into the sea[21]

Note: The problem of protecting Maltese territory from invasion by plague from overseas had been an issue of extreme concern for state officials and the health authorities since at least the time of the Black Death of 1348. Elaborate precautions in the form of a quarantine system were later devised to prevent "contagious" or contaminated persons and merchandise from conveying the "contagion" of plague to the inhabitants. Devastating invasions of the disease in 1592-3 and 1675-6 had wrought great mortality and crippled communications and trade. The microbial origin of the illness (*Yersinia pestis*), the rat-flea chain of conveyance to humans (*Rattus rattus* and *Xenopsylla cheopis*) was then unknown. In their ignorance the health authorities saw their only security in the strict isolation of the plague-stricken at the Lazzaretto and the total annihilation of the diseased corpses by fire.

Parotitis

A Spanish seaman, twenty-six years old, died of a malignant fever, from which he had been suffering since five months, on 2 March 1792. A swelling had appeared in the right parotid seven days before his death. It subsided along with the fever before it could be incised. It reappeared after a few days, festered and kept discharging pus inspite of the remedies applied. "The absorption (of the pus) by the blood (stream) caused a slow, continuous fever which led to a marasmus that eventually brought about his death"[22].

Note: Was this a case of bacterial parotitis arising from a streptococcal infection of the throat? or a malignant tumour of the gland complicated by an abscess? or an obstruction of Stensen's duct by a calculus with a supervening secondary infection?

Liver disease

A French sailor of fifty-six years had been labouring under a "chronic indisposition" for four months before he was landed at the Lazzaretto to undergo quarantine on 12 July 1788. He had dropsy which disappeared after fifteen days of treatment. This was followed by bouts of fever at intervals of a few days from which he recovered completely. However, because of the long-standing "obstructions involving the region of the liver and because of the corruption of the bile" due to the excessive use of wine, he completely lost his appetite and developed an aversion to food. The lack of nutrition led to great weakness and death[23].

Note: Is this an instance of viral or amoebic hepatitis complicated by alcoholic cirrhosis?

Peripheral arterial occlusion

A sailor (age ?), admitted on 28 February 1757, had fever for twelve days after which he developed necrosis in the left hand and in two fingers of the right one with initial gangrene in his cheeks and in the left pinna (external ear) together with jaundice. He survived and was granted pratique after a two months stay at the Lazzaretto[24].

Note: Presumably this was a case of perpheral arterial occlusion (thrombosis?). Was it a vaso-spastic disorder such as Raynaud's Disease? Or an instance of ergot poisoning complicated by liver obstruction? How did the blood supply — and to what extent — re-establish itself?

Heart disease complicated by alcoholism

Surgeon Pietro Galea from Valletta but living at Siggiewi, forty years of age, died on board the corsairing xebec on 31 December 1782. During the previous four months — and perhaps earlier — he had been suffering from recurrent shortness of breath accompanied by pain in the region of the sternum and complaining of a dry distress-

The Lazzaretto today — as seen from Valletta. *P. Zammit.*

ing cough. He refused all forms of relieving measures; in fact, instead of availing himself of the necessary remedies, he often abused of wine which ultimately produced inflammation and suppuration in the lungs. In the end he was seized with excruciating pain in the region of the heart and died[25].

Post mortem Caesarean section

On 11 December 1780 a woman passenger of twenty-three years was eight months pregnant when landed at the Lazzaretto suffering from malignant fever. An Assistant Surgeon (*Prattico di chirurgia*), Fedele Zammit, was sent to the Lazzaretto to attend to her and to be in readiness on the spot "to open the body in the event of the patient's death and save the baby if possible". The woman died on the 13th. A Caesarean Section was immediately carried out. A male baby was extracted but he died after an hour[26].

Note: The preoccupation of the Catholic Church with the performance of Caesarean section on dead pregnant women goes back to the Middle Ages when the church counselled the carrying out of the operation immediately after the death of the mother. In Malta an edict of the Archbishop Fra Vincenzo Labini (1788) obliged the parish priest to perform it himself "under a grave sin" in the absence of a surgeon[27].

Concepts of Aetiology

Physicians were not familiar with the aetiology of illness for there was as yet no real physiology and pathology of disease much less of the causal role of microbes as agents of sickness.

The "bad air" arising from marshes in the Greek regions of Patras, Nauplia (Napoli in Romania) and the Gulf of Arta were blamed for the occurrence of quotidian, tertian and quartan fevers from which mariners in the Mediterranean often suffered especially in the summer season[28].

On 20 October 1688 the Galley Squadron of the Order of St. John, consisting of eight ships, returned to Malta from Negroponte (Greece) with five hundred thirty two sick men described as "one hundred seventy-seven with fever, nineteen at the point of death and three hundred and forty convalescents". The physician of the squadron, Dr Pietro Paolo Bonnici, reported that the illnesses consisted of tertian fevers and fluxes (dysentery). The sick were taken to the Lazzaretto where thirty-seven of them eventually died[29].

The same squadron, on 4 October 1691, brought three hundred and eight sick men from Corfu (Greece) of whom one hundred and eleven suffered from fevers and the rest were convalescing from "tertian fevers and fluxes"[30].

"Foul vapours" emanating from passengers crowded in restricted compartments and corridors on board ships were also regarded as causative of fevers[31].

Diagnosis

Physicians based their diagnosis on the account of the illness as narrated by the patient and on the observation of such clinical phenomena as the type of fever (tertian, quartan, etc.), skin discolouration (jaundice and petechiae), recognition of a pox, swelling of lymph glands and dropsy. The feeling of the pulse, the inspection of urine, faeces and sputum also formed part of the diagnotic procedures. On the whole medical diagnosis was based upon personal experience and familiarity with similar cases.

Surgeons, on the other hand, reached more rational and accurate diagnostic deductions because they had a good grounding in human osteology and myology; of the location and mutual relationships of internal organs; and a wealth of experience derived from the frequent occurrence of external trauma in those days of combats at sea.

Treatment

A section of the Lazzaretto, known as the *infermeria*[32] was set apart for the treatment of the wounded by the barber-surgeon (*barberotto*) and of the sick by an Assistant Physician (*prattico*). These practitioners were members of the professional staff of the Holy Infirmary of Valletta or of the Galley Squadron of the Order of St. John and were sent to the Lazzaretto as the occasion arose. This arrangement had become standard practice by the 14 October 1684[33].

At the end of their duties, this personnel had to spend a term of quarantine before they were allowed to leave the Lazzaretto and return to their posts at the Holy Infirmary or the Galley Squadron because they had been in contact with passengers and crews under surveillance for the possibility of harbouring "contagious" maladies[34].

When patients were numerous, a hospital attendant (*serviente*) from the Holy Infirmary was also sent to nurse the sick and wounded; but, at times, crew members of the ship that had disembarked its injured and sick at the Lazzaretto were sent to this establishment to assist in the nursing of their shipmates[35].

Cases of suspected plague were examined by the *protomedico* and dealt with according to his instructions[35]. He likewise examined cases of "lung diseases with fever" and when these were found to be suffering from phthisis their clothes were burned at his order[36].

The clinical case histories contain only fragmentary information about the type of treatment given beyond brief references to evacuation of pus from incised abscesses and from the brain substance in open fractures of the skull; amputation of limbs with gangrene or with open comminuted fractures; and the removal of musket balls from muscles[37].

Surgical operators were impotent in tackling internal injuries because there was as yet no chest and abdominal surgery since the concepts and practice of asepsis and anaesthesia were still a century away in the future.

For medical cases there was little to offer beyond phlebotomy which was useful in some instances of apoplexy and heart disease but harmful in other conditions such as acute infections. These bleedings were carried out by the barber-surgeons. These practitioners had no academic standing and could only apply external medications but were not allowed to prescribe internal remedies. All this was in line with the accepted division of the medical and of the surgical roles then prevailing in the healing profession in Europe.

Post Mortem Examinations

Patients dying in quarantine were buried in one of the graveyards enclosed within the Lazzaretto complex; but before burial the body was "viewed" or inspected externally for any signs of "contagious" illness, the wording of the official entry being "after the usual viewing of the cadaver in which no signs of a contagious illness were observed"[38]. The "viewing" was done by the *protomedico* — a practice that was already established by 1660[39].

It is not recorded what signs of a "contagious illness" the *protomedico* looked for but presumably these were the clinical manifestations usually associated with bubonic plague i.e. ecchymoses in the skin and the swellings of lymph glands in the inguinal, axillary and cervical regions. These swellings, known as bubos, sometimes formed abscesses with

suppuration. This clinical picture was considered to be so pathognomonic of plague that it could be diagnosed without the evidence of a post mortem examination. Occasionally, however, one comes across records of an autopsy having been performed.

A French steersman of thirty-seven years died on 18 September 1750 "of an acute febrile illness from inflammation of the lungs and of the liver ... as was demonstrated by the opening (of the cadaver) and by the minute observation of the lungs and liver"[40].

A laconic entry of 12 September 1767 states that a sailor died of phthisis and a post mortem examination was performed "as a measure of greater security" to ensure that the internal organs showed no changes suggestive of a "contagious malady".

Another brief reference to an autopsy is that carried out in December 1769 on the cadaver of the clerk of a French vessel who was found to have died "of inflammation of the lungs"[41].

The most detailed description is that of a sea-captain who, on 6 January 1769, was found dead in his cabin when this caught fire. The record states:

"The cranium was opend to find out the cause of death. It was ascertained that he died of apoplexy from inhaled smoke. As a result of the obstructed respiration, there was a blocking of the blood flow in the brain so as to produce an extravasation of blood"[42]

Apart from plague, no other manifestations of "contagious" diseases seem to have been regarded as presenting a dangerous focus for an outbreak on an epidemic scale. In fact a passenger dying aboard a ship that entered Malta harbour in March 1752 was diagnosed as having smallpox yet his cadaver, following the usual examination by the *protomedico* was declared to have shown "no signs of a contagious illness". The same opinion was expressed in the case of a Venetian seaman who died of smallpox in September 1777[43]

Summary

Twenty-two clinical case histories of illnesses and injuries suffered by passengers and crews admitted to the Malta Lazzaretto in the 18th century with four post mortem reports are here studied and published for the first time.

These records furnish documentation for the reconstruction of the pattern of the medical experiences of our predecessors.

They reflect the health risks of life at sea in the days of sail in the Mediterranean two hundred years ago.

They add to our knowledge of the medical history of Malta.

They show how the dominant concern of the Government of Malta, through its Port Sanitary Authority, was the detection of cases of plague without delay and the application of their strict isolation within the precinct of the Lazzaretto — the only measure then available to prevent the introduction and spread of plague with its catastrophic devastation of the medical, social and economic life of the Maltese Islands.

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ENGINEERING IN THE BLOOD

For those of us who feel squeamish at the thought of a spider crawling up our legs, how about a creep-crawlie that gets inside the body and swims about in the blood stream? It's not a bad dream, nor even a good Hitchcock movie, just a sober project dreamed up by Professor Iwao Fujimasa and a team of engineers at Tokyo University.

If you recall the micro-robots being devised by the Massachusetts Institute of Technical Sciences for cleaning windows then this is just the same principle scaled down another couple of orders of magnitude. Fujimasa, whose work is being taken very seriously by companies like Toyota and Hitachi, believes that within ten years it will be possible to create micro-robots that can be injected into the body and which will be able to swim through the bloodstream to the site of some obstruction or lesion. There they'll perform an operation by remote control and then swim away when the job is complete. So seriously is this bizarre prospect being taken that the Japanese Ministry of International Trade and Industry (MITI) is expected to contribute about £20 million to get the work under way.

In engineering terms the obstacles are phenomenal. Today's chips are much too large for the control and communications aspects of the micro-robot; sensors and power supplies are even more so. But the truly amazing prospects are those of micro-miniaturizing mechanical parts such as motors and gears. In the USA, gear trains have already been cut at sub-millimetre size by lithography, but the Japanese are actually planning to make micron-

Cont. on page 26

THE MEDICAL EXPERIENCE OF THE MALTA MARATHON 1988

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Abstract

Marathon running is known to be associated with orthopaedic and medical injury. The aim of this study was to observe, report and analyse injuries occurring during the Malta Marathon, held on 21 February, 1988.

Observations showed that the commonest specific problems were muscle cramps and, upon completion of the event, hypotension. The significance of these, and other injuries in the context of long-distance runs is discussed.

Introduction

A broad spectrum of orthopaedic and medical injury is known to be associated with marathon and long distance running. In many events, musculoskeletal complaints such as cramps, tendonitis, sprains, blisters and fatigue fractures are very common (1, 2). Thermoregulatory disorders occasionally happen in such physically demanding events and the consequences of heat injury include disseminated intravascular clotting and acute tubular necrosis (3). Hypothermia may develop even on relatively warm days in the course of a long run (4). Rhabdomyolysis may also be another consequence of marathon running and may at times have a fatal outcome (5). Such complications have been observed not only in amateurs but also in trained professional athletes. Transient abnormalities which disappear after adequate rest are also known to occur and include haematuria and proteinuria (6).

This study is the first of its kind in Malta and focuses on the injuries occurring during the course of an international marathon held on 21 February 1988. It was organised in the light of a previous experience with thermoregulatory disorders exhibited by some of the participants during a locally organised long run (7).

The Marathon started at 9.00 a.m. and 310 participants were expected to complete the 42 km. course in approximately $3^1/_2$ hours. Runners however had the option of participating in a half marathon run. 268 (86%) of runners were males and 42 (14%) were females. The maximum ambient shade temperature for that day was 17°C, and the relative humidity was 48%. Drinking stations were sited at intervals of 5 km. Fig. 1.

Methodology

In order to study the injuries occurring throughout the marathon, a team of observing medical officers was briefed beforehand about the wide range of problems that were likely to be encountered. A standard questionnaire was prepared, such that allowed a quick comprehensive assessment of casualties. Participants were to be identified by their competition number. The last station passed, time, type of injury and cause together with vital parameters and initial management, where relevant, were to be recorded.

Three medical officers supervised the race throughout in separate ambulances, while another six were stationed at the finish line. At this point, all participating runners were directed into a large enclosed area where medical facilities were available. Back-up facilities were available at the local general hospital, which was informed beforehand of the event.

Results

The number of contacts made by athletes with first-aid posts along the route and at the finish line was 54. The number of individuals seeking care was 52 out of a total of 310 participants (17%), two runners making contact twice with medical staff. The injuries observed were grouped into the following five main categories:

(a) Muscle cramps, (b) Non-specific complaints. This category included a diversity of problems that could not be grouped under the above headings such as nausea, vomiting, blisters, abrasions, chest tightness, dyspepsia, decreased hearing and tinnitus. (c) Hypotension occurring after the finish. (d) Orthopaedic injuries (e.g. sprained ligament, back pain, locking of knee). (e) Hypothermia.

Injuries occurred during the latter half of the race and were mainly of a musculoskeletal nature. Most of the injured athletes sought medical care at the finish line. It is possible that some runners ignored their symptoms when they first occurred and consulted the medical staff on finishing the race. A large number of runners experienced muscle cramps at the finish line and required muscle stretching for relief. Cramps mainly occurred in knee extensors, calf muscles and abdominal

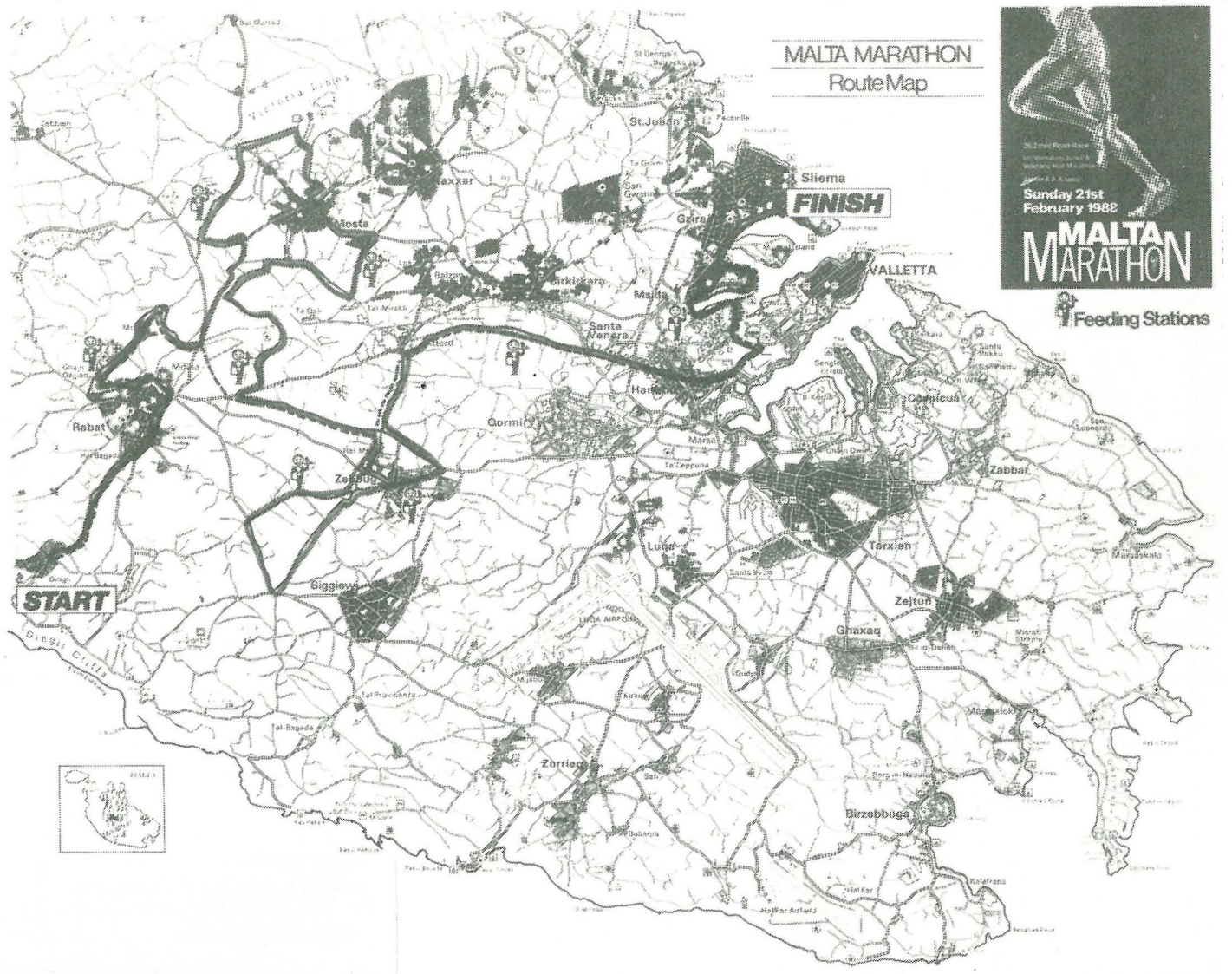

Figure 1: Drinking Stations.

muscles, the hamstring muscles being less commonly involved.

Hypotension secondary to hypovolaemia and vasodilatation a few minutes after the finish gave rise to about one fifth of casualties. None of the athletes required intravenous fluid replacement but responded well to rest, oral fluid therapy and elevation of the lower limbs.

TABLE 1.

	Muscle Cramps	Non-Specific	Hypotension	Orthopaedic	Hypothermia
Distance from start					
<20km	0	0	0	0	0
20km	0	0	0	1	0
25km	0	0	0	1	1
30km	5	1	0	0	0
40km	2	0	0	0	0
Finish 42km	16	14	10	3	0

Number of contacts made by runners with first-aid posts along route.

TABLE 2.

	Muscle Cramps	Non-Specific	Hypotension	Orthopaedic	Hypothermia
Males	19 (35%)	12 (22%)	10 (19%)	4 (7%)	1(2%)
Females	4 (7%)	3 (6%)	0 (0%)	1 (2%)	0 (0%)
	23 (42%)	15 (28%)	10 (19%)	5 (9%)	1 (2%)

Number of contacts made by runners with first-aid posts and frequencies N=54.

Eight of 54 contacts at first aid posts (15%) were made by female runners. 14% of participants commencing the race were female. Only one case was severe enough to warrant transfer to hospital. This was an athlete suffering from acute locking of the knee and he was eventually discharged that same day.

89% of participants (276) completed the event.

Discussion

Out of 310 runners, four presented with orthopaedic disorders, which involved the back and the lower limbs. Three of these runners managed to complete the marathon. One of the athletes presented with pain and numbness in the outer aspect of his right leg, which symptoms progressively got worse during the final 10 km of the marathon. He had a positive

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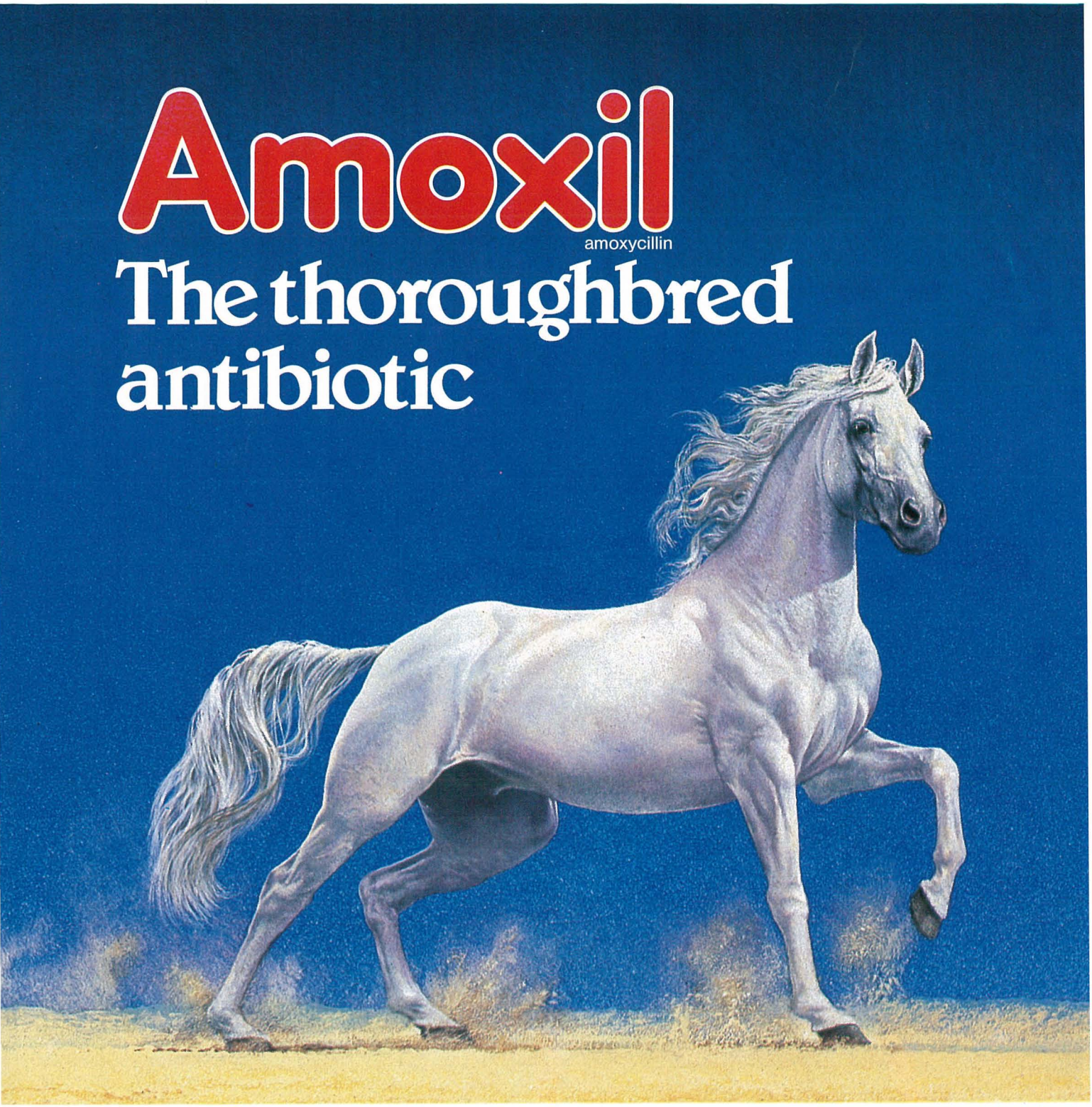

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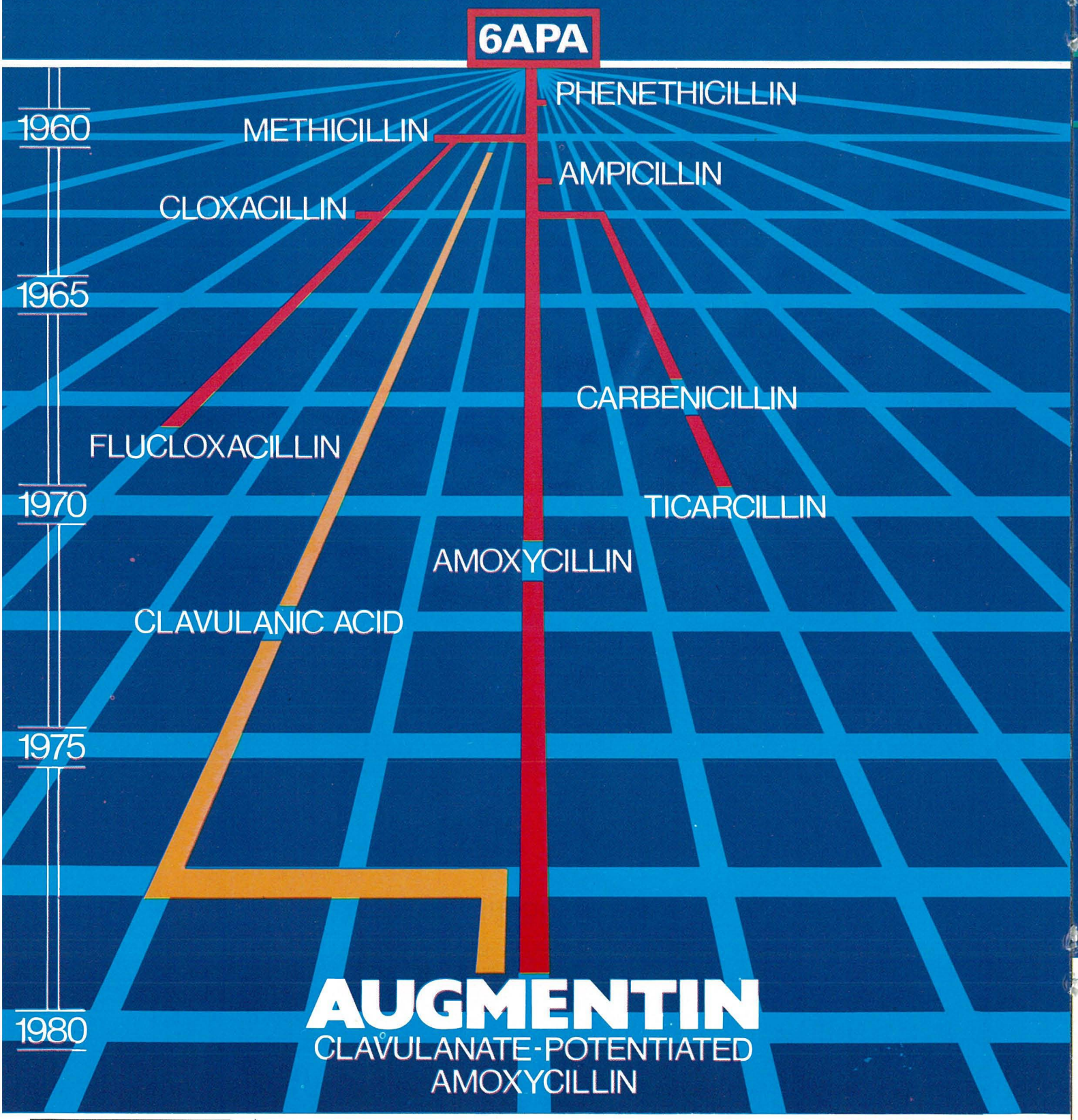

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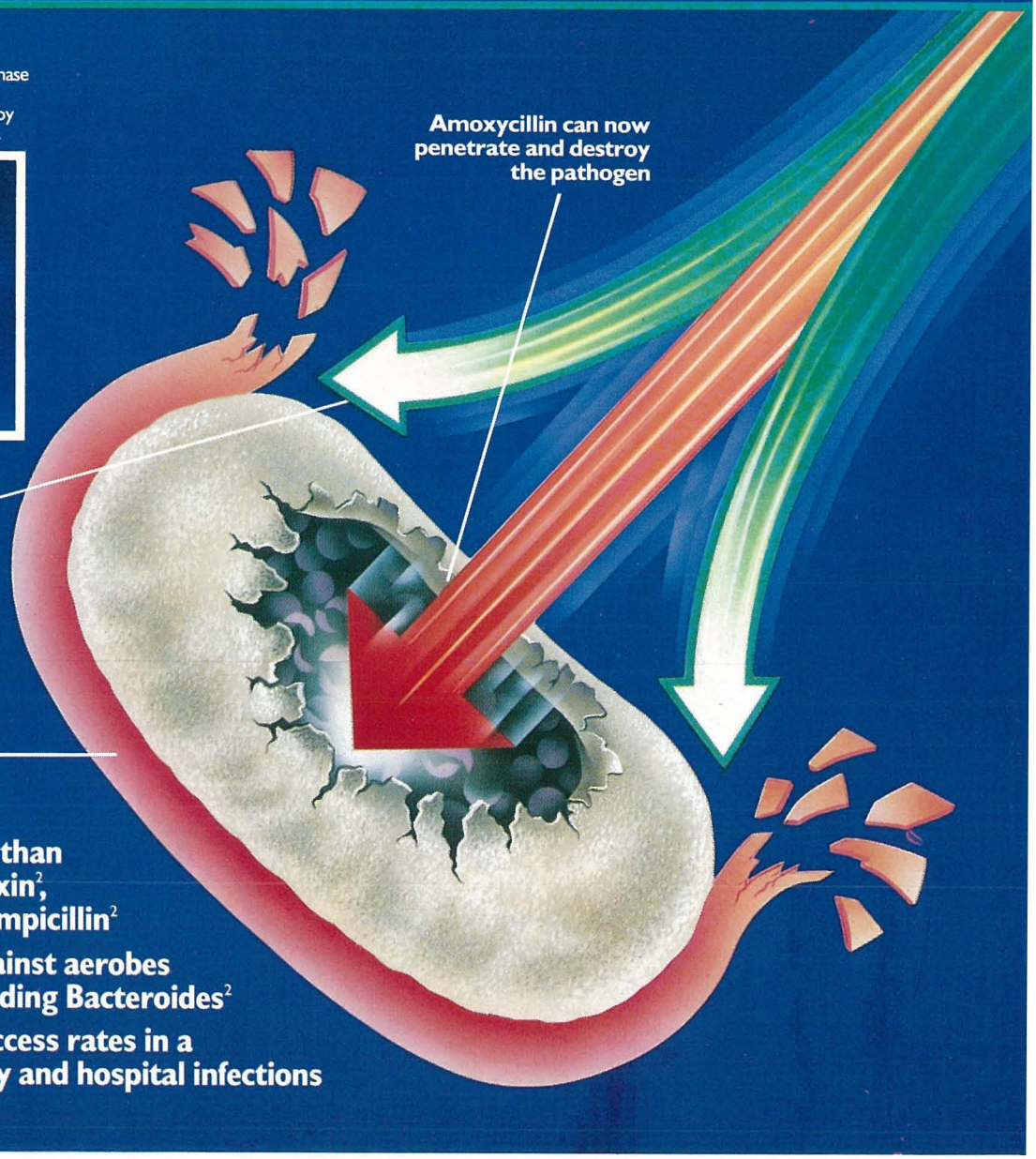

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Oral dosage: Adults and children over 12 years: One tablet tds. Children 7-12 years: 10ml of 156mg syrup tds. Children 2-7 years: 5ml of 156mg syrup tds. Children 9 months-2 years: 2.5ml of 156mg syrup tds. Children below 9 months: No suitable presentation currently available. In severe infections the dosage may be doubled.
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Storage and Stability: See pack insert leaflet.

References: 1. Med Int., (1984), **2,** (2), 41. 2. Excerpta Medica, (1980). **ICS 544,** 58.

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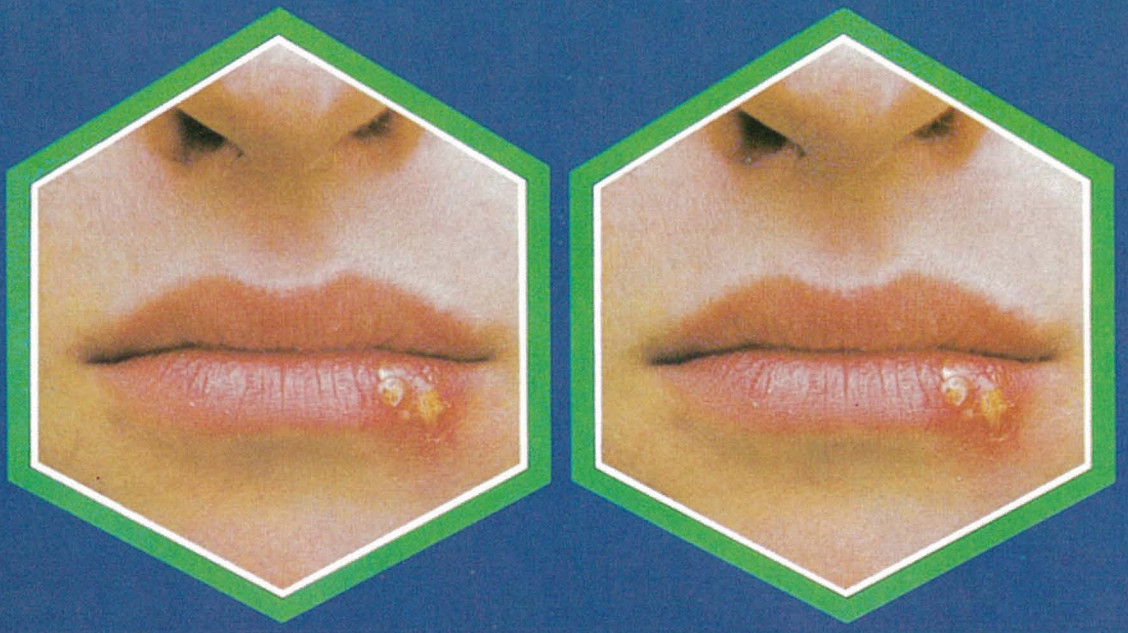

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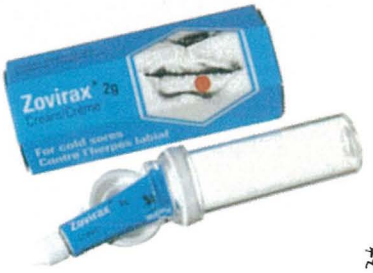

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Wellcome

"Tinel" sign over the neck of the right fibula and admitted to a past history of a right common peroneal nerve compression. A female athlete twisted her ankle two days before the marathon and twisted it again during the run. She subsequently developed gross swelling and marked tenderness over the calcaneofibular ligament of her left ankel with pain on passive inversion of the foot in keeping with a ligamentous sprain. The two other orthopaedic problems were back-pain and a locked knee. The participant with back-pain managed to finish the marathon but the individual who developed a locked right knee joint had to be taken to hospital where he gave a 5 week history of instability of the same knee.

Considering the number of runners and the often uneven road surface, the incidence of orthopaedic injuries was small and all the ones that presented had a significant past history relating to their complaint. This reflects the good state of musculoskeletal preparation of the participating athletes as a group.

Ligamentous injuries to the back or lower limb joints are bound to get worse during marathon runs where the state of the running surface and any prevailing winds increase the stress on the joints and their supporting ligaments.

Muscle cramps featured predominantly during the marathon run especially along the final 10 km. and at the finish. Muscle stretching exercises performed before the start, together with adequate fluid and electrolyte replacement during the run are simple precautions that runners should take in this regard.

It may thus be concluded that the medical facilities organised for a marathon event where 310 runners took part were adequate both for the number and variety of complaints. Although back-up facilities at the local general hospital were well geared for the event, no additional workload fell on the local health services.

The authors would like to thank Drs L. Attard, A. Buttigieg, J. Casha, B. Coleiro, I. Esposito, T. Esposito, G. Farrugia and A. Lapira for their cooperation and help in gathering medical data and Mr E. Attard of the Malta Marathon Organising Committee, who supplied valuable information and statistics about the event.

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INFRA-RED WAVEGUIDE FOR BLOODLESS SURGERY

ERA Technology, in conjunction with the technology transfer organization Cogent, has developed a novel hollow glass waveguide for directing infra-red energy from CO_2 lasers. Several prototypes based on a non-toxic oxide glass have recently been fabricated at ERA's laboratories in Leatherhead and are currently being evaluated for surgical applications.

Carbon dioxide lasers, operating at mid-infra-red wavelengths of around 10μm are particularly useful for tissue cutting and cauterizing; they permit virtually bloodless surgery and thus reduce the immediate trauma and after-effects for the patient.

For a CO_2 laser to be used to the maximum effect, its energy needs to be transferred from the rather bulky laser itself to the precise point at which it's needed. The only problem is that radiation as long as 10μm cannot be transmitted along conventional optical fibres because of the extremely high attenuation due to molecular vibration or rotation.

ERA Technology has therefore adopted a different technique, replacing optical fibres with hollow glass optical waveguides. The air-cored waveguide, with an internal diameter of 1mm, uses a glass cladding whose optical properties have been tuned to ensure maximum internal reflection (i.e. minimum attenuation) of a wavelength near 10.6μm. Laboratory prototypes transmit about 80% of the incident energy through a straight waveguide one metre long, but this reduces to 40% when the waveguide is bent to a 50cm radius. It's Not marvellous compared to the performance of optical fibres at shorter wavelengths, but it should permit a whole new degree of freedom for surgeons using CO_2 lasers. What's more, ERA Technology and Cogent are already predicting considerably improved performance when the waveguide is manufactured using precision machine-drawn fibres. They are at present looking for suitable partners to develop the technology further.

Ultimately the development of disposable high-efficiency optical waveguides should make possible a whole range of virtually non-invasive surgical procedures. ERA believes that there is now a very real prospect that major heart surgery such as coronary bypass operations could be conducted on an out-patient basis. All a surgeon would need to do would be to feed the waveguide and an optical fibre viewing device into a major blood vessel through a small hole in the skin, and then direct it to the site of action. The rest could be done with little more than a screen, a mouse and a button marked 'zap'!

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RATIONAL PRESCRIBING OF ORAL CONTRACEPTIVES

C. SAVONA VENTURA MD MRCOG

Department of Obstetrics and Gynaecology
St. Luke's Hospital, Malta

Oral contraceptives are amongst the most popular drugs, at present about 60 million women are using this highly effective form of contraception. Following the classic demonstrations by Pinchus and Rock (1958) interest has centred on progesterone-oestrogen combinations as oral contraceptives. The first oral contraceptives to be introduced contained high doses of oestrogen and progesterone. Since then there has been a gradual, but significant reduction in both components, leading to a decrease in adverse effects. A large number of oral contraceptive pill formulations are available with an even greater number of proprietary preparations (Kestelman, 1981). Further preparations are being developed (Eyong, 1987).

Many women appear to be suited by any pill formulation they are offered, but some find only one formulation acceptable. Unfortunately there are no simple rules for identifying which formulation is suitable for a particular patient, and if the first choice of oral contraceptive formulation proves unsuitable, the second choice must be better and based on the knowledge of the composition of available varieties and the relationship to each other.

Types of Oral Combined Contraceptives

The most widely used oral contraceptive type continues to be a fixed combined daily dose of a progestagen plus an oestrogen — MONOPHASIC PILLS. These pills are usually started on day 5 of the menstrual cycle and taken for 20-22 days depending on the individual product. These are followed by a 6-8 day treatment-free or placebo interval during which a withdrawal bleed occurs.

A second type of oral contraceptive consists of tablets containing variable amounts of progestagen and oestrogen during the 21 day pill cycle — SEQUENTIAL PILLS. This group of oral contraceptives were developed with a view of producing cycles more closely resembling the natural ones. The incidence of vaginal spotting and bleeding and the incidence of amenorrhoea associated with the use of low-dose monophasic combined pills is thus decreased, while maintaining reduced overall doses of steroids in each cycle. BIPHASIC PILLS provide in succession two oestrogen-progestagen combinations in increasing doses, while the TRIPHASIC PILLS provide a continuous dose of oestrogen combined with a progressively increasing dose of progestagen from week to week. The advantages of lowered steroid dosages in sequential pills is exemplified by the formulations represented in Figure 1.

Pharmacological Considerations

The molecular structures of steroidal contraceptives are related to those of oestrogen and progesterone, but are modified to render them effective in low dosage by mouth. The contraceptive combined pill formulations are made up of a combination of an oestrogen and a progestagen.

OESTROGEN: A great number of chemical substances have oestrogenic activity, including steroidal oestrogens, non-steroidal synthetic oestrogens like stilboestrol, and many phenols. Only two synthetic oestrogens have so far been used in commercial oral contraceptive products: Ethinyloestradiol and mestranol (Figure 2) Ethinyloestradiol is a structurally more stable derivative of oestradiol, resisting hydroxylation and conjugation thus giving a more prolonged action, being

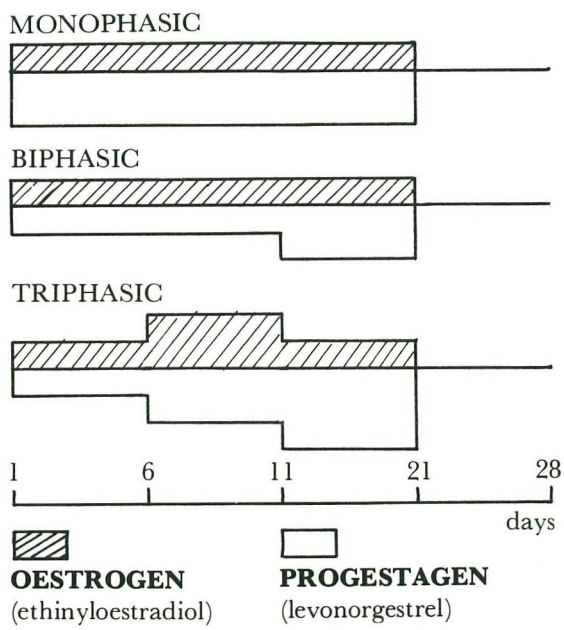


Figure 1: Representation of amounts of oestrogen and progestagen in monophasic, biphasic and triphasic Pills throughout cycle.

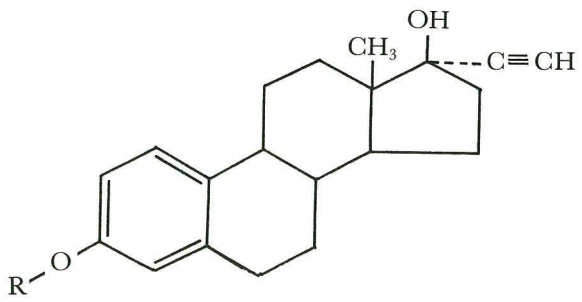


Figure 2: Oestrogen Structures ethinyloestradiol R = H mestranol R = CH_3

effective for 24-36 hours when taken orally. Mestranol is the C3 methyl ether of ethinyloestradiol. In the body it is inactive until metabolized to ethinyloestradiol. Weight for weight it is equipotent with its parent ethinyloestradiol. Only two preparations containing mestranol Norinyl-1 and OrthoNovin 1/50 are presently marketed.

Both oestrogens resemble natural oestrogens in their actions on the reproductive tract and hypothalamus, affecting Luteinizing Hormone production. They also alter lipid metabolism and blood coagulation in a manner similar to the changes found in pregnancy.

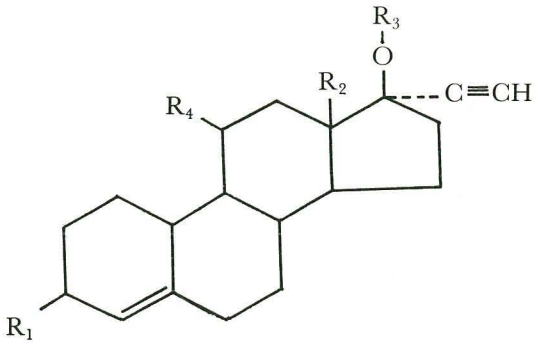
PROGESTAGENS: In contrast to the oestrogens, there is a very large range of progestagens which have been used for oral contraceptives. The synthetic progesterone-like substances are structurally related to four parent compounds: testosterone, 19-nortestosterone, 17*a*-hydroxyprogesterone and progesterone itself. All progestagens, except cyproterone acetate, currently used in combined oral contraceptives are derivatives of 19-norethisterone which is itself derived from the androgen, ethisterone (17*a*ethinyltestosterone). Taken orally, these progestagens remain active for 24-36 hours. They resemble progesterone in their action, inducing secretory changes in the oestrogen-primed endometrium, producing viscous cervical mucus, affecting Luteinizing Hormone production and inhibiting ovulation. In contrast they will not maintain pregnancy in oophorectomized animals, do not increase basal body temperature and are not metabolized to pregnanediol. Because of their relationship to testosterone, these progestagens have some androgenic effects occasionally aggravating acne and coarsening existing body hair. The next generation progestagens, desogestrel, gestodene and norgestimate show a higher ratio of binding to progresterone receptor sites than androgen sites giving less undesired androgenic effects especially on lipid metabolism. Cyproterone acetate is an anti-androgen with marked progestational action.

The progestagen present in a particular preparation determines the properties of that preparation. Current pill formulations are made up of nine different progestagens (Figure 3).

1. NORGESTREL has a very powerful antifertility action making it possible to reliably use low oestrogen dosages (30 ug ethinyloestradiol). Norgestrel does not affect endometrial development as much as the other progestagens and withrawal bleeding will not be reduced as dramatically.

It is thus not the treatment of choice in patients with menorrhagia from dysfunctional uterine bleeding. Common preparations are listed in Table 1.

2. NORETHISTERONE ACETATE has marked effects on endometrial development resulting in regression of the secretory changes in the endometrial glands and relative atrophy of the glands. The stroma appears oedematous but of relatively low vascularity. These changes in the endometrium often result in very light, or even failure of, withdrawal bleeding. This makes this group of preparations very effective at controlling menorrhagia of dysfunctional uterine bleeding, or in the management of endometriosis. These preparations however require a high dose of oestrogen (50 ug ethinyloestradiol) to effect reliable contraception, though one preparation of this group contains less oestrogen than any other combined pill. While this is useful when side-effects occur with higher doses of oestrogen, it is not as reliable for contraception, and may be associated with troublesome early spotting and breakthrough bleeding. Common preparations are listed in Table 1.



Compound	R1	R2	R3	R4
Norgestrel	O	C_2H_5	H	H_2
Norethisterone	O	CH_3	H	H_2
Norethisterone acetate	O	CH_3	CH_3CO	H_2
Lynoestrenol	H_2	CH_3	H	H_2
Ethynodiol diacetate	OCH_3CO	CH_3	CH_3CO	H_2
Desogestrel	H_2	C_2H_5	H	CH_2
Gestodene	O	C_2H_5	H	H_2
Norgestimate	NOH	C_2H_5	CH_3CO	H_2

Figure 3: Progestagen Structures

TABLE 1:
Classification of the Combined Oral Contraceptive Pills

TYPE	*OESTROGEN* *EE: ethinyloestradiol* *M: mestranol*	*PROGESTAGEN*	*PROPRIETARY NAME* *(eg)*
		Levonorgestrel	
Triphasic	EE: 30/40/30 ug	50/75/125 ug	Logynon; Trinordiol
Biphasic	EE: 30 ug	75/150 ug	
Monophasic	EE: 30 ug	150 ug	Microgynon 30; Ovranette
Biphasic	EE: 30/40 ug	150/200 ug	Adépal
Monophasic	EE: 30 ug	250 ug	Eugynon 30; Ovran 30
Biphasic	EE: 50 ug	50/125 ug	Binordiol; Sequilar
Monophasic	EE: 50 ug	125 ug	Microgynon 50
Monophasic	EE: 50 ug	250 ug	Neogynon
Monophasic	EE: 50 ug	500 ug	Eugynon 50; Ovran 50
		Norethisterone acetate	
Monophasic	EE: 20 ug	1000 ug	Loestrin 20; Nogest
Monophasic	EE: 30 ug	1500 ug	Loestrin 30
Biphasic	EE: 30/40 ug	1000/2000 ug	Miniphase
Monophasic	EE: 50 ug	1000 ug	Minovlar; Orlest 21
Monophasic	EE: 50 ug	2500 ug	Norlestrin; Orlest 2.5
Monophasic	EE: 50 ug	3000 ug	Gynovlar 21
Monophasic	EE: 50 ug	4000 ug	Anovlar 21
		Norethisterone	
Monophasic	EE: 35 ug	500 ug	Ovysmen; Brevinor
Triphasic	EE: 35 ug	500/750/1000 ug	TriNovum
Triphasic	EE: 35 ug	500/1000/500 ug	Synphase
Biphasic	EE: 35 ug	500/1000 ug	BiNovum
Monophasic	EE: 35 ug	1000 ug	Neocon 1/35; Norimen
Monophasic	M: 50 ug	1000 ug	Ortho-Novin 1/50
		Lynoestrenol	
Monophasic	EE: 50 ug	2500 ug	Lyndiol; Minilyn
		Ethynodiol diacetate	
Monophasic	EE: 30 ug	2000 ug	Conova 30
Monophasic	EE: 50 ug	500 ug	Demulen 50
Monophasic	EE: 50 ug	1000 ug	Ovulen 50
		Cyproterone acetate	
Monophasic	EE: 35 ug	2000 ug	Diane-35
Monophasic	EE: 50 ug	2000 ug	Diane
		Desogestrel	
Monophasic	EE: 30 ug	150 ug	Marvelon
		Gestodene	
Monophasic	EE: 30 ug	75 ug	Gynera; Mirulet
		Norgestmate	
Triphasic	EE: 35 ug	180/215/280 ug	
Monophasic	EE: 35 ug	250 ug	Cilest

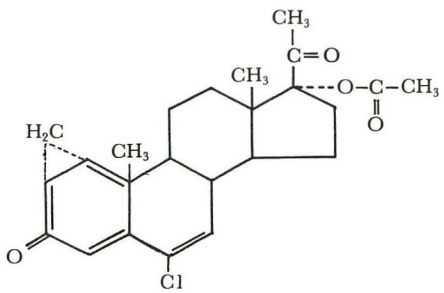


Figure 4: Anti-Androgen: cyproterone acetate

3. NORETHISTERONE is similar in its effects on the endometrium to norethisterone acetate. It is the only progestagen which is marketed in oral contraceptives employing mestranol. By incorporating ethinyloestradiol it became possible to reduce the oestrogen content to 35 ug while maintaining reliability. The preparations are listed in Table 1.

4. LYNOESTRENOL has more oestrogenic activity than the other progestagesn in common use. It is thus useful in managing androgenic problems such as acne and dysfunctional uterine bleeding caused by an atrophic endometrium. It is also a good alternative if the patient suffers progesterone dominant side-effects with lower progestagen dosages, particularly if norgestrel preparations were used. Only one formulation is currently available (Table 1) containing 50 ug of oestrogen.

5. ETHYNODIOL DIACETATE preparations are well-tried pills, but are available only in high oestrogen dosage formulations (Table 1).

6. CYPROTERONE ACETATE (Figure 4) blocks the effect of endogenously produced and exogenously administered androgens at the target organs by means of competitive inhibition. Besides its main anti-androgenic effect, cyproterone acetate has a marked progestational effect reaching, on subcutaneous injection, to about 100 times the effectiveness of progesterone, effecting not only the endometrium but also giving rise to an anti-gonadotrophin effect. Combined with ethinyloestradiol, it results in a reliable contraceptive useful for women who suffer from features of androgenization such as acne and hirsutism.

7. DESOGESTREL is one of the new generation progestagens. It has clear progestational activity and strong anti-oestrogenic activity. It has minimal androgenic and anabolic properties. Only one preparation is presently marketed combined with 30 ug of oestrogen.

8. GESTODENE has been shown to have very potent progestagenic effects with no oestrogenic activity. There appears to be no androgenic activity at clinical doses. Only one formulation combined with 30 ug oestrogen is presently marketed.

9. NORGESTIMATE is a lower-potency progestagen which exhibits virtually no androgenic response or oestrogenic activity. A triphasic preparation is in the late stages of development combined with 35 ug of oestrogen.

Selection of oral Contraceptives

The large variety of oral contraceptive formulations on the market makes it difficult to identify the right formulation for a particular patient. Based on acceptable pharmacological principles, the lowest effective dose of a compound should always be used, though the very lowest dose may not prove to be the eventual choice in a particular patient.

The triphasic pills are especially designed to provide sufficient steroids to maintain inhibition of ovulation while reducing substantially the dosages and hence the risks of side-effects of the steroid constituents. The phasic pills are probably the best first choice in oral contraceptive therapy today. When side effects such as acne, mastalgia, pre-menstrual tension or inadequate cycle control occurs, it may become necessary to change to the higher dose monophasic formulations.

In patients with normal menstruation, it may be best to start with a preparation containing norgestrel. The lowest dose formulation available is started and this is increased if spotting persists during the following three pill cycles. Breakthrough bleeding is not uncommon in the first two cycles, but if it persists or occurs when the patient is well established, a preparation with a higher progestagen content should be prescribed. Breakthrough bleeding may also occur in some patients on very low doses of oestrogen and in these cases an increase in oestrogen content may rectify the situation. If breakthrough bleeding still persists full gynaecological assessment is mandatory.

In patients where cycle control remains unacceptable with preparations containing norgestrel or in patients who have a previous history of dysfunctional uterine bleeding causing menorrhagia, a preparation containing norethisterone or norethisterone acetate should be prescribed. Low dose preparations are started, increasing the dose only if cycle control or side effects persist. It has been said that nausea, leucorrhoea premenstrual tension and relatively heavier uterine bleeding are probably associated with higher than usual levels of circulating oestrogens, while weight gain, premenstrual breast discomfort and scantier periods are more likely to be evidence of a stronger progestational effect.

In patients who have markedly dominant progestagen side-effects with low doses or in those with dysfunctional uterine bleeding from an atrophic endometrium, preparations containing ethynodiol diacetate may be useful. In patients with marked androgenic features such as acne and hirsutism, cyproterone acetate preparations may play a role.

The role of the new generation progestagens has not been fully elucidated, but clinical and pharmacological data indicate that these progestagens have very little effect on lipid and carbohydrate metabolism. The absence of androgenic effects makes these preparations useful in women susceptible to androgenic symptoms like acne and hirsutism.

It has been recommended (IPPF, 1987) that no more than four combined formulations be available in family planning programmes within the following ranges:

a) 30-50 ug oestrogen with the lower dose to be given first, and

b) 150 ug levonorgestrel or 1 mg norethisterone or its equivalent related compound.

TABLE 2:
Contra-Indications of Oral Conctraceptive use

ABSOLUTE CONTRA-INDICATIONS

* Hormone dependent tumours: malignancy of breast or genital tract
* Venous thromboembolism or predisposing conditions
* Cerebrovascular accident
* Undiagnosed vaginal bleeding
* Focal migraine
* Familiar hyperlipidaemia

RELATIVE CONTRA-INDICATIONS

* Patient's age over 40 years
* Smoking more than 20 cigarettes/day
* Mild hypertension or a history of hypertension during pregnancy
* Epilepsy
* Diabetes mellitus or impaired glucose tolerance
* History of bouts of depression
* Recent history of oligomenorrhoea/ammenorrhoea
* Gallbladder or liver disease (including a past history of idiopathic cholestatic disease of pregnancy)
* Uterine fibroids
* Sickle-cell anaemia

Contra-Indications to Oral Contraception

There are a number of situations where oral contraceptive use is absolutely contra-indicated (Table 2). There are also other situations where medical assessment of risk and benefits should be made before a woman is put on oral contraceptives (Table 2). In women who are otherwise well, oral contraceptive use may be continued for many years and there is no justification for the periodic withdrawal of the use of oral contraceptives.

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1. Eyong, E. (1987), 'Developments in new progestagens for oral contraception' IPPF Med. Bull. 21(2): 3-4.
2. I.P.P.F. (1987), 'Statements on steroidal oral contraception' IPPF Med. Bull. 21(1):4.
3. Kestelman, P. (1981), Directory of contraceptives +95p. IPPF; London.
4. Pincus, G. and Rock, J. (1958), 'Effects of 19-norsteroids upon reproductive processes' Ann. N.Y. Acad. Sci. 71:677.

Cont. from page 13

sized moving parts.

Fujimasa is confidently predicting that by the end of next year he will have a prototype micro-robot capable of travelling around in the body and communicating its whereabouts. Later, but still within the foreseeable future, he expects to be able to add simple sensors for doing reconnaissance jobs around our innards. Thereafter it will be on-board micro-lasers to zap our clots and beam up our tumours. Utterly incredible, but it doesn't half give you a creepy feeling....

EPOKELAN

Scalp Lotion

MINOXIDIL 2%

SIGNIFICANT REGROWTH IN MALE PATTERN BALDNESS

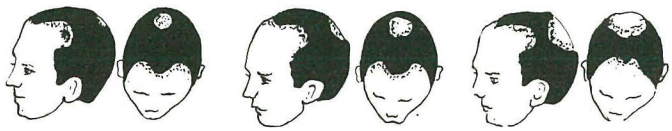
Clinical trials reveal excellent responce in certain groups of patients

BALDING AT CROWN

Significant results were shown in patients of this group

BALDING TYPES IIIv, IV, V

Most patients in clinical trials belonged in these groups as per the modified Hamilton people classification.



The clinical studies examined also the relationship between the duration of baldness, diameter of bald area and clinical response in patients with male pattern baldness treated with EPOKELAN concluding:

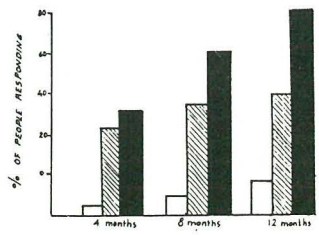
DURATION OF BALDNESS

Patients balding from 2-10 years respond greater to EPOKELAN than those who had been balding for 10-21 years.

DIAMETER OF BALDING AREA

Patients with balding area less than 10cm in diameter show better improvement than those with larger balding area.

Fig. Percentage of 619 patients with male-pattern baldness treated with topical **Minoxidil 2%** lotion who rated their hair growth as dense (□) or moderate (▨) and who grew non-vellus (intermediate or terminal hair as assessed by the investigator) hair (■) in a 12-month multicentre trial (Editorial 1986)



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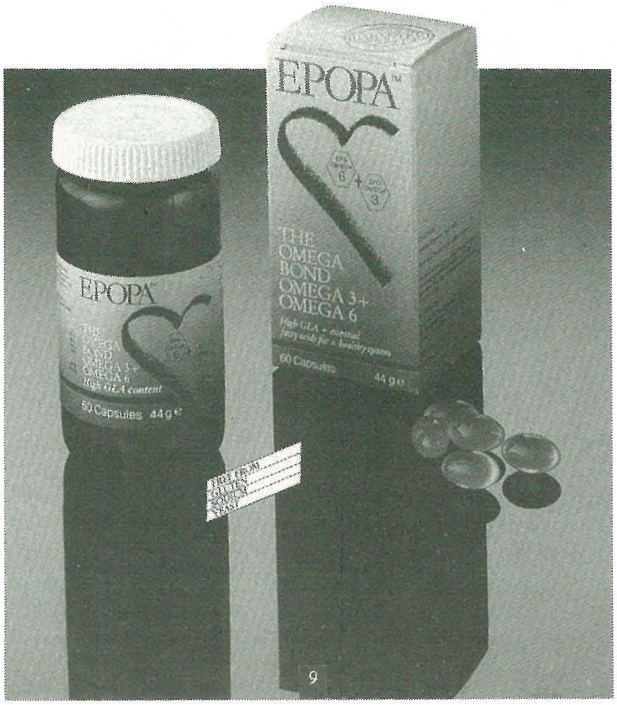

EPOPA – The Omega Bond

Greenland eskimos, whose diet is rich in fish, have one of the lowest incidence of coronary heart disease in the world and scientists now believe that it is the essential fatty acids found in fish oil that protects them.
As the body cannot produce these essential fatty acids they have to be included in your food or as a supplement.
EPOPA brings together four oils from natural sources – Evening Primrose, Borage, Salmon and Safflower oils – forming a blend rich in Omega-6 and Omega-3 polyunsaturated fatty acids and low in saturates.
Both Evening Primrose and Borage oils are rich in Gamma-linolenic acid of the Omega-6 series, with Salmon oil containing polyunsaturates of the Omega-3 series.
EPOPA is a unique formula of nutrients combining the ultimate sources of the essential Omega-3 and Omega-6 fatty acids, the nutrients concerned in maintaining normal blood fat levels.
Natural source Vitamin E is also added to stop the essential fatty acids breaking down to ensure they give maximum benefit.

CAPSULE CONTENTS

Safflower Oil (Linoleic acid)	200mg
*Pure Salmon Oil Concentrate 18/12	100mg
Borage Oil (Minimum 20% GLA)	100mg
Evening Primrose Oil	100mg
Natural Vitamin E (d-alpha Tocopherol)	10mg
Nicotinic Acid	2mg

* 18/12 denotes
18% Eicosapentaenoic acid (EPA)
12% Docosahexaenoic acid (DHA)

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Gerimax – The Ultimate One a Day.

TABLET CONTENTS

Ginseng Extract (Panax 250 mg Ginseng)	85 mg	Vitamin C	45 mg
Vitamin A 5,000 I.U. =	900 mcg	Vitamin D 450 I.U. =	10 mcg
Thiamin (Vit B1)	1.5 mg	Vitamin E	12 mg
Riboflavin (Vit B2)	1.8 mg	Iron	18 mg
Vitamin B6 HCl	2.0 mg	Zinc	15 mg
Vitamin B12	3.0 mcg	Copper	2.0 mg
Folic Acid	100 mcg	Manganese	3.88 mg
Niacin	20 mg	Molybdenum	250 mcg
Pantothenic Acid	10 mg	Iodine	150 mcg
Rutin	20 mg	Selenium	125 mcg
		Chromium	125 mcg

In addition there are small amounts of Biotin, Inositol and 18 amino acids, including 8 essential ones.

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LEAD POISONING:
A Pathophysiological Overview

DAVID SCERRI

Medical Student

Environmental lead

During the last century, there has been a steep decline in the incidence of industrial lead poisoning and a similar decrease, in the number of deaths due to lead poisoning. However, many people are chronically exposed to high atmospheric lead concentrations, which although not causing lead poisoning, may cause subclinical effects, i.e. metabolic disturbances undetectable by usual clinical procedures. Table 1 compares the lead concentrations in an uncontaminated environment with today's levels and their effects on body lead. The 'safe' upper limit is considered to be about 70ug of lead per decilitre of blood.

TABLE 1
Comparison of lead concentrations in different environments; all values are approximative and vary widely.

	Uncontaminated Sites	Preindustural Sites	Industrial Sites
Atmospheric lead (ug/m^3)	0.0005	0.05	2
Blood lead (ug/dl)	0.25	5	20
Total body lead (mg)	2	60	120

Acute lead poisoning is commonest in children who ingest flakes of paint or other lead-containing materials. Food contaminated with lead may also cause acute lead poisoning. More commonly, the disease develops gradually, especially in factory workers exposed to excessively high atmospheric lead concentrations, notably those working in battery manufacture.

The commonest source of lead in the general environment is tetraethyllead ($Pb(C_2H_5)_4$), an antiknock additive in petrol. Thus, the greater the amount of traffic in a city, the higher is its atmospheric lead content.

Lead absorption

For lead to exert its toxic effects, it must first enter the body and the general circulation. The two commonest routes of entry are the respiratory and gastro intestinal tracks.

About 30 to 60% of inhaled lead is deposited in the lungs, according to particle size. This is either absorbed into the blood or phagocytosed by macrophages. The smaller the particles and the greater their solubility, the more is the amount entering the circulation.

Only about 5 to 10% of ingested lead is absorbed by the adult gut. This value may be as great as 50% in growing children. Dietary calcium and vitamin D levels effect the amount of lead absorbed by the gut. Vitamin D — induced calcium binding proteins bind lead with a greater affinity than calcium, with both ions competitively competing for the calcium-binding sites. This explains why a high dietary calcium content decreases the amount of lead absorbed by the gut, while vitamin D increases it. Similarly dietary zinc and iron also decrease lead absorption.

Body lead and its excretion

Absorbed lead enters the circulation, so that blood lead levels are usually indicative of recent exposure. Only minute quantities are present in the ionized form, most of the lead rapidly binding to the erythrocyte cell membranes, blood lead is also bound to plasma proteins. Part of this binding of lead to erythrocytes and proteins occurs by the same mechanism with which it exerts its pathological effects in lead poisoning, as will be explained later.

There is a dynamic equilibrium between the free plasma lead and the portion bound to the erythrocytres; a similar equilibrium exists between blood lead and extracellular lead, the ionized fraction comprising the 'active pool', (Fig. 1). Lead enters tissues and cells through the same routes taken by calcium, and binds particularly strongly to mitochondria. Bone is the commonest site of lead deposition, comprising over 90% of total body lead. It is laid down, together with calcium, at sites of active bone formation and it may also displace calcium in the bone apatite crystals. This provides a method of removal of blood lead, which may otherwise cause more severe effects. However bone is not static and when there is an increased demand for calcium, some of the lead is also

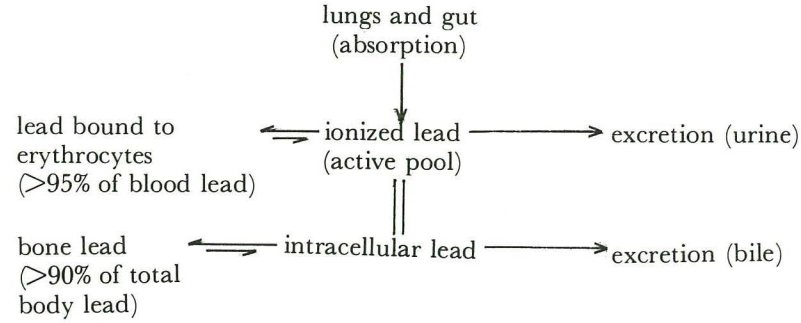


Figure 1: Relationship between lead in various body compartments and its excretion.

mobilized. In fact, blood lead may double during pregnancy due to this fact.

Excretion of lead takes place mainly via faeces, lead being secreted in the bite as salts with other compounds such as fatty acids. The kidneys also play a part in lead exretion, most of this occuring simply through glomerular filtration.

Figure 1 summarizes the distribution of lead in the body.

The Pathological Effects of Lead

Besides sharing some properties with calcium, lead also has other properties which enable it to inhibit certain enzymes. Like other heavy metals, lead has an affinity for sulphydryl groups. It may also bind to other ligands containing electron donors, such as carboxyl, hydroxy, phosphate, amino and imidazole groups, although less avidly than to sulphydryl groups. Dithiol groups are particularly susceptible to attack by lead. If the protein is an enzyme, it is usually inhibited due to irreversible denaturation and hence loss of its active site. The biochemical pathway most sensitive to inhibition by lead is that of haem biosynthesis.

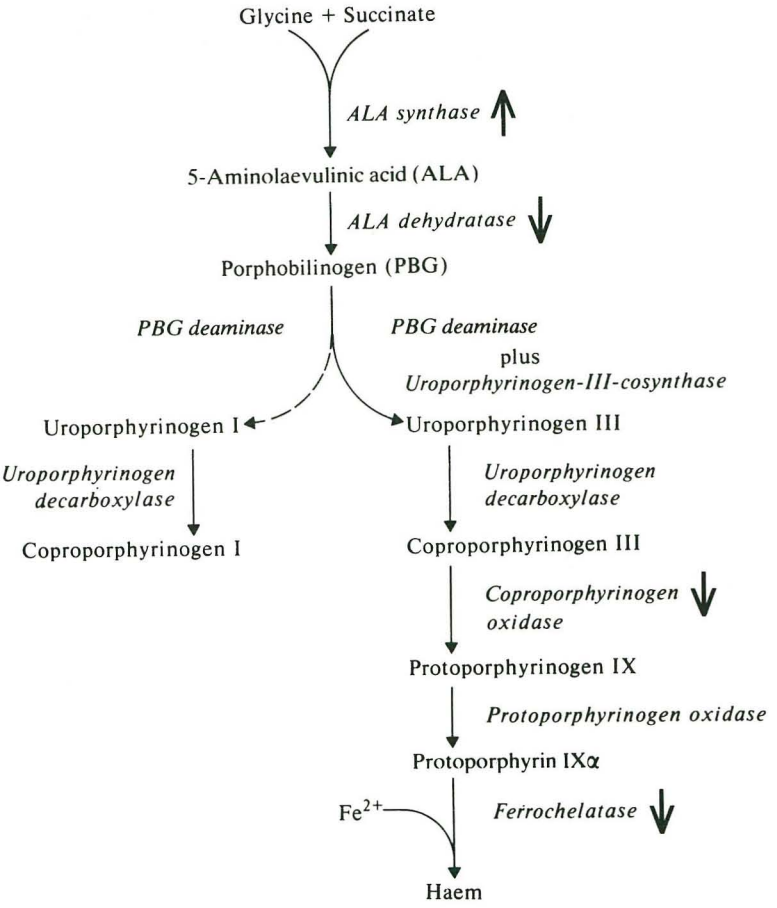


Figure 2: The biosysthesis of haem showing the enzymes that are inhibited (↓) by lead and the resultant induction (↑) of ALA synthase.

Haem biosynthesis

Before stating the effects of lead on haem biosynthesis, it is important to consider the synthesis and regulation of porphyrins (see Fig. 2). This occurs in virtually every metabolically active cell, but is most active in red bone marrow and liver tissue, where the porphyrins are used primarily for haemoglobin production.

The first step in the pathway involves the condensation of glycine and succinyl coenzyme A into delta-aminolevulinate. This is the rate-limiting and regulatory step for haem biosynthesis and is catalysed by the mitchondrial-bound enzyme delta-aminolevulinate synthase (succinyl coenzyme A: glycine C — succinyltransferase). This enzyme is very specific and will not accept other aminoacids or acyl coenzyme A compounds as substrates. It is controlled primarily by negative feedback inhibition by haem, the end-product of this pathway. Thus, anything that depletes haem, inhibits its synthesis or increases its metabolism, will cause an increased activity of delta-aminolevulinate synthase.

Lead particularly inhibits delta-aminolevulinate dehydratase, coproporphyrinogen oxidase and ferrochelatase. These contain exposed sulphydryl groups (of cysteine residues) with which lead can combine easily. The active site of these enzymes is thus irreversibly blocked, with a greater amount of these enzymes inhibited at higher lead concentrations. The lead does not have to bind necessarily to the active site, for a change in the three-dimensional configuration of the enzyme will still denature it. Thus, inhibition here is of the noncompetitive type, with an increase in substrate concentration being virtually useless. Inhibition of these enzymes causes increased activity of delta-aminolevulinate synthase with accumulation of delta-aminolevulinate and other intermediates. (See Fig. 2).

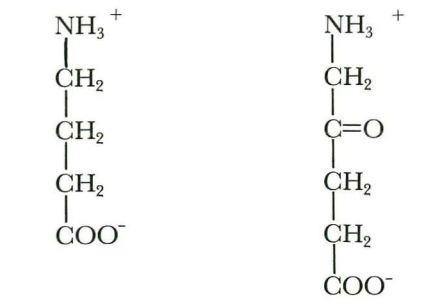
Haem synthesis is depressed with blood lead levels over 15ug/dl leading to anaemia. At lower lead concentrations, the increased activity of delta-aminolevulinate synthase is enough to maintain a normal haemoglobin level.

The anaemia of lead poisoning is rarely severe and is a normocytic, hypochromic type of anaemia, although macrocytosis may develop if it is prolonged. Decreased activity of cytochrome P450 in the liver has been observed in lead poisoning and other systems requiring porphyrins may also be affected.

It is the increased levels of intermediates in the haem biosynthetic pathway that are responsible for most of the toxic manifestations in lead poisoning.

Lead neuropathy

Probably the worst effect of lead



gamma-aminobutyric acid *delta-aminolevulinate*

Figure 3.

poisoning is the development of associated neuropathy. Both central nervous system and peripheral nerve abnormalities occur in lead poisoning, CNS impairment occuring earlier. This is detectable at blod lead levels over 40ug/dl, even in the absence of clinical lead poisoning.

The main cause for lead encephalopathy is probably the result of delta-aminolevulinate competing with the neurotransmitter gamma-amino-butyric acid for its receptor sites on post-synaptic membranes. Figure 3 shows the similarity in structure betwen these two compounds.

Other Mechanisms for lead encephalopathy have been proposed. The inhibition of essential enzyme systems in nervous tissue as well as the blockade of dopamine D_2 receptors may play a role.

Lead poisoning in children usually causes a more severe encephalopathy, with cerebral oedema, due to the fact that the blood-brain barrier is still not fully developed. Inhibition of brain sodium-potassium adenosine triphosphatase by lead is probably one of the main factors causing the oedema. The electroencephalogram is normal in lead poisoning and is thus of no use in diagnosis of this condition.

Peripheral nerves in lead-poisoned patients show signs of segmental demyelination and remyelination and also axonal degeneration in some cases. Motor nerves are especially affected, with a reduction in their mean maximum conduction velocity, while sensory nerves remain unaffected. These changes are present even in people with subclinical lead poisoning. The exact cause of these features is unknown. It is important to stress that the effects of lead on the nervous system and their consequences may remain even after complete disappearance of other symptoms, although some improvment always occurs after reduction of exposure.

Inhibition of the pentose phosphate shunt

The pentose phosphate shunt is the source of reduced nicotinamide dinucleotide phosphate (NADPH + H^+). This provides a reducing atmosphere in cells and is especially important in erythrocytes. NADPH is used to produce reduced glutathione; which is an important reducing agent, and also plays a part in maintaining the integrity of the red cell membrane. (See Fig. 4).

Lead inhibits glucose — 6 — phosphate dehydrogenase, the first enzyme in the pentose phosphate shunt. This results in a lower concentration of reduced glutathione within the red blood cell. The loss of reducing power makes the cell sensitive to oxidant stress, leading to haemolysis and a shortened red cell life-span. Thus the anaemia of lead poisoning also has a haemolytic component.

Lead Nephropathy

The proximal tubules are mainly affected in lead poisoning. The epithelial cells show structural abnormalities with the mitchondria showing the greatest changes. The characteristic finding here is intranuclear inclusion bodies. These occur in all cases of lead poisoning and appear soon after exposure to lead. Their number is proportional to the degree of exposure. They consist of proteins rich in sulphydryl groups and have a high lead content. The protein p32/6.3 is unique to these inclusions. They seem to act as protective devices to reduce the amount of circulating lead by binding it in an inactive form. This is even safer than the deposition of lead in bone, as bone lead is mobilized with calcium, when the latter is required. Lead itself probably induces the formation of these proteins, limiting its harmful effects. Chronic renal damage however does not seem to follow lead poisoning.

Lead also reduces the ability of the kidneys to excrete uric acid, causing saturnine gout. However, this does not occur in all cases of lead poisoning.

Other effects of lead

Theoretically, any enzyme containing exposed sulphydryl groups can be inhibited by lead.

Thyroid dysfunction may occur in lead-poisoned patients. They seem to have impaired uptake of iodine by the thyroid. Lead may cause this by binding to sulphydryl groups on a protein sulphonyl iodine carrier or by displacing the iodine in the protein.

Muscular weakness is another common feature of lead poisoning. Essential enzyme systems may be partially inhibited by lead. Besides enzyme inhibition through sulphydryl groups, lead can also bind to troponin C, with even greater affinity than calcium. This may contribute to the muscle weakness by directly interfering with the mechanism of contraction.

The activity of other enzymes, such as alkaline phosphatase and cholinesterase, has been found to be reduced in lead poisoning. Lead in the nucleus has the ability to alter nucleic acid conformation, degrade RNA, increase misincorporation in DNA synthesis and stimulate chain initiation by magnesium-activated RNA polymerase. It may affect cell proliferation, producing chromosomal abnormalities and therefore lead to neoplastic transformation.

Lead can also affect the cardiovascular system. Myocardites, ECG abnormalities, increased cardiac arrhythmogenicity and altered myocardial contractility have all been observed in certain cases. Alterations in blood pressure-regulating mechanisms (renin secretion, vagal and sympathetic tone), together with lead nephropathy, may contribute to the development of hypertension.

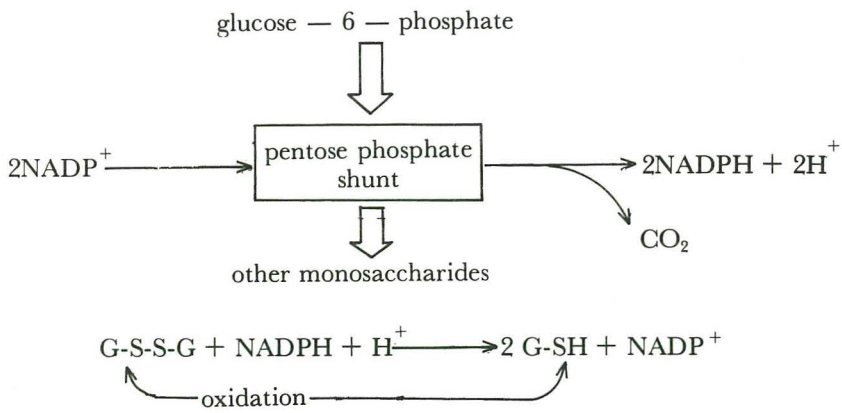


Figure 4: Features of the pentose phosphate shunt; G represents glutathione (a tripeptide: ygiu - cys - gly).

Diagnosis and Treatment of Lead poisoning

There are no symptoms particular to lead poisoning and this may lead to difficulty in diagnosing the condition. A history of exposure to lead (or its ingestion) is probably the most useful diagnostic tool. The features of organic and inorganic lead poisoning exhibit some differences. Table 2 lists the various symptoms of the disease.

Encephalopathy is common in children and peripheral neuropathy may be obvious in some cases. Burton's blue line (deposits of lead on the gingival margin) may be present in chronic cases. Radiography of the long bones may show "lead lines" at their epiphyses. It is thought that this "lead line" is not necessarily lead but is caused by lead interfering with the normal deposition of calcium at these sites.

Tests for lead **absorption** are based on the lead content of blood, urine, teeth, hair and bones. For lead **poisoning**, urine aminolevulinate and coproporphyrin levels are the most useful tests. Erythrocyte aminolevulinate and protoporphyrin also give very useful information. Porphobilinogen may be excreted in the urine in severe cases.

TABLE 2
Symptoms of lead poisoning listed in their order of frequency as presenting symptoms, depending on state (organic lead is mainly T.E.L.)

INORGANIC		ORGANIC
Adults	*Children*	disturbances in sleep pattern
abdominal pain	drowsiness	nausea
constipation	irritability	anorexia
vomiting	vomiting	vomiting
non-abdominal pain	gastrointestinal	vertigo and headache
asthenia	symptoms	muscular weakness
paraesthesiae	ataxia	weight loss
psychological	stupor	tremor
symptoms		diarrhaea
diarrhea	fatigue	abdominal pain
		hyperexcitability
		mania

Treatment

Chelating agents are used to treat lead poisoning. These compounds contain electron-donating groups that enable them to bind with lead and are subsequently excreted in the urine. The three agents in common use are BAL, EDTA and D-penicillamine, the latter being the one of choice. A high enough dietary calcium is required during treatment, for the chelates are not specific for lead and will bind other divalent metal ions such as calcium. DMSA (2,3-dimercaptoniccinic acid) is more specific for lead and causes less side-effects.

An excess of chelate over lead is required, otherwise this may have the effect of simply redistributing the lead in the body. If insoluble lead is still present in the gut, chelating agents may have the adverse effect of solubilizing it, worsening the situation.

Conclusion: differential diagnosis

Being an uncommon disease with no specific symptoms, lead poisoning should be considered in the differential diagnosis of patients presenting with anemia, psychogenic disorders (seizures, mental retardation, behavioral disorders, pica), abdominal pain, growth retardation and other development problems.

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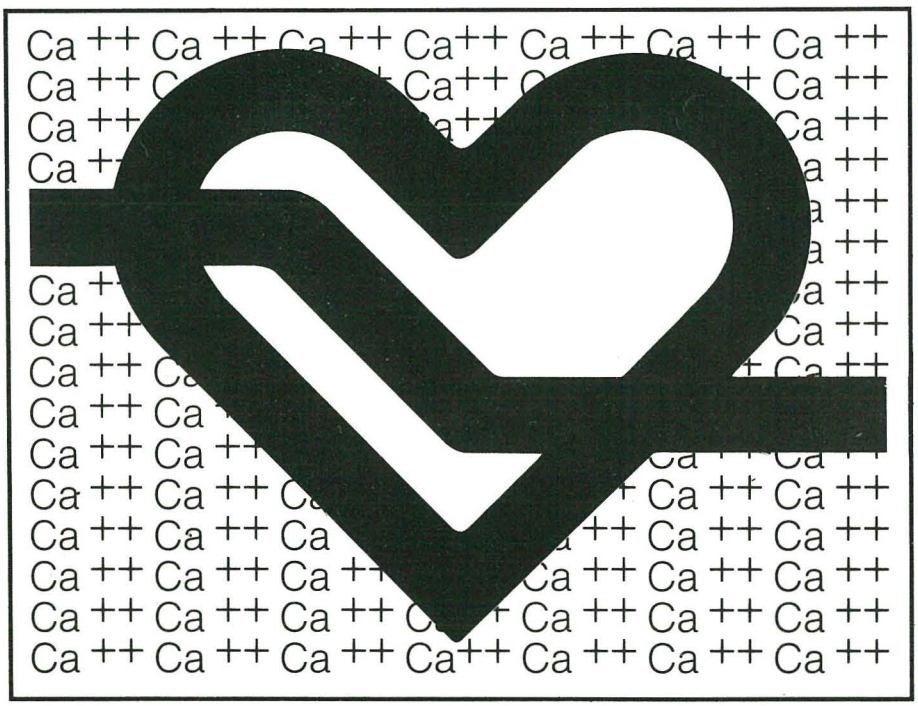

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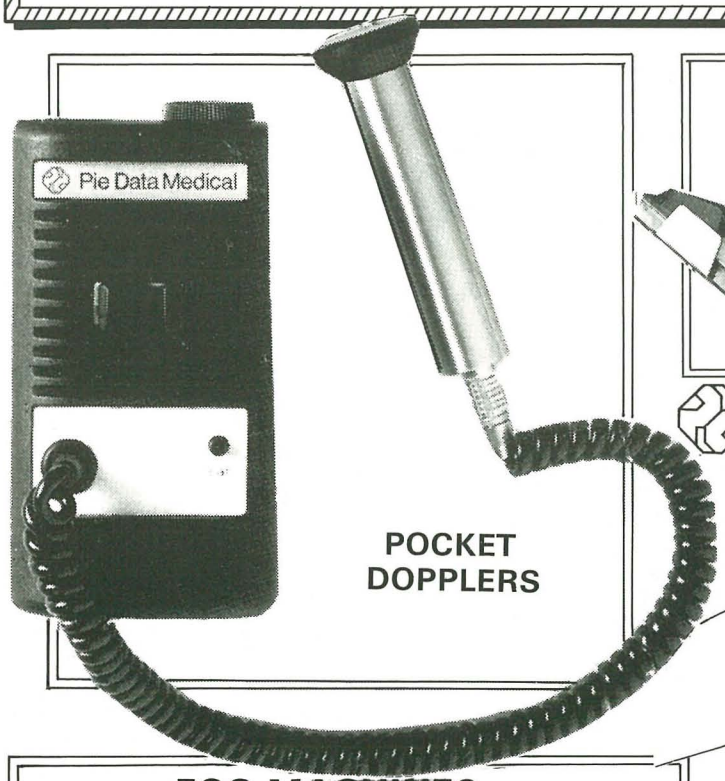

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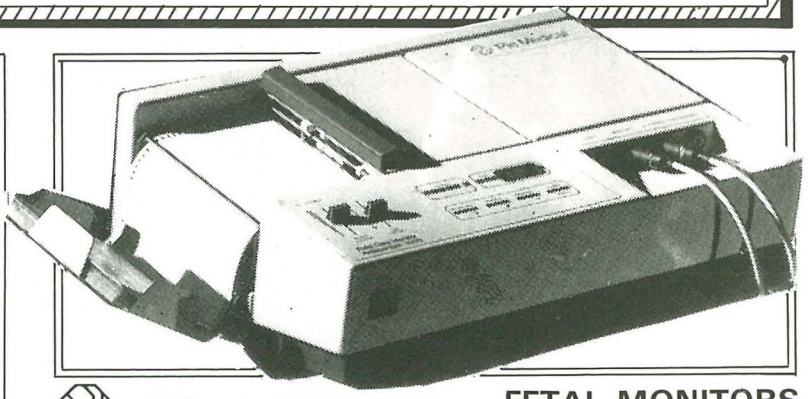

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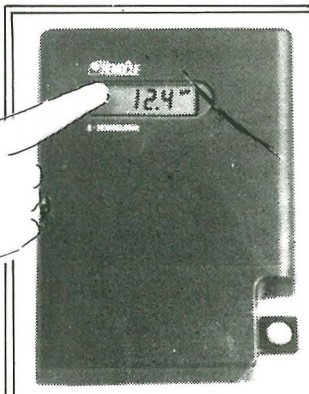

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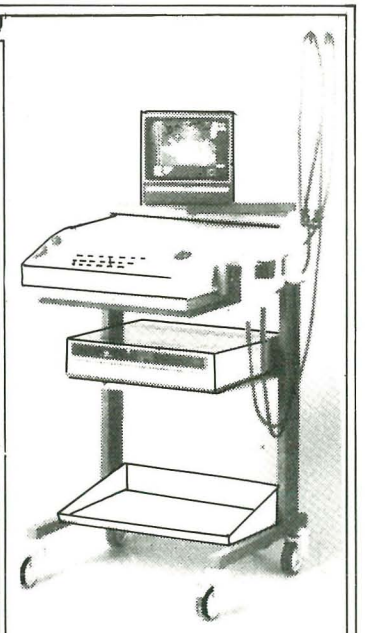

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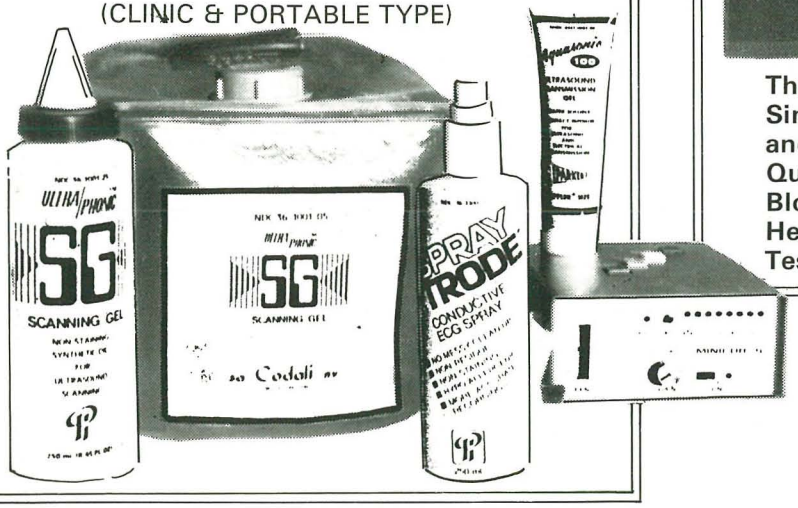

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FIRST-AID IN TRAUMATIC AMPUTATIONS

MARK BUGEJA M.D.

Senior Casualty Officer
St. Luke's Teaching Hospital, Malta.

Traumatic amputation of limbs or digits are fortunately not very common occurrences on our islands; however, enough cases are seen to warrant a modest discussion on how to tackle the situation before the patient is received by the surgeon. I do not claim to present a complete synopsis on the subject but I hope to succeed in emphasizing sufficiently well the basic first-aid measures which should be adopted by all those who may be involved in the management of these patients.

Aetiology

Amputations follow a traumatic event often caused by circular electric saws or motor vehicle accidents. Other cutting implements have been implicated, such as broken glass and washing machines.

Amputations may be complete i.e. with the distal part of the effected limb clearly dismembered from the rest of the body, or partial i.e. with the part still attached by tissue to a greater or lesser extent. It is always safer and wiser to consider a badly severed appendage or limb as *completely amputated* and to manage as such than to overlook the damage and risk irreversible ischaemic harm to the tissues that may, at a glance, appear viable warranting nothing more than a splint.

Prognosis

The outcome of the amputated part depends on a multitude of factors:

1. Extent of the Injury;
2. Nature of wound;
3. Level of amputation;
4. Time interval between accident and eventual surgery;
5. Ambient temperature;
6. First-aid and resuscitative measures;
7. Facilities for replantation surgery;
8. Post-operative complications;
9. Age and general health of the patient.

Success of replantation surgery relies basically, as far as first-aid is concerned, on what is done to the patient and his traumatised limb within the first hour or so of the injury. Every attempt must be made to ensure optimal management as this may be of critical importance to the individual patient. A manual worker may not be effected by the loss of a forefinger segment whereas a musician would be badly incapacitated. Loss of a finger may not matter much to many individuals but a thumb is essential for the use of the whole hand in any situation.

Ischaemic time

Muscle has a very low ischaemic tolerance when compared with other tissues, hence, the pre-operative ischaemic time permissible in major replantations (proximal limb injuries) is considerably shorter than for minor (more distal) replantations.

Irreversible muscle damage often occurs after 6 hours of anoxaemia without cooling. In our hot summer weather this duration of tolerance is shorter still! It follows that by cooling the amputated part to about 4 degrees celsius immediately, ischaemic tolerance can be greatly prolonged by several hours by the decrease in the metabolic rate, and therefore, of the oxygen demand of anoxic tissue at this temperature.

First-aid measures

1. *Tourniquets:* On **NO** account should these be employed. Bleeding wounds should be packed well and a firm but not too tight bandage applied over the packing. Tourniquets often stop venous return but not arterial blood flow promoting more bleeding! Well applied, they not only aggravate the trauma by crushing the tissue over which they are applied but deprive healthy tissue between them and the wound of a vital circulation and occlude anastomotic channels that may be providing sufficient physiological support to incompletely amputated limb segments. They also predispose to more extensive intravascular clotting of blood not to mention the risks when these tourniquets are subsequently removed in hospital.

2. *Resuscitation:* After the wound is packed well an intra-venous line should be established and normal (physiological, 0.9%) saline infusion started. It is important to note that these measures for upper limb injuries should spare the opposite limb veins; hence in such circumstances all drips should be set up in the lower limb veins. Vessels in the intact upper limb may be crucial for choosing and transplanting the correct calibre vascular auto-grafts to the severed area. Pulse and blood pressure should be recorded and a patent airway, adequate ventilation and systemic circulation ensured. Blood should be saved for cross-matching before O negative blood, plasma or dextran is infused.

3. *Amputated part:* (See illustration)

(a) Every severed part must be saved no matter how badly damaged it appears to be.
(b) It should be wrapped in compresses moistened (not dripping) with physiological saline or Ringer's solution.
(c) It should be placed and sealed in a plastic bag.
(d) This bag is then placed inside another bag containing 2/3 water and 1/3 ice.
(e) The outer bag is fastened below the closure of the inner bag to prevent unphysiological water coming into contact with the tissue.

Cooling the part in this fashion reduces its temperature to about 4 degrees celsius without the danger of inducing frost-bite which would make

Illustration: Correct storage of an amputated part.
Note: Further protection is afforded by placing in a suitable container, such as a cardboard box or plastic lunch box.

the tissue non-viable and therefore useless. Tissue preserved thus has been shown to survive for over 20 hours!

Time taken in performing these measures before transportation to hospital, is time well spent. One must remember that although our island is small and distances are short, there is no guarantee that the patient will arrive in hospital in good time for these measures to be instituted there. Ambulances and their drivers are not immune to mishaps which may grossly delay the journey to the detriment of the patient. Although ambulances are often equipped with swabs, dressing and saline bottles, ice and plastic bags can easily be obtained from nearby houses, shops (grocers and butchers), bars or hotels.

One must not be over-enthusiastic in executing first-aid treatment. Wound surfaces should not be tampered with in an attempt to clean them, nor should any antibiotics or antiseptics be applied. Cleaning of these wounds is to be undertaken only by the surgeon so that further trauma to the delicate neurovascular endings is prevented and reconstructive surgery and subsequent healing processes are not jeopardised needlessly.

In the case of large limb segments or parts which are only partially amputated, similar management is called for. However, since it is not practically possible to put such limbs in bags as described earlier, ice-bags containing 1/3 ice and 2/3 water are placed over the limb which has been first covered by compresses moistened with physiological solution and splinted.

On arrival in hospital these measures are ensured by checking what may have been already done on site or by instituting them without further delay. Apart from briefly enquiring about mechanism of injury, medical history and noting of allergies, the patient must be promptly examined to exclude other major injuries, resuscitated as necessary, ATT and ATG given prophylactically, blood taken for base-line urgent investigations and cross-matching and urgent X-rays taken accordingly. Infusions are started before blood is available (saline, Ringer's solution, plasma or plasma substitutes e.g. Dextran-70 or GELAFUNDIN) and a record is kept of all infusions given. Wide bore cannulae are preferred to allow rapid infusions in shocked patients (colour codes of VENFLONS — grey or green at least). More than one line is often necessary and a subclavian or jugular line may be required in cases of severe hypotension and this is performed by an anaesthetist. Catheterisation of the bladder is necessary in assessing fluid balance and ensuring adequate urinary output in shocked patients.

Conclusion

Whereas the general condition of the victim of traumatic amputations demands priority in management, all attempts to recover and preserve dismembered body parts must be made. Cooling of amputated tissues to about 4 degrees celsius by the methods described will prolong their ischaemic tolerance and viability and favours successful replantation surgery lessening morbidity and subsequent disabilities.

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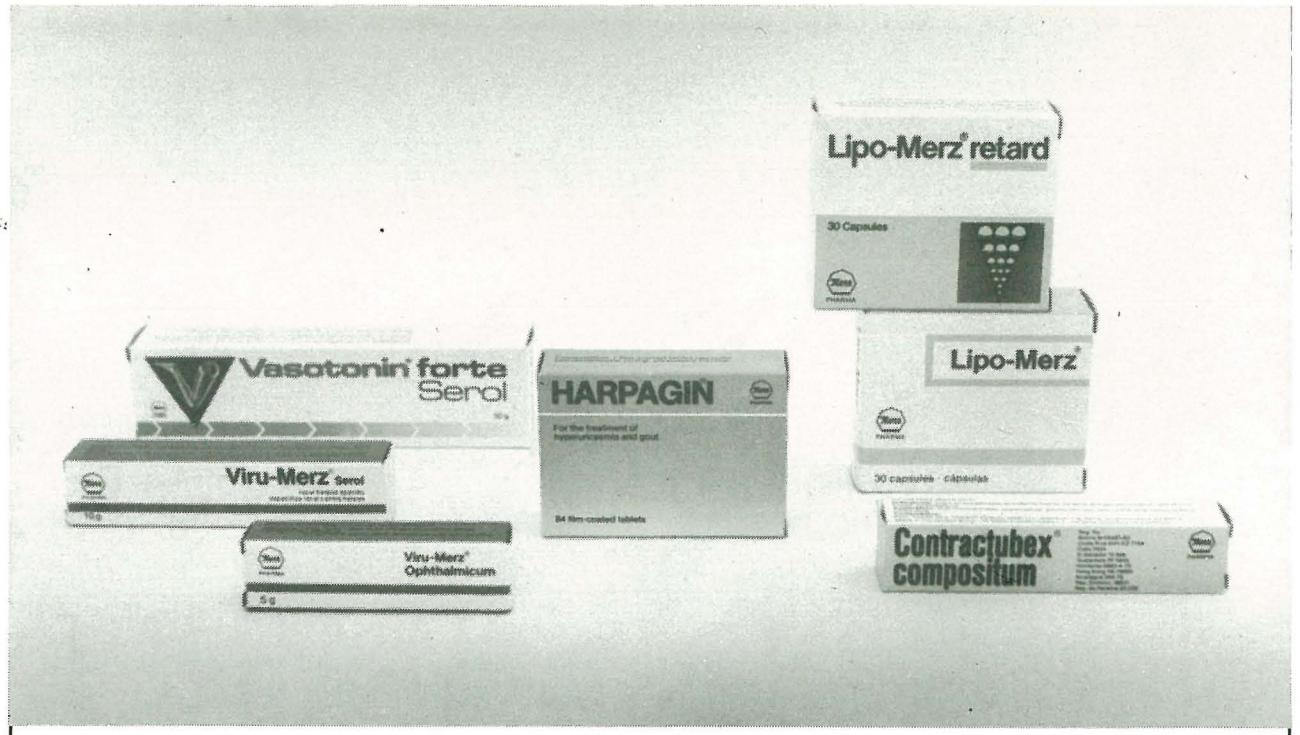

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Letters to the Editor are welcome, particularly those which take up points from material published in the journal. They should not normally exceed one type-written page in length and may include an illustration or table.

The Editorial Board would like to take this opportunity to thank all those who help in materialising each issue of **Medi-Scope** as well as those who by their kind words, constructive criticism and suggestions are helping in making this a fine journal. The Board will be pleased to discuss any problem or difficulties as may arise in connection with **Medi-Scope.**

International Committee of Medical Journal Editors. Uniform Requirements for Manuscripts Submitted to Biomedical Journals.
Br. Med. J. (1982) 284: 1766-70.
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ERRATA CORRIGE. ISSUE No. 12, SPRING '89

Contents:
'Medival' *should read* **'Medical'**
'Psychiotric' *should read* **'Psychiatric'**
Page 1 Column 1 Line 31:
'reduced to premature' *should read* **'reduced in premature'**
Page 6 Column 1 Line 34:
'avove' *should read* **'above'**
Column 2 Line 8:
'trasnparent' *should read* **'transparent'**
Transposition of Columns 2 and 3 of:
'The Deafening Smell Of Pollution'
Page 9 Column 3 Upper two lines missing are:
'... important than frequency. The elimination of various factors, such as ...'
Page 11 Column 1 Line 6:
'control to the' *should read* **'control of'**
Page 13 Figure:
'Proposed HIV Sponsor' *should read* **'Proposed HIV Sensor'**
Page 14 Title:
'ON' *should read* **'OF'**
Column 2 Add **... Custò (1822)** below **... Pisani (1788)**
Page 22 Column 1 Line 2:
'though' *should read* **'thought'**
Column 2 Line 23:
'defaection' *should read* **'defaecation'**
Page 27 Column 3:
'Errata Corrigendum' *should read* **'Errata Corrige'**

COD PIECE

I have frequently observed in these columns how far electronic measuring instruments have come since the first Avo appeared on the market. But if a digital AIDS meter is still a few years off, the same is not true for an invention from the Department of Materials Science and Engineering at Nagasaki University. There they have developed a sensor likely to form the basis of every housewife's dream — a device that measures directly the freshness of raw fish!

Fish freshness factor, K (say that without your dentures) is defined by the percentage of two chemicals, inosine and hypoxanthine, present in the raw fish. Hitherto that has only been measurable by destructive testing (i.e. cooking) — not very popular in oriental cuisine. What the Nagasaki engineers have done is to develop an electronic sensor that measures, not inosine or hypoxanthine, but a smelly gas, trimethylamine, which is also given off in progresively greater quantity as fish becomes time-expired.

The sensor, (*Plantinum Metals Review*, 1989, Vol. 33 No. 1) was developed initially using stannic oxide doped with gold, palladium or ruthenium. When coated on to an alumina tube heated from a coil inside, this device will respond to a trimethylamine concentration of 300p.p.m. at a temperature of 555°C. Other sensors, equally sensitive, have been developed using zinc, tungsten or titanium oxides with small additions of ruthenium.

When practical sensors were built and tested on actual fish, the Japanese researchers found that the readings could be calibrated and reliably compared to the so-called K values determined by chemical analysis. It looks therefore as if it won't be long before we'll be able to challenge the "caught yesterday, guv" claim with the same digital precision we use to turn out a perfect cod mornay.

Research Notes are by John Wilson of the BBC World Service's science unit.

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Indications Acute primary bacterial skin infections, e.g. impetigo and folliculitis.

Dosage and Administration Adults and children: BACTROBAN ointment should be applied to the affected area up to three times a day, for up to 10 days. The area may be covered with a dressing or occluded if desired.

Precautions When BACTROBAN ointment is used on the face care should be taken to avoid the eyes. Polyethylene glycol can be absorbed from open wounds and damaged skin and is excreted by the kidneys. In common with other polyethylene glycol based ointments, BACTROBAN ointment should be used with caution if there is evidence of moderate or severe renal impairment. Use in Pregnancy: Studies in experimental animals have shown mupirocin to be without teratogenic effects. However, there is inadequate evidence of safety to recommend the use of BACTROBAN during pregnancy.

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

Side Effects During clinical studies some minor adverse effects, localised to the area of application, were seen such as burning, stinging and itching.

Further information is available on request from

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