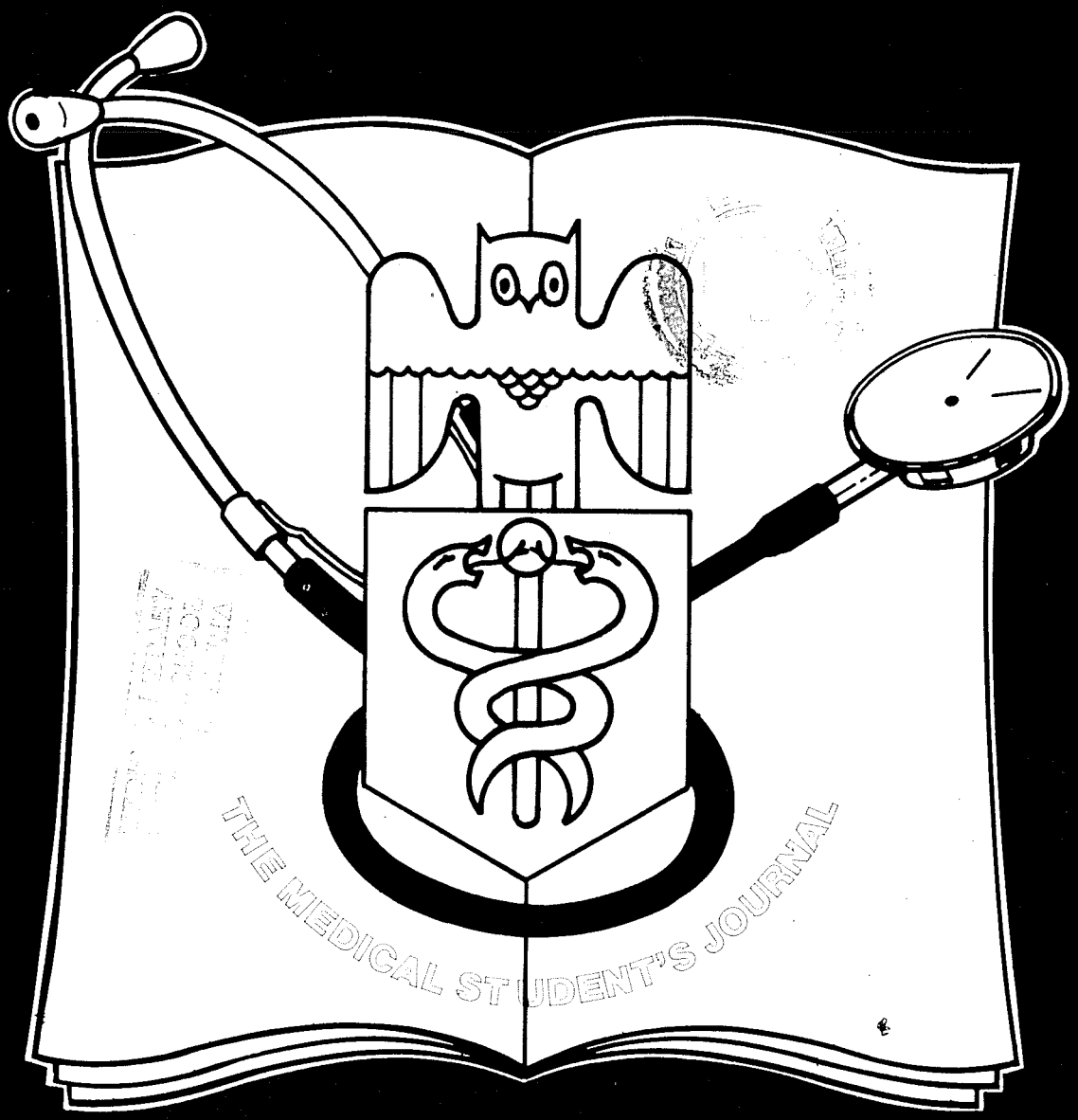
Medi-Scope

ISSUE No.7 1985



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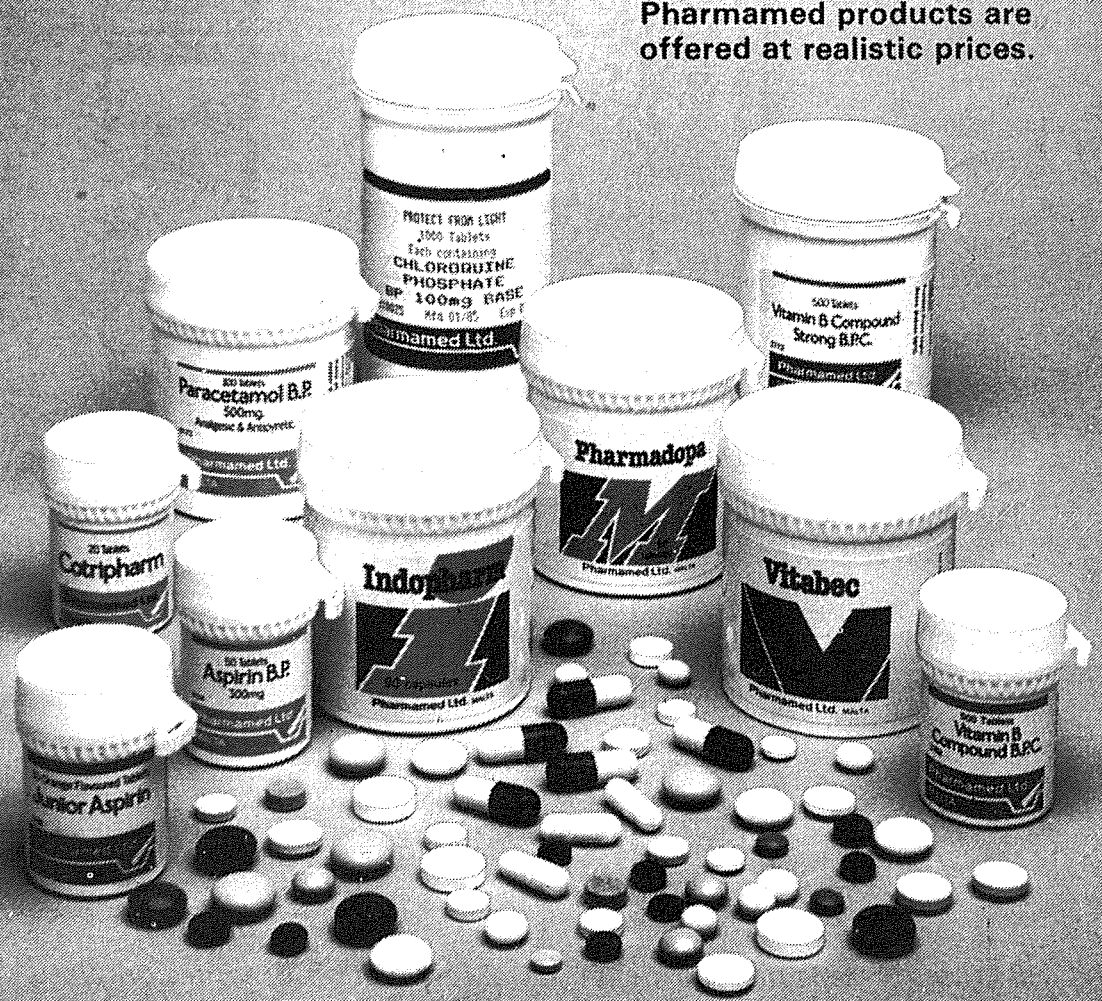

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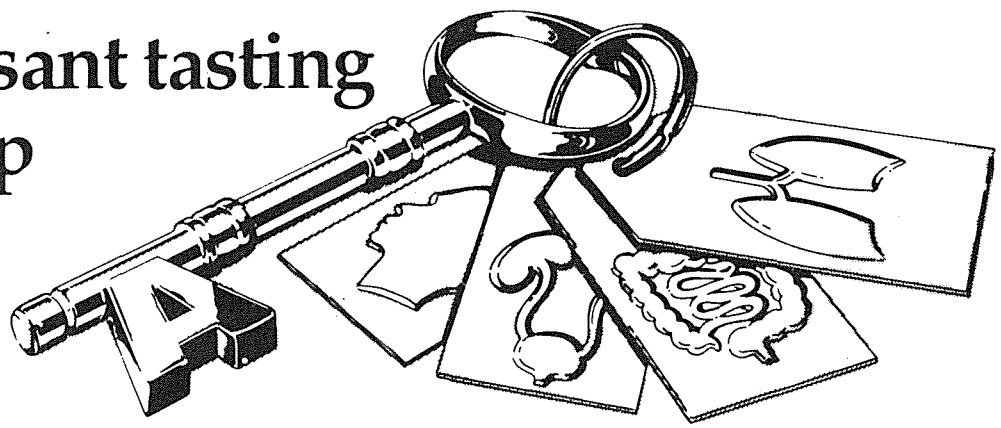

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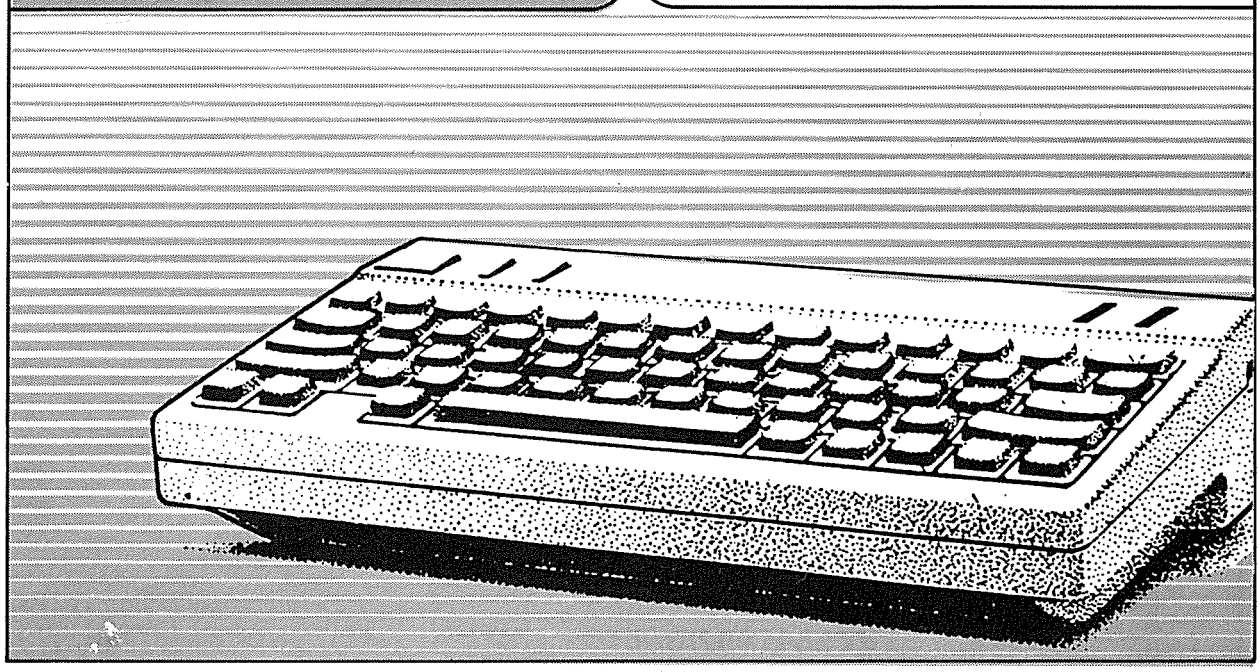

Editor's Letter

Medi-Scope Issue No. 7 1985

Medical Students Journal
University of Malta Medical School
G'Mangia.

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'Absence makes the heart grow fonder'. As fervent readers may have noted, punctuality of publication is not our faith. I would like to thank all those who contributed to and encouraged our efforts in publishing this edition of **Medi-Scope,** especially our Printers, **Dormax Press**, whose patience reaches far beyond the call of duty.

As can be seen, most of the Editorial Board is composed of Vth. year students. As of the next edition, this magazine will change its format slightly but will still remain the Maltese Medical Journal. I shall be handing over the job to Mark Bugeja M.D., our previous editor whose efficiency is well proven.

I would also like to appeal to any medical student, within the large student body, whose interests occasionally rise above the academic, to join the editorial board so as to further the reputation of this fine magazine within the pregraduate sphere.

In this issue the quiz that was ever so popular is being re-introduced and I hope that the answers forwarded will be more numerous than in previous editions. This issue also has an additional 4 pages.

I now sign off, leaving you with a magazine that may not quite fulfill your wildest dreams but will hopefully increase your knowledge.

THE EDITOR

Contents:

Lysol Poisoning

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DR. BERNARDETTE SPITERI, MD
FROM PROFESSORIAL UNIT DEPARTMENT OF MEDICINE

The term "Lysol" was originally registered by a German firm, but following the First World War this registration was cancelled. It is still a protected trademark in certain countries notably USA.

Lysol or Liquor Cresolis Saponatis is a 50% solution of Cresol (3—Methyl Phenol $CH_3C_6H_4OH$) in a saponified vegetable oil. It replaced carbolic acid as a less toxic disinfectant.[1]

Lysol has an amber or red brown colour and a distinctive phenolic odour. At the beginning of this century, fatalities from carbolic acid or phenol poisoning were exceedingly common. Glaister (1902) stated: "Its use is familiar to the lay public as a popular disinfectant and of late years by reason of its facility of purchase and its common use has given rise suicidally and accidentally to more deaths than any other poisonous substance."[2]

The reason lay with the ease with which it could be purchased, it being sold frequently to the general public without any form of restriction. The large number of phenol induced deaths made it necessary to prevent its misuse by including it as a scheduled poison.

Instances of phenol, cresol and lysol poisoning, although much less infrequent, still occur as a means of suicidal or accidental deaths.

The patient usually presents with the characteristic odour about the body and internal organs, and the pronounced brown staining is present round the mouth, drinking being the most frequent method of ingestion. The following case recorded here is particular in that the mode of administration of lysol was by I.V. injection.

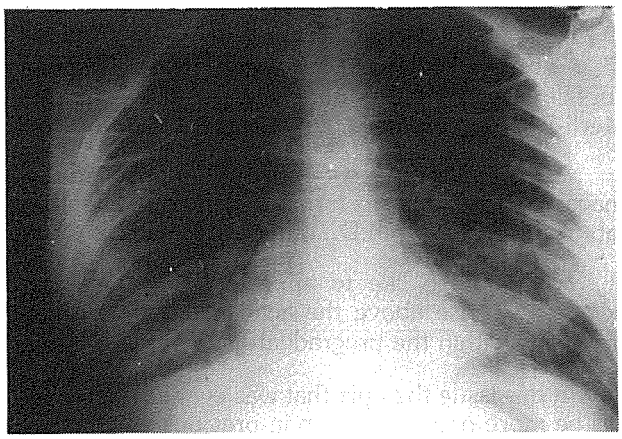

Fig. 1.

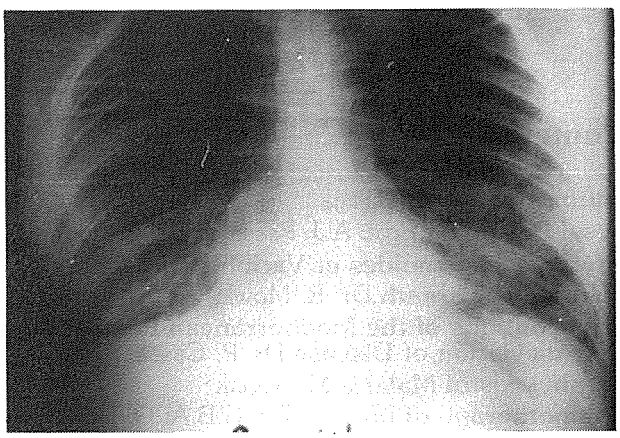

Fig. 2.

Case Report

This case deals with a 36 year old married man, who had been a heroin addict for about 1 year. He

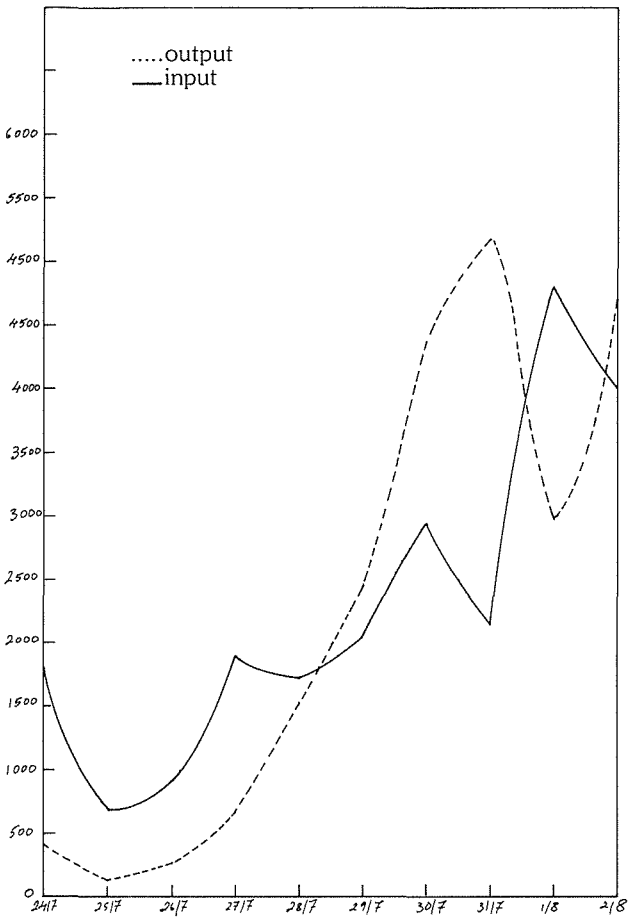

Fig. 3. Graphic representation of table 1.

had been undergoing medical and psychiatric treatment for his drug addiction and suffered periods of depression. He presented at 3.00 am at the Casualty department after having injected 5cc of lysol I.V. in a suicidal attempt, the lysol having been bought that respective evening from a chemist. His last I.V. injection of heroin had been 3 days previously.

The patient was fully conscious and quieted. On examination the patient was tachypnoeic with a respiratory rate of about 36/min and had a mild tachycardia. He suffered a slight drop in B.P. 100/80 and was running a temperature of 99 F. On auscultation there was a good air entry on both sides; rhonchi and scattered wheezing could be heard in both lung fields. No abnormalities could be detected abdominally or in the CNS.

As emergency treatment an I.V.I. of N. Saline with 250 mg. Aminophilline, (6 hourly) was set up. Boluses of hydrocortisone 100 mg I.V. and Lasix 60 mg I.V. were given 6 hourly. Blood for toxicology, including phenol levels were taken.

Within the next few hours the patient developed a more severe tachypnoea, cough and cramping epigastric pain. He was sweating profusely and on auscultation one could hear coarse rhonchi and wheezing. He was transfered to I.T.U.

The patient's urinary output became increasingly impaired and by the 25.7.84 — 1 day post admission the patient was suffering from acute renal failure. On CXR markedly prominent patchy shadows in the

Date	Input	Output
24/7	1800cc	377cc
25/7	693cc	138cc
26/7	922cc	272cc
27/7	1806cc	665cc
28/7	1480cc	1283cc
29/7	2080cc	2450cc
30/7	2950cc	4370cc
31/7	2150cc	5180cc
1/8	4800cc	2950cc
2/8	4000cc	4750cc

Table 1. Daily fluid intake and urinary output (see graphic representation - *Fig. 3.*)

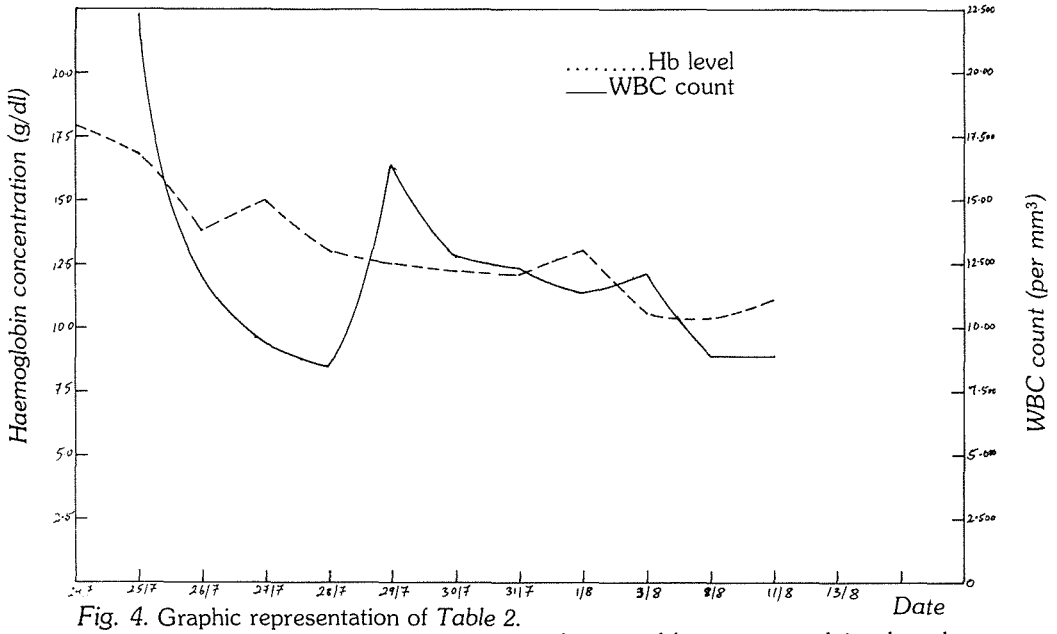

Fig. 4. Graphic representation of *Table 2.*

paracardial basal regions could be seen on both sides indicating interstitial pneumonitis Fig. 1, 2, 6, 7. The patient had his first session of haemodialysis (blood urea 167 mg/dl) on 26.7.84. Subsequent to this the patient had 3 more sessions of haemodialysis but during the third session he developed runs of ventricular ectopics and the haemodialysis was stopped prematurely.

On the 4th day post admission the patient developed continuous abdominal pain with diarrhoea. He was treated with Lomotil 1 tab. t.d.s.

On the 31.7.84 the diuretic phase of acute renal failure set in, the patient passing 5180 cm^3 of urine. His lung problem was resolving hourly.

Following this the patient made a satisfactory recovery being discharged on 13.8.84 that is 19 days post admission. His general condition was good, his main problem being a residual anaemia (Hb 11.1 g/100 mls) and bouts of depression. He is currently still under medical and psychiatric supervision.

Discussion

Cresol poisoning, as mentioned previously is almost invariably due to one or other of the coal tar disinfectants e.g. Lysol or Teyes' Fluid. When the mode of ingestion is oral, lysol burns are frequently present on the lips and may extend over the face and neck as corrosive fluid trickles away. The stains are

Date	Hb g/100mls.	WBC per mm^3	PCV %
24.7.84	17.8		
25.7.84	17.3	22,300	55
26.7.84	13.6	10,200	50
27.7.84	15.0	9,400	30
28.7.84	13.0	8,400	37
29.7.84	12.6	16,100	
30.7.84	11.8	12,800	31
31.7.84	11.6	12,000	
1.8.84	13.0	11,300	35
3.8.84	10.7	12,200	32
8.8.84	10.3	8,900	31
11.8.84	11.1	8,800	
13.8.84		DISCHARGED	

Table 2. Daily haemoglobin concentration, WBC count and PCV (see graphic representation - *Fig. 4*)

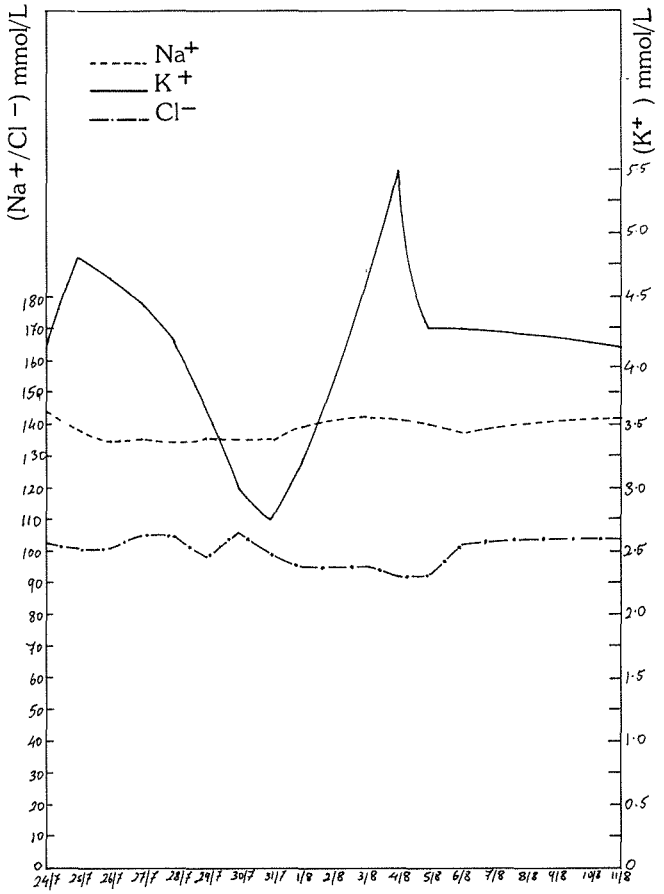

Fig. 5 Graphic representation of *Table 3.*

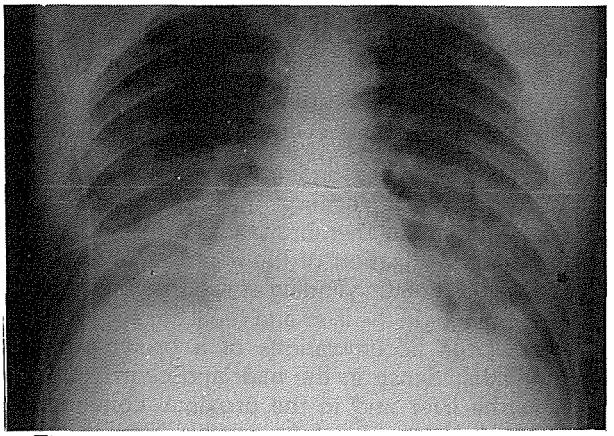

Fig. 6

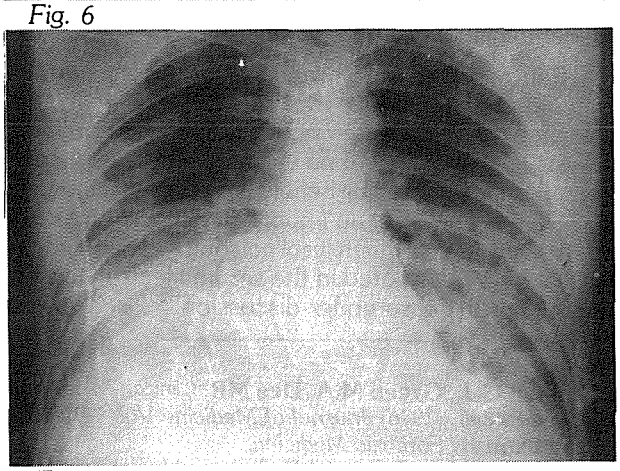

Fig. 7

Date	Na^+ (mean) in mmol/L		K^+ (mean) in mmol/L		Cl^- (mean) in mmol/L	
24/7	144		4.1		103	
25/7	138		5.1		101	
25/7	139	139	5.0	4.8	101	103
25.7	139		4.4		105	
26/7	137		4.8		105	
26/7	134	135	4.0	4.4	98	102
26/7	135		4.1		106	
27/7	135	135	4.3	4.2	19	97
27/7	135		4.2		95	
28/7	134		3.9		95	
30/7	135		3.0		95	
31/7	134		2.8		92	
1/8	137		3.2		93	
1/8	141	139	3.7	3.3	101	98
1/8	141		3.7		102	
3/8	141		4.7		96	
4/8	144		4.4		96	
5/8	140		4.2		97	
6/8	137		4.7		102	
11/8	142		4.1		105	

Table 3. Daily electrolyte concentration in the serum (see graphic representation - *Fig. 5.*)

light brown in colour, but the smell of the breath, even the odour in the mouth of the dead is usually strong and unmistakable. In the case under discussion there were no signs of burns not even at the site of puncture.

Interesting are the findings at post-mortem — wrinkled greyish leathery hardening of the oesophageal mucous membrane and a softer flaking brown corrosive fixation of the gastric mucosa are present.[3] An interesting finding as recorded by Bruce et al. are changes in the liver and renal cortex. In both there are large accumulations of a brown-orange pigment, most dense in the mid- and centri-lobular zones in the liver and in the proximal convoluted tubules and glomerular tufts in the kidneys. the pigment was found to be lipofuscin.[2]

Peritoneal dialysis and lysol poisoning is mentioned in the literature.[4] It appears that in the presence of adequate renal function peritoneal dialysis appears to be of no value in removing phenol from the body. It may be beneficial in preventing a rise in Serum K^+ possibly an important factor in the early deaths which occur with lysol poisoning. This incidental rise in K^+ was noted in the serum electrolyte estimations of the case under discussion.

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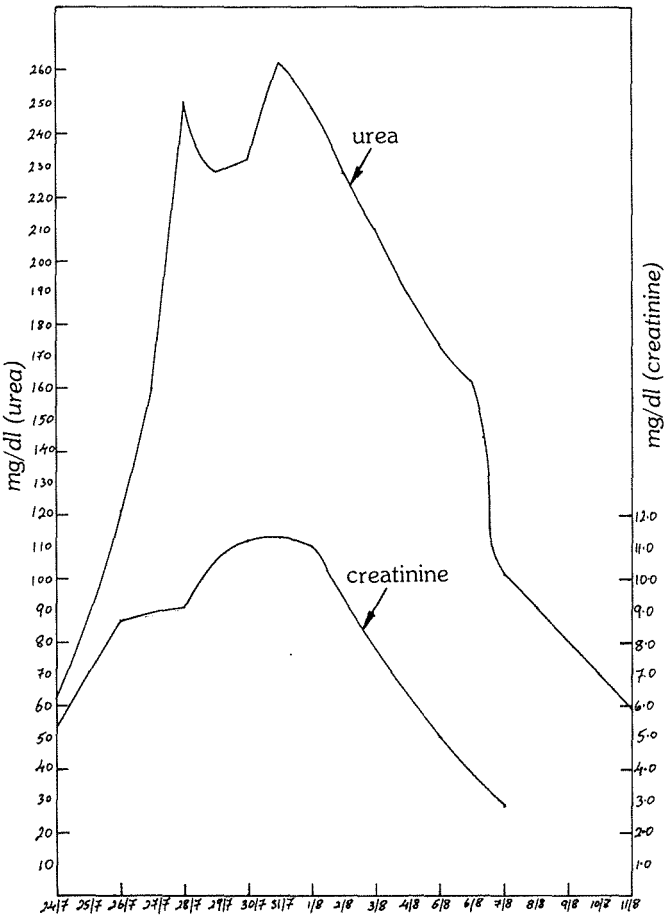

Fig. 8. Graphic representation of *Table 4.*

Date	Urea mg/100 mls.	(Urea Mean)	Creatinine mg/dl.
24/7	63		5.2
25/7	108	111	8.7
25/7	100		
25/7	126		
26/7	167	160	
26/7	148		
26/7	167		
27/7	234	250	9.2
27/7	265		
28/7	228		10.6
30/7	262		11.2
31/7	248		11.3
1/8	236	227	11.0
1/8	226		
1/8	220		
2/8	210		
3/8	190		
4/8	172		5.0
6/8	101		2.9
11/8	58		

Table 4. Daily blood urea and serum creatinine estimations (see graphic representation - *Fig. 8*)

Pityriasis Lichenoides et Varioliformis Acuta

(PLEVA; Mucha-Habermann disease): *A Case Report*

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History

G.C. an 8 year old boy from Senglea, presented in July 1983 with crops of erythematous papules rapidly evolving into vesicles and ulcers with haemorrhagic crusts. Lesions healed spontaneously with post-inflammatory hyperpigmentation, but heavily infected ones left scars. The rash started on the face but soon became generalized.

Examination

The child looked remarkably well in spite of the rash and a temperature of 100°F. There were several cutaneous lesions at various stages of evolution (Fig. 1). The general examination was otherwise negative.

Investigations

A freshly blistered lesion was sampled for routine histology. This showed a mononuclear infiltrate surrounding blood vessels and invading a degenerating epidermis (Slide No.: 3546/83).

The E.S.R. was 35 mm in the 1st hour (Wintrobe method). The Hb, WBC count and differential, blood film, urinalysis and agglutinin titration were normal. A throat swab yielded no pathogens and his ASOT was less than 200 IU/ml.

Treatment

He was treated initially with systemic antibiotics and topical astringents. Subsequently he received oral prednisolone for a period of six months (2.5 mg in the morning on alternate days) and topical adrenocorticosteroids for the more troublesome lesions. The rash subsided and did not relapse on withdrawal of the steroids..

Comment

This child had Pityriasis Lichenoides. In the milder form of this disease, called Pityriasis Lichenoides chronica, individual lesions evolve slowly and remain papulosquamous, inviting clinical confusion with psoriasis or lichen planus. In the more severe form, called Pityriasis Lichenoides et Varioliformis Acuta, the lesions evolve much more rapidly and epidermal involvement produces papulonecrotic lesions which may be misdiagnosed initially as chickenpox.

Histologically, the disease is a lymphoid vasculitis. This may be the result of a hypersensitivity reaction to an infective organism but so far all attempts to isolate a culprit have failed.

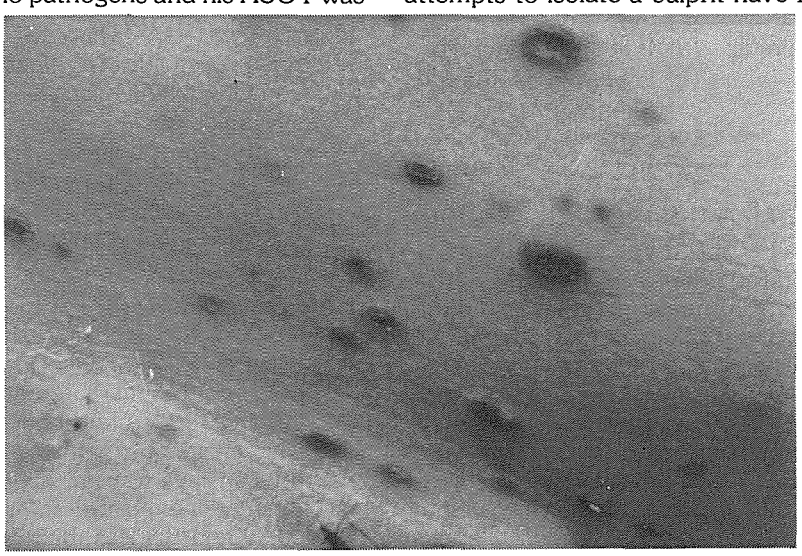

Fig. 1. Papulonecrotic lesions in the right iliac fossa

Baby's First Breath — Consideration of Some Physiological Aspects

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The Onset of Respirations

Baby's first breath is probably the most important event in the delivery room for everybody concerned. The factors which cause this to happen have always fascinated doctors and scientists for a long time and it is through extensive research with animal newborns and later with humans that today we are perhaps beginning to understand the complex factors which help the baby in the initiation of the first breath. However, the factors discussed below are not necessarily *all* the factors, because, there are definitely many more factors which we are not fully aware of as yet.

The First Breath

With the clamping of the cord, the newborn establishes and sustains a pattern of regular respirations within about 60 seconds.

The various factors involved are:-

(1) Physical Stimuli: (a) Influence of gravity.
(b) Lowering of the skin temperature.
(c) Sensation and stimuli from the skin, e.g. tapping etc.

(2) Chemoreceptors — Responding to the changes in PaO_2 and $PaCO_2$.

(3) The Respiratory Centre:- C.N.S. Activity.

(4) Aeration of the Lungs:- Normal inspiratory pressure is about 70 cm of H_2O in the mature newborns.
On radiological studies, the lungs show evidence of aeration within 3 seconds of the onset of breathing.

(5) Clearance of Lung Liquid:- Lungs contain approx. 3 ml/Kg of fluid at birth — a volume equal to the Functional Residual Capacity (FRC). Up to 35 ml of fluid drains from the infant's mouth during a normal vaginal delivery.

(6) Pulmonary Perfusion.

(7) Lung Compliance:- Changes in the volume in ml for unit change in pressure in cm H_2O. Normally — 5 cm H_2O [1].

(8) Airways Resistance.

What is Surfactant?

(1) It is a layer of lipoprotein, which keeps the pressure constant within the alveoli irrespective of their diameter.

(2) Lowers surface tension *in vitro* to less than 10—15 dyn cm^{-1}

(3) Synthesised in the Type II or Granular Pneumonocytes in the alveolar epithelium.

(4) Stored in the Lamellar bodies of the cells.

(5) Released by fusion of the Lamellar body membrane with the cell wall.

(6) Complex biochemistry — but basically it has:
(A) Lipids (85%) —
(a) Phospholipids,
(b) Neutral lipids,
(c) Cholesterol,
(d) Sphingomyelin.
(B) Proteins (15%).

How Does Surfactant Work?

(1) All the components of surfactant must be present and must interact in order to achieve its striking surface tension lowering action.

(2) The enzymatic pathways for lecithin synthesis are sensitive to cold, hypoxia and acidaemia.

(3) Postnatal exposure to temperatures less than 35°C and pH less than 7.5 causes a rapid fall in the amount of available surfactant.

(4) Surfactant and Type II Pneumonocytes appear in the human lungs at about 20 weeks gestation. The amount increases slowly until a surge occurs at about 30—34 weeks when a large amount of surfactant suddenly becomes available.
(5) Detection of this surge prenatally indicates pulmonary maturity and means that the infant should *not* develop Hyaline Membrane Disease when delivered.
(6) Prenatally the amount of surfactant present in lungs can be assessed by analysis of liquor amnii, since surfactant is constantly being washed up the fetal airways with the fetal lung fluid.
(7) Infants with HMD have lower levels of T3 and T4 in their blood than gestation-matched control babies. Congenital hypothyroid babies have an increased incidence of Hyaline Membrane Disease.
(8) A normal thyroid function is required for a normal surfactant development.
(9) At birth the surfactant has to be released and spread out on the alveolar surface. This is primarily dependent upon ventilation and distension of alveoli.
(10) Surfactant, once released, has a half-life of 10—14 hours. The rate of breakdown is increase by breathing pure O_2 and over-ventilation and using inflation pressures of 40 cm H_2O.

How Do You Measure Surfactant?

The amount of Surfactant present in various fluids has been measured in four ways:-
(1) By comparing the ratio of Lecithin to Sphingomylin (L/S Ratio).
(2) By measuring the absolute amount of Lecithin present.
(3) Measuring the amount of Palmitate (from DPL).
(4) Assessing the surface tension lowering properties of the fluid in the 'Shake test'.

Physiological Changes in H.M.D.

(A) *Changes due to Deficiency of Surfactant:*
1. Lung compliance falls to about 25% of normal. Decreased FRC (Functional Residual Capacity) and TGV (Thoracic Gas Volume). Increased Dead Space.
2. Greater effort is required to achieve alveolar ventilation — with increase in the work of breathing.
3. Intrapulmonary shunting of blood past completely or partially collapsed alveoli causes hypoxaemia.

(B) *Changes due to Hypoxaemia*
1. C.V.S.: Pulmonary artery pressure remains at fetal level leading to Right to left Shunt aggravating the hypoxaemia. Also ductus fails to close.
2. Vascular drainage causing transudation of fluid and peripheral oedema.
3. Anaerobic metabolism — leads to accumulation of lactic acid and severe acidaemia. Also acidaemia and hypoxaemia are aggravated by low blood volume and hypotension.
4. Diminished organ perfusion leads to acute renal failure, necrotising enterocolitis and possibly brain damage.

Prevention of H.M.D.:

1. This can be attempted by minimising those conditions which, during labour, or in the first few minutes inhibit surfactant synthesis.
2. Induce surfactant synthesis in the fetal lungs prior to delivery.
   This can be done by:-
   (1) Giving narcotics (opiates etc.) to the mothers.
   (2) Use of glucocorticoids.

Physiological Principles of H.M.D. Treatment

1. Once HMD has developed, surfactant cannot as yet be replaced in the lung.
2. Attempts using purified DPL aerosols have failed.
3. The aim of treatment is to keep the baby alive in good condition so that endogenous synthesis of surfactant may take place.
4. Avoidance of hypoxaemia, acidaemia, and hypothermia which causes 'Consumption' of surfactant.
5. Continuous Positive Airways Pressure (CPAP).
6. Intermittent Positive Pressure Ventilation (IPPV).

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Contributions of the Mediterranean Peoples to the Control and Alleviation of Disease

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The main contributions of the Mediterranean peoples to the control of disease and the alleviation of the sick have been:

a the rise and development of the concept of hospital care and treatment;
b the promotion of the organised teaching of medicine and surgery;
c the adoption of practical measures for the preservation of public health on the supra-national plane;
d the elucidation of the causes and means of transmission of infectious illnesses which led to the adequate control of communicable diseases.

The Hospital Idea

Mediterranean medicine can trace its beginnings to Babylonia and Egypt. Babylonia medicine was mainly based on astrology so that various parts of the body were allocated to the Zodiac signs and the outcome of disease was worked out by observation of the particular constellation involved. As Babylonian civilization matured, the practice of medicine emerged as a separate entity and its practice was governed by a set of regulations that laid down in detail how the practitioner was to conduct himself in carrying out the various treatments. It also prescribed the scales of fees which he was entitled to charge and fixed the penalities for malpractice. These laws form part of the Code of Hammurabi (1948-1905 BC) which dates from the 20th century BC and forms the basis of our professional ethics.

Around 1500 BC the Egyptians recorded their medical knowledge on papyri. It consisted of a mixture of religious practices, incantations and pharmaceutical prescriptions for various ailments. They also stressed the importance of personal hygiene and cleanliness of house and city to ensure healthy living.

This medical knowledge of Babylonia and Egypt reached the Mediterranean through the succeeding civilisations of Greece and Rome becoming more scientific in the process. Greek medicine attained its climax of development with the physician Hippocrates who was active in the 4th century BC. He promoted a new line of thought in medicine by regarding illness as a natural phenomenon and rejecting astrological and mythological influences in the causation and outcome of disease. The supernatural element, however, was not immediately shed but persisted for many years afterwards and was responsible for the origin of the hospital idea.

The earliest proto-types of hospitals were founded at Cos, Epidaurus and other places in Greece. They centred round temples dedicated to Aesculapius, the Greek god of medicine, the son of Apollo. These temples were placed in healthy

surroundings remote from urban centres and usually in the vicinity of hot springs and medicinal waters. Buildings were constructed for the accommodation of the sick who went to these shrines to plead to the god for recovery of their health. Consulting and treatment rooms formed part of the temple complex. Thus were the first hospitals born. After obtaining a cure the grateful patient gave a thanks offering to the god which usually consisted of a model of the diseased part in silver or gold or other material; and a votive tablet recording the history of the case was hung in the temple. This hospital concept eventually crossed over from Greece to Rome. In 293 BC an epidemic broke out in Rome and as the inhabitants found themselves unable to control the ravages of the disease they asked the Greeks to lend them one of their gods for whom the temple of Aesculapius was erected in Rome.

The sick who resorted to him for deliverance from illness were motivated by religious reasons but later on the Emperor Claudius, who reigned from AD41 to 54, turned the temple into a place of refuge for the sick poor. the temple thus became a hospital although of a rudimentary form. These hospitals, where free care was given as a Christian duty, were usually rough buildings with straw on the floor for beds and where patients with all kinds of diseases were mingled together.

A more advanced type of hospital was developed by the Romans in connection with their army medical services. A chain of such hospitals was set up for the care of sick and wounded soldiers on lines similar to the field ambulance, clearing stations and base hospitals of modern military organisations.

The conquest of Spain by the Arabs from North Africa in the 8th century AD, provided a great stimulus to hospital building. Magnificent hospitals flourished in association with Arabian schools of medicine at Seville, Toledo and Cordova. From Spain the hospital idea spread to other places in Europe so that the Middle Ages saw an increase in the number of these institutions which were primarily intended for the care of the indigent sick. They were built by town administrators, by charitable bodies, by rich benefactors and by religious organisations.

One of these religious organisations was responsible for the construction of a chain of hospitals extending, at different periods, from the Eastern Mediterranean to the Maltese Islands. This was the Order of the Knights Hospitallers of St John who founded their first hospital in Jerusalem about the middle of the 11th century for the nursing of pilgrims who fell sick while visiting the Holy Land. They carried out their hospital work in Jerusalem until they were expelled from that city by the Moslems and had to return to Acre in 1191. Here they established a hospital near the centre of the city. When Acre was lost by the Christians in 1291, the Knights of St John crossed over to Cyprus where they founded a hospital for the sick,poor and pilgrims at Limassol. In 1310 they passed over to Rhodes where they again erected another hospital which was replaced by a larger one between 1440 and 1478. This building, in Gothic style, still stands in the Street of the Knights[1].

When the Knights of St John came to Malta in 1530 they founded a hospital at Birgu which became known as the *Infermeria*. It was governed by the same rules that had been in force in Rhodes and was reserved exclusively for men. Besides the sick and the wounded it also cared for orphans and foundlings. This infirmary, however, was not the first hospital to be set up in Malta for as early as the 14th century (1372) a hospital had been functioning at Rabat near the old capital city of Mdina. It was originally known as St Francis Hospital but later was given the name of *Santo Spirito* Hospital. Initially it was administered by the Friars Minor Conventuals but in 1433 it passed into the hands of the administration of Mdina. It received patients of both sexes in the 16th century but later was reserved entirely for women and foundlings.[2] It was enlarged in subsequent centuries and continued to serve the community as a hospital until 1967 when it was closed down for reasons of economy. The building, however, still stands.

When the Knights moved from Birgu to Valletta they embarked on the construction of a new hospital in 1574. This Holy Infirmary, as it came to be called, became known to all travellers who criss-crossed the Mediterranean and earned the praise of foreign visitors for its spaciousness, the competence of its medical and surgical staffs, its orderly management and discipline and the classification of the sick in separate wards according to their type of illness. When Napoleon came to Malta in 1798 and expelled the Knights of St John he took over the Holy Infirmary for the use of his troops. The British, who ousted him in 1800, did the same and continued to use it until 1920.

From the Mediterranean the hospital idea spread all over Europe as far north as Great Britain where it gave rise to such ancient hospitals as those of St Bartholomew and of St Thomas in London in 1123 and 1215 respectively.

The Organised Teaching of Medicine and Surgery

This was another development that originated in the lands of the Mediterranean in the fourth century BC. It began in the small island of Cos situated in the Eastern Mediterranean near the coast of Asia Minor. Here Hippocrates, one of the most outstanding physicians of all time, was born in 460 BC and here he spent the greater part of his life. His pre-eminence in the medical field is due to the fact that he (a) initiated the separation of medicine from mythology, mysticism and philosophy; (b) gave existing medical knowledge a systematic order and based it on the bedside observation of the patient; (c) laid down the principles of ethical conduct that to this day bind members of the profession in their dealings with the patient and with one another; and (d) was the

founder of the earliest medical school to emerge in Europe.

This school in the island of Cos gave rise to a collection of medical writings known as the Hippocratic Corpus which is made up of over 60 distinct works. Emphasis was laid on the careful observation of the patient's complaints and symptoms, on reaching the right diagnosis and on recording the history of the patient's illness. These case records are set out so accurately that the physician of today can recognise the diseases described in these medical writings. The only material relic of Hippocrates and his school that has survived is an ancient plane tree which stands in the centre of the town of Cos. Under its branches Hippocrates is reputed to have taught his pupils holding an open-air clinic.

Hippocratic medicine passed from Greece across the Mediterranean to the city of Alexandria on the Mediterranean shore of Egypt giving origin to the medical school of Alexandria in the fourth century BC where the first studies in the anatomy and physiology of the human body were carried out. Alexandrian medicine infiltrated into Rome when Egypt was absorbed into the Roman Empire (30 BC) reaching its climax in the person of Galen who, though born in Pergamos in Asia Minor, spent most of his life in Rome where he practised, wrote and taught in the 2nd century AD. Of his works only about 80 remain extant which were copied and recopied many times during the Middle Ages. Not all of his ideas and speculations corresponded to actual anatomical and physiological facts but it was not until the Renaissance that many of his theories were shown to be untenable by Andreas Vesalius (1514-64) and Ambroise Pare (1510-90) in the 16th century.

Following the fall of Rome and the break up of the Roman Empire, Mediterranean medicine passed into the hands of Arab scholars who travelled in the steps of the Moslem conquerors along the shores of North Africa into Spain.[4] They brought with them Arab translations of Greek medical works to which they added original observations of their own especially in the fields of surgery and pharmacy. Arabic medicine was especially active in the 9th and 10th centuries. One recalls such names as that of Rhases (AD 860-932), the author of a textbook of medicine; Avicenna (AD 980-1037) who also wrote a textbook of medicine which remained in use in many medical schools such as that of Montpéllier until 1650. Albucasis (AD 936-1013) who produced the first illustrated work on surgery; and Maimonides (AD 1135-1204) who among other treatises, wrote one on poisons and the harmful effects of the bites of scorpions, dogs etc. All this Arabic medical literature was carried to Sicily, Southern Italy and

Spain where schools of medicine flourished at Cordova, Seville and Toledo.

Arabic medicine declined in the mid-13th century with the break up of the Moslem Empire but concurrently with this decline another medical school was developing in the Middle Sea on a sound basis. This was the school of Salerno, some 35 miles south of Naples, which came into being about the 9th century reaching its zenith of fame in the 10th and 11th centuries. This school was the first to lay a definite course of studies and to institute a qualifying examination in medicine and to grant the title of "doctor" to medical men.

The school of Salerno started to lose ground in the 13th century when it gave way to the newly established universities in various parts of Europe. Thus, the centre of medical leadership shifted northwards to the cities of France and Italy such as those of Paris and Montpéllier, Bologna and Padua. The school of Salerno, however, survived until the 19th century when it was closed down by Napoleon in 1811. To this school and to the school of Montpéllier had flocked Maltese young men who wished to embark on a medical career as no provision for medical studies was existant in Malta until the late 18th century when Grand Master Emanuel Pinto founded our university with the Faculties of Theology, Law and Medicine in 1771. Training in surgery, however, had been available since 1676 when Grand Master Nicholas Cotoner founded and endowed the Chair of Anatomy and Surgery at the Holy Infirmary of Valletta. Only those who knew how to read and write were eligible for the course in surgery which in 1682 was fixed at ten years to ensure that the surgeons who qualified from the school were proficient in their craft. A dissection room was built in 1716 being furnished with the necessary instruments supplied by expert makers from Paris. Public lessons in anatomy with demonstrations on the cadaver were started in 1723. By the late 18th century the school became so renowned that it attracted not only Maltese but also foreign pupils from far away as the Eastern Mediterranean. With the foundation of the university in 1771, the Chair of Anatomy and Surgery was incorporated into the Faculty of Medicine. From this union has sprung and flourished our present medical school that can boast 300 years of progressive and active life with many of its graduates scattered over Europe, Australia, Canada and the United States.[5]

Preservation of Public Health

The concept of quarantine, i.e., the isolation of people, animals and merchandise suspected of harbouring communicable diseases is an old one. It is enunciated in the Bible where we read: "He is unclean; he shall dwell alone; without the camp his habitation shall be".

The Byzantine Emperor Justinian is credited with the enactment of the first quarantine laws in the 5th century A.D. but what gave the impetus to the widespread safeguarding of health by the use of quarantine measures in Mediterranean ports was the so-called Black Death or the plague epidemic that devastated Europe in 1348. As treatment was unavailing against this illness, Mediterranean countries tried to forestall its occurrence by the adoption of preventive measures. These consisted in isolating ships arriving from the Levant and Egyptian special areas of their ports and in detaining travellers and crews in *ad hoc* establishments called Lazzarettes for 40 days - an arbitrary period said to be derived from the time Jesus spent in the wilderness; hence the word quarantine from the Italian *quaranta giorni*. This measure was first enforced at Ragusa on the Adriatic in 1377. The port of Marseilles took similar steps in 1383. Venice established a maritime quarantine station in 1403 and drew up a code of quarantine regulations in 1448. This code served as a model for other countries for over 400 years.

In general the procedure laid down in the Middle Ages in the Mediterranean when a ship approached port with suspected plague was as follows. The ship was relegated to a special area of the harbour and the master was required to deposit a sum of money as security that he would not leave port before he was given pratique or permission to depart. To make doubly sure that he would not sail away the rudder was removed from the ship. Passengers and crew were sent ashore to the Lazzarette where they were exposed to the fumes of boiling pitch and afterwards washed with vinegar. Their garments were taken away; some of this clothing was burned, and some was washed, aired and "perfumed" for 50 days. Cargoes were washed with sea-water and vinegar; cloth was unrolled and hung from the rigging of the ship. The sails, too, were submerged in the sea. The vessel was fumigated by boiling pitch in cauldrons between the decks. Cotton received special treatment in the sense that the bales were broken open and their contents were thrown about by "expurgators" daily for 50 days. Severe punishments, including the death penalty, were laid down for those who tried to contravene the quarantine regulations.

Similar measures were employed on land. Thus in 1577, Naples tried to protect itself from pestilence by stationing guards at the city gates, by having sentinels, on foot and on horse-back, patrolling the city walls to prevent clandestine entrance.

The Knights of St John had evolved quarantine rules during their stay in Rhodes so that by the time they came to Malta in 1530 they had a well-developed system of quarantine. It was based on the Lazzaretto which they constructed on Manoel Island in Marsamxett Harbour which became known as the Quarantine Harbour. However, quarantine measures were already being enforced in Malta during the Middle Ages by the Municipality of Mdina as early as 1458. The Knights were very strict in the application of quarantine rules and no regard was

paid to personal liberty, property or international commerce once there was the possibility that disease, especially plague, could be introduced into the Island. Punishments ranged from the imposition of heavy fines, the burning of merchandise, of homes and of ships to the infliction of the death penalty.

In about 1600 the Bill of Health was introduced. This was a document issued by governments to sea captains and to passengers declaring the state of the public health at the port of departure. This document was then examined by the sanitary authorities of the port of arrival before the ship was allowed to discharge cargo and passengers.[6]

To keep itself informed of the public health conditions prevailing in the various ports of the Mediterranean, the government of the Order of St John maintained a regular correspondence with the sanitary authorities of such ports as Venice and Naples besides obtaining reports froms its various embassies in the capitals of Europe.[7]

The most dreaded epidemic disease was plague of which Malta, as part of the Mediterranean world, has had its share right up to 1945. Smallpox, yellow fever and cholera invaded the Mediterranean in epidemic proportions for the first time in the 19th century. By the 1850s it became increasingly obvious that the traditional quarantine regulations had not always been effective in controlling the spread of epidemic disease and that their enforcement was causing delays in the flow of commerce and the movement of passengers. However, the fear of epidemics persisted and when the First International Sanitary Conference opened in Paris in 1851 the delegates were so undecided on how to facilitate trade in the Mediterranean without endangering the public health that the conference ended inconclusively and the old quarantine measures remained in force for a very long time afterwards. In fact the production of a Bill of Health by ship captains did not cease to exist until about 1960. Meanwhile, through its quarantine system Malta safeguarded not only its own public health and that of other Mediterranean countries but also protected commercial interests against the disruption of the economic and social life that followed in the wake of epidemics that swept over the Mediterranean.

Elucidation of the Means of Transmission of Infectious Diseases

The emergence and growth of the science of bacteriology led to a better understanding of the causation and transmission of communicable diseases and to a better control over their spread. Bacteriology saw its greatest development in France and Germany thanks to the pioneering work of Louis Pasteur (1822-95) and Robert Koch (1843-1910). They discovered, among other germs, the microbes responsible for surgical infections, for rabies, for tuberculosis and for anthrax; but the Mediterranean was no less active in the search for other microbes and parasites and their vectors that were causing widespread harm in the lands bordering the Middle Sea and other distant parts of the globe.

Four of these outstanding discoveries were - the parasite of malaria and its vector; the germ of undulant fever and its host; the role of the body louse in spreading epidemic typhus; and the identification of the Phlebotomus in the transmission of sand-fly fever.

The parasite of malaria was discovered by the Frenchman Alphonse Laveran (1845-1922), a military surgeon working in Algeria in the service of the French army between 1878 and 1883. While he was engaged in the study of malaria in Bonne he discovered the plasmodium parasite while carrying out the microscopic examination of blood of patients suffering from this disease on November 6th, 1880. This discovery not only established the identity of the organism causing malaria but also stimulated interest in protozoal disease agents thus opening the field of other research workers and extending our knowledge of similar organisms. In recognition of his researches concerning the role of protozoa in causing diseases, Laveran was awarded the Nobel Prize in 1907.

Among those who built on the foundations of Laveran were Sir Ronald Ross (1857-1932) who demonstrated how the parasite of malaria was spread by the anopheles mosquitoes; and Camillo Golgi (1843-1926) of Pavia who, between 1886 and 1893, showed that some plasmodia required 48 hours and others 72 hours for their release from the red blood corpuscles and that these different periods corresponded to the afebrile intervals of tertian and of quartian fevers [8]. Another Italian investigator, Giovanni Grassi (1854-1925) of Rome, proved that the spotted-winged mosquito (anopheles) was the only genus capable of transmitting the malaria parasite to man.

The second important contribution to bacteriology from the Mediterranean was the discovery of the microbe of undulant fever. The disease is known as brucellosis from the fact that the germ was discovered by David Bruce (1855-1931) while working in Malta as a British Army Surgeon in 1886. In spite of the significance of this discovery, however, it remained unknown, for many years afterwards, how the microbe gained access to human beings. Indeed it was not until 1905 that an investigator - this time a Maltese physician - found the microbe in the blood of the goat. The man was Sir Themistocles Zammit (1864 - 1935).[9] The full cycle of the infection was thus demonstrated and preventive measures for its eradication could be taken - as in fact they were - by the enforcement of the pasteurisation of goats' milk on a national scale. Today, thanks to Zammit, undulant fever has practically disappeared from Malta and other Mediterranean countries.

Until 1909 no one knew how epidemic typhus was propagated. It was a close friend of Sir Themistocles Zammit - the Frenchman Dr. Charles Nicolle (1866-1936), Director of the Pasteur Institute of Tunis - who, on investigating typhus patients admitted to the native hospital of Tunis, found that the *Rickettsia prowasekii* responsible for causing typhus fever, was transmitted by the body louse. Because of this discovery effective steps could be taken for the control of this disease by delousing the population. For work on typhus Dr. Charles Nicolle was awarded the Nobel Prize in 1928[10].

The significance of Nicolle's discover was amply demonstrated in October 1943 when as typhus epidemic broke out in Naples where sixty new cases were appearing daily. Thanks to the knowledge that the disease was conveyed by lice, the population of Naples was deloused by the newly found insecticide DDT. In three weeks 1,300,000 persons were thus treated and the outbreak was brought to an end. This experience was repeated in Japan three months after its occupation[11].

Finally Nicolle also contributed in drawing the distinction between the louse-borne epidemic typhus and the murine endemic variety due to *R. mooseri* with its reservoir in rats and its transmission to man by the rat-flea[12].

Malta appears again on the medical stage of the Mediterranean in connection with a fever called in the past "simple continued fever" or "three day fever", now known as sand-fly fever. This infection, which is common in the Mediterranean littoral and the Middle East, had been known to British Medical Officers in Malta and elsewhere since 1799. One of the earliest references to it comes from W. Burnett of the British Navy in his 'A Practical Account of Mediterranean Fever' published in 1814 [13].

In 1908, R. Doerr, while investigating this disease among Austrian soldiers on the Dalmatian coast showed that this illness was spread by the insect vector Phlebotomus papatissii[14]. Lt. Col. C. Birth, working in Malta and Crete, confirmed this finding in 1910[15]. In the same year, the entomologist R. Newstead was in Malta searching for the breeding places of this sand-fly[16]. In 1921 the British Royal Air Force appointed a Sandfly Fever Commission to enquire into the life history of the sandfly in our island, the research being carried out at the RAF Flying Boat Base in Kalafrana. The results were published in 1923[17].

In this year two members of this commission published a paper suggesting the hygienic and environmental measures needed for eliminating the sandfly[18]. This was some twenty-years before the commercial production of DDT when the control of the sandfly with this insecticide became an easier and more effective matter.

In this brief survey I have tried to show how the lands of the Mediterranean have participated in the progress of medical research and care. Thanks to these contributions the invalidity and mortality from infectious diseases have been reduced considerably and in some cases eliminated; the hazards to health that previously accompanied expansion in trade between nations have been effectively controlled; the great economic waste in human and material resources resulting from the ravages of epidemic disease has been adequately checked; while a sound basis has been laid down for the promotion and maintenance of a healthy environment to ensure the well-being and welfare of all mankind.

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Prophylaxis of Malaria

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Introduction

Travelling to a malaria endemic zone is becoming more of a problem to health authorities because of the great amount of developed resistance by the Plasmodium parasite to the known and established prophylactic antimalarial drugs. The problem is greatest with travellers who have never been exposed to the parasite before and therefore have no natural immunity against the disease. For practical purposes the problem of drug resistance is confined to Plasmodium falciparum which causes the greatest mortality of all other strains. P. falciparum has developed resistance to Proguanil, Cycloguanil, Pyrimethamine, and Chloroquine. The growth of resistance can be attributed to the selection of existing resistant mutants through drug pressure since antimalarials are now widely available. Various drugs have been advocated for the prophylaxis of Malaria.

4-Aminoquinolines (Chloroquine, Amodiaquine)

These drugs are not effective against the sporozoites injected by the anopheline mosquito but act on the erythrocytic form of the parasite causing its destruction. This is called suppressive prophylaxis. These drugs should be started, a week before intended entry into a Malaria zone, in doses of:

Chloroquine — 600 mg weekly for the first six weeks*
— 300 mg weekly thereafter
Amodiaquine — 600 mg weekly for the first eight weeks*
— 400 mg weekly thereafter.

8-Aminoquinolines (Primaquine)

These drugs act on the hepatic form of the parasite. However, they have proved to be too toxic for long term prophylactic use and should **not** be used.

Antifolates (Proguanil, Pyrimethamine)

These destroy the pre-erythrocytic stage of Plasmodium falciparum and erythrocytic forms of other species of Malaria. Due to the great amount of resistance now present they are often combined with sulphonamides and sulfones which form a synergistic combination with pyrimethamine. They should all be started on entry into a Malarial zone.

Pyrimethamine — 25 mg once weekly.
Proguanil — 100 mg once daily
(There is less tissue binding with this drug.)

Pyrimethamine — 12.5 mg
+
diaminodiphenyl sulphone (Dapsone) — 100 mg
} one tablet weekly**

Pyrimethamine — 25 mg
+
Sulphadoxine — 500 mg
} one tablet weekly **

The above drug combinations are marketed as Maloprim and Fansidar respectively.

All drugs are to be continued up to six weeks after leaving the Malarial zone to destroy forms being given out from the liver cycle. This sometimes exceeds six weeks, so awareness to this fact is important.

Course to follow

This, of course, depends on the country which the traveller intends to visit and on the prescribing doctor's own experience. It would be very unwise to prescribe Chloroquine only (which seems to be the standard practice in Malta) in areas where there is known chloroquine resistance (South East Asia, Central and South America, and Central and East Africa).

Consequently, it would be best to give *both* Chloroquine *and either* Maloprim *or* Fansidar. The latter combination is said to be more effective. Unfortunately resistance to chloroquine and pyrimethamine frequently co-exists (Chloroquine and Proguanil can also be given together).

Maloprim, Fansidar or Proguanil can also be given alone but again due to the high resistance developing this would be unwise. Some authorities maintain that due to the high resistance developing to Chloroquine one should not use a combination of Chloroquine plus something else but rather a single drug such as Proguanil, so that if Malaria does develop it will not be resistant to Chloroquine which is the drug of choice in treatment of the acute case. There are three types of resistance (vide **Chemotherapy of Malaria**). However, since other drugs are available to treat Chloroquine-resistant Malaria, I think that combination prophylaxis is the best solution.

On reading this article one might think that it would be just as well taking nothing at all. This is far removed from the truth and it would be sheer folly and a grave mistake to miss out on prophylaxis of whatever form.

Other forms of prevention

These are really common sense but go a long way in keeping the disease away.

(1) Use some form of insect or mosquito repellant.
(2) Use insecticidal spray (Flit) or mosquito coils around your habitat when possible.
(3) Sleep under a mosquito net.
(4) Keep your body well covered (arms and legs) especially in the evenings and nights when most mosquitoes come out to feed, or under the shade of trees.
(5) By next year, a vaccine against Malaria should be launched on the market. Hopefully it will be effective not withstanding the large degree of variant antigenic forms of the parasite. If successful this vaccine could rid the world of one of the most threatening killers.
(6) In pregnancy all the above drugs are safe and should be prescribed in endemic areas to prevent abortion from parasitisation of the maternal side of the placenta or the rare congenital Malaria. Folate supplements are usually needed.

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*This early loading dose of the drug is advocated by some authorities for prophylactic purposes but other authorities do not recommend it.

** Some authorities prefer one tablet twice weekly but many others maintain that this dose is too toxic even though the blood levels may not be effectively high towards the end of the week.

Chemotherapy of Malaria

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The recent emergence of resistant Plasmodium falciparum strains to chloroquine has created major problems in the chemotherapy of Malaria. In East Africa for example there have been increasing reports of chloroquine resistance over the last few years since 1978. Although most of the resistance is still at the RI level, there are now several cases of RII & RIII resistance.

According to the World Health Organization (WHO) resistance is classified into 3 groups i.e.

RI — In this case the parasitaemia clears but there is recrudescence within a week.
RII — There is reduction in the parasitaemia but no clearance.
RIII — No effect of chloroquine at all.

In the chemotherapy of Malaria in chloroquine sensitive areas, this drug should still be used in the recommended dose of 600mg stat then 300mg after 6 hours and then 300mg daily for 3 days. But when resistance is known or suspected then the following drugs are useful.

1. Quinine — this is given for 7—10 days.
2. Fansidar (pyrimethamine and sulfadoxine combination) is still useful. Since it is long-acting, if the patient is very ill he should be given Quinine initially to get things under control and the given Fansidar 3 tablets at once. Resistance to Fansidar is already well recognised.
3. Tetracycline is useful in resistant cases.
4. *Sulphones* can be used in resistant cases. This group of compounds is used in leprosy e.g. Dapsone.
5 Other long acting sulfas combined with pyrimethamine are useful.

A clone of resistant parasites may consist of relatively resistant to completely resistant ones. Also of interest is the fact some parasites show less resistance in-vivo as compared to in-vitro tests.

Pharmacology of Antidiabetic Preparations

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Insulins

Indications

(i) Insulin dependent (type I) diabetes mellitus
(ii) During pregnancy — when hyperglycaemia is present.
(iii) During acute insulin deficiency states uncontrolled diabetes with ketosis hyperglycaemia with dehydration and hyperosmolarity.
(iv) Hyperglycaemia complicated by acute infections, major surgery, severe trauma and/or steroid therapy.
(v) Diabetic patients with severe kidney disease or serious liver damage.
(vi) Certain cases of type II diabetes — not controlled by diet and manifesting oral hypoglycaemic agent failure.

Insulins are commonly extracted from beef and pork, produced in conventional purity and highly purified forms and available in different strengths — the common ones stocked being U40/ml and U80/ml — duration of action subdivides the preparation into short-, intermediate- and long-acting insulins. All these insulins are derived from pork, except for 'Lente' and 'Rapitard' which are beef and pork, and 'Ultralente' which is beef.

Storage

Insulins should preferably be stored between 2° and 8°C and not exposed to heat or sunlight. They should never be frozen. The vial in use could be kept at room temperature (max. 25°C) for a few weeks.

Mixing

When longer-acting insulins are mixed with shorter-acting insulins the latter should be drawn into the syringe first, and the mixture injected immediately.

Highly Purified Preparations

The main indications for considering the use of these insulins include:

(a) newly diagnosed juvenile type I (IDDM) diabetics.
(b) cases of genuine allergic reactions to conventional purity insulins.
(c) cases of lipodystrophy at injection sites.
(d) cases of genuine insulin resistance — daily doses in excess of 100U/day.

Table 1.

Type of Insulin	Degree of Impurity		Average time of Action (hours)		
	Conventional	Highly Purified	Onset	Peak Action	Duration
Short-acting and rapid results.	'Neutral' or 'soluble'	'Actrapid' or 'Velasulin'	1/2	1 1/2 — 4	8
Intermediate acting	'Lente' or 'N.P.H.'	'Monotard or 'Insulatard'	2	5—12	23
Long-acting and slow-onset		'Ultralente MC'	6	10—24	30
Biphasic (mixture of short intermediate acting)		'Rapitard'	3/4	4—10	23

A reduction in dose may be necessary when transferring patients from conventional purity to highly purified insulins. The mixing of conventional and highly purified preparations should be avoided.

Strategy of Insulin Therapy

Insulin dependant diabetics usually need intermediate insulin twice daily to cover their basal needs and very often the addition of one or two doses of short acting insulin (mixed with the above) to cover the challenges of meals.

Non-insulin dependant diabetics, especially during periods of 'stress' eg. intercurrent serious illness, may need insulin for a time in order to achieve better metabolic control — in these cases the use of intermediate insulin may often be sufficient.

Satisfactory control — as measured from blood glucose levels fasting and 2 hours after meals (HbA_1 levels) and urine samples checked before meals — would present with blood glucose levels ranging between 80 and 160 mg/dl; (HbA_1 values less than 8.5%), with essentially absent glycosuria in adults. 'Strict control' could mean the need of more intense insulin therapy.

The timing of the insulin injections, especially in relation to food; proper insulin injection technique and suitable meal planning are essential for adequate management.

In cases of uncontrolled hyperglycaemia, stabilization could be attempted with short-acting insulins given 4—8 hrly. according to blood glucose levels and body weight. Cases of diabetic ketoacidosis and hyperglycaemic, hyperosmolar non-ketotic acidosis should be managed with short-acting insulins only.

Complications of Insulin Therapy

These include:
1. Hypoglycaemia
2. Chronic overdosage (average daily dose well above 1.0U/Kg body weight)
3. Lipohypertrophy and/or lipoatrophy.
4. Insulin allergy.
5. Insulin antibodies.
6. Insulin resistance.

Oral Hypoglycaemic Agents

Clinical Use

There are two types of oral hypoglycaemics with different modes of action: sulphonylureas and biguanides. The former are generally preferred to the latter, especially, as first line treatment because they are more potent and have fewer side-effects.

Indications

These preparations are usually only indicated in uncomplicated, type II (non-insulin-dependant) diabetics where dietary compliance, daily exercise and body weight control fail to achieve satisfactory metabolic control. They are contra-indicated in type I (insulin-dependant) diabetics (at least as monotherapy); in uncompensated diabetes with ketosis, and during pregnancy. In certain serious 'stressful situations' like severe infections, major surgery and severe trauma, temporary substitution with insulin may be indicated.

Table 2

Pharmaceutical Preparations

Preparation	Tablet Strength	Mean Daily Dose	Potency	Duration of Action
Tolbutamide	500mg	500—2000mg	mild	short
Chlorpropamide	100mg; 250mg	100— 500mg	Intermediate	long
Glibenclamide	2.5mg; 5mg	2.5— 15mg	strong	intermediate
Metformin	500mg	500—1000mg	mild	intermediate

Special remarks: *In the case of glibenclamide - avoid high doses in the elderly and/or those with renal impairment. Metformin may give rise to lactic acidosis. Hence, avoid in elderly patients, in alcoholics, in states of shock, and in those patients with liver disease, serious cardiac or pulmonary disorders.*

It is often safer to start with low doses of the less potent sulphonyureas, increasing gradually the dose as needed, up to the maximum dose. If control remains poor, substituting for a stronger preparation seems advisable (e.g. tolbutamide then chlorpropamide then glibenclamide), and should the metabolic condition still remain unsatisfactorily stabilized, addition of a biguanide may be considered in selected cases. Both primary and secondary failure of sulphonylurea therapy occur, the causes are often not known — in such cases resorting to insulin might have to be considered especially if hyperglycaemia and symptoms persist in spite of dieting and maximum doses of oral hypoglycaemics. However, one must constantly remember that the commoner causes of 'loss of diabetic control' include: infection, changes in diet, body weight and/or exercise, emotional stress, erratic administration of medicines and drug-induced effects.

Side-Effects

Adverse effects are relatively uncommon, the ones more frequently met including:

(i) variety of skin rashes, often accompanied by pruritis.
(ii) upper gastro intestinal symptoms — anorexia, dyspepsia, nausea, vomiting, abdominal fulness.

and less often:

(iii) severe skin eruptions — including sensitivity reactions.
(iv) bone marrow suppression.
(v) cholestatic jaundice.
(vi) porphyria-like syndrome.
(vii) disulfiram-like reaction in certain cases of alcohol intake whilst on chlorpropamide.

Drug Interactions in Diabetics

Drugs taken by diabetics for reasons other than control of blood glucose may effect the response to insulin or oral antidiabetic drugs. The mechanisms of these drug interactions may involve the alteration in the

(a) absorption,
(b) distribution,
(c) metabolism (biotransformation) or
(d) excretion of the primary agent.

The factors predisposing to clinically significant drug interactions include, two or more drugs taken simultaneously or close together; taken for several days or longer; or if given to patients with underlying hepatic or renal disease; undefined genetic differences; and/or when an agent is added to or deleted from a previously effective therapeutic programme.
Summerizing the principal adverse drug interactions of clinical importance to diabetics consist of:

(a) drug interactions that may make diabetes worse:-
  (i) glucocorticosteroids;
  (ii) oral contraceptives;
  (iii) oral diuretics, especially the salt losing thiazides;
  (iv) diazoxide;
  (v) sympathomimetic agents; and
  (v) nicotinic acid.
(b) drug interactions causing potentially significant hypoglycaemia in diabetic patients:
  (i) alcohol;
  (ii) bishydroxycoumarin;
  (iii) phenylbutazone;
  (iv) salicylates;
  (v) sulphonamides;
  (vi) propranolol.

One must remember that a not insignificant proportion (estimated probably to be circa 30%) of elderly type II diabetics are also often suffering from concomitant diseases like cardiovascular disorders (especially congestive cardiac failure, ischaemic heart disease or hypertension) anxiety states and/or osteoarthritis — for which they are also frequently receiving treatment that could possibly interact with their antidiabetic therapy (be it oral hypoglycaemic agents — of which the commoner are glibenclamide and glymidine with chlorpropamide and metformin less common — and/or insulin preparations). Among the medical drugs probably more often concurrently being prescribed and taken are diuretics (thiazides and frusemide), digitalis, potassium supplements; benzodiazepines (especially diazepam) methyldopa and betablockers (esp. propranolol). Possibly, also not infrequent are preparations like indomethacin, hydralazine, nitrates (short or longer acting), nifedipine, vitamin supplements, bronchodilators and clofibrate.

Other disorders frequently of a temporary nature, also often encountered in diabetics but which rarely require chronic medication include obesity and hyperlipidaemia.

Drugs may also interfere with tests for glucose or ketones in the urine or those estimating glucose in the blood. Regarding the latter, the commoner preparations that can give rise to a false positive or false negative with the estimation of blood glucose include adrenaline, amino-salicylic acid, levadopa, ascorbic acid, dextran, hydralazine, tetracyclines and iron sorbitol. With urine tests, false negatives can occur in glucose oxidose test strips with ascorbic acid (esp. high doses) and levodopa, whilst false positives can occur in copper reduction tests with ascorbic acid, nalidixic acid, cephalosporins, methyldopa, probenecid, and salicylates, streptomycin, isoniazid and para-amino-salicylic acid (with Benedict's test).

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The Insulin Gene and Diabetes Mellitus

A New Approach

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Diabetes mellitus comprises a heterogeneous group of disorders characterized by chronic hyperglycaemia, and a propensity to develop microangiopathy, neuropathy, nephropathy and atherosclerosis. It is a common condition and is seen in all ethnic groups. The causes of diabetes are poorly understood, but appear to involve some form of interaction between hereditary and environmental factors.

The genetics of diabetes is still unclear, but a picture is slowly emerging. Recently, associations with two HLA-DR antigens 3 and 4 (coded for by genes on chromosome 6) have been demonstrated with insulin-dependent diabetes, but are not sufficient to explain the entire genetic component of this disease. It has been postulated that a second gene locus might be involved. One such gene may be the human insulin gene which is located on the short arm of chromosome 11.

Direct Gene Analysis

The last 10 years or so has seen the emergence of a new technology called Recombinant DNA analysis which has enabled the scientist to study inherited disorders at a DNA level. Not only have these techniques afforded the ability to analyse variations in DNA in man but they have been put to commercial use in the invaluable production of several hormones and vaccines such as human insulin itself, growth hormone and interferon.

The procedures that are used are somewhat complex, but the thumbnail sketch of these strategies and their application to inherited disorders such as diabetes now follows.

It is known that DNA in chromosomes — the 'genome' — is double-stranded with one strand having a nucleotide base sequence complementary to the other. This is by virtue of the fact that the nitrogenous

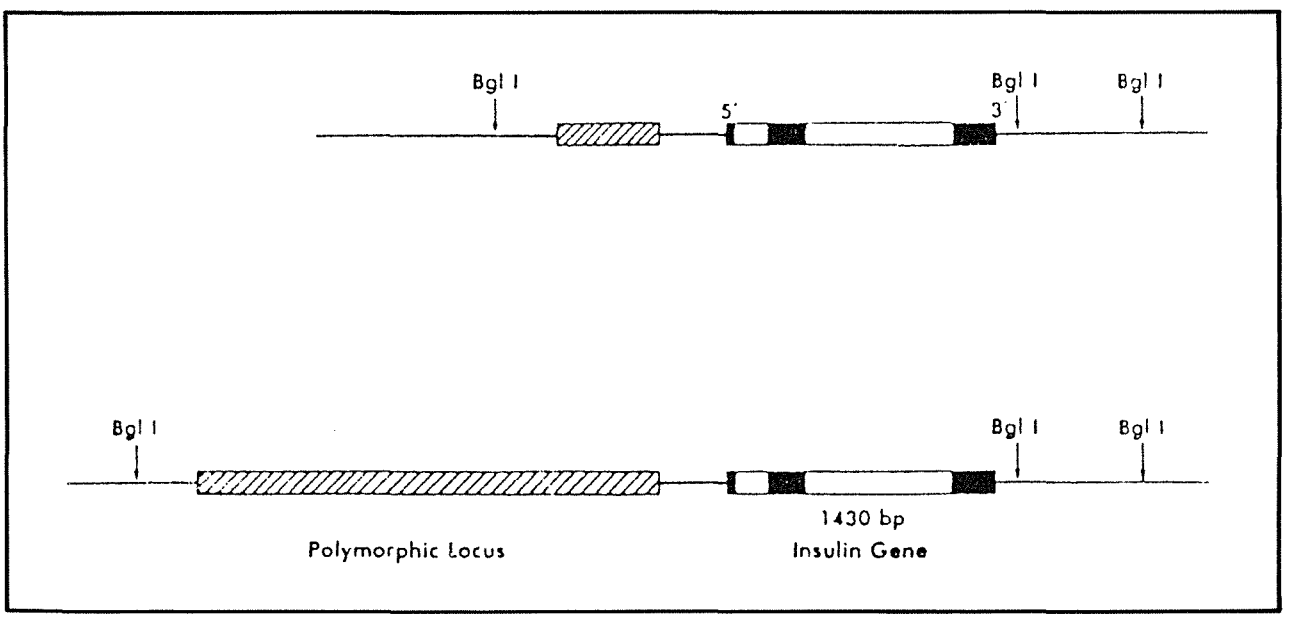

Fig. 1. A diagrammatic map of the human insulin gene illustrating the short DNA insertion (above) and long DNA insertion (below) just before the gene. Bgl 1 is the name of the Restriction Enzyme that cuts the DNA at the sites indicated, resulting in fragments that when 'hybridized' with the insulin probe result in radioactive bands, as seen in Figure 2.

base adenine only pairs with thymine and guanine only pairs with cytosine. Now, the total amount of DNA in a single human cell is about 6×10^9 bases long, whereas a single gene, on average, is about 1,000 bases in length. There are probably only about 50,000 genes in the human genome and therefore a large proportion of the genetic material, roughly 95% does not code for proteins. Nevertheless, to isolate just one of these genes seems a formidable task. This is not so, however. Using a special enzyme called reverse transcriptase, a DNA copy (cDNA) of the messenger RNA of a particular gene can be synthesized under certain laboratory conditions. Messenger RNA can be relatively easily isolated if the amino acid sequence of the protein (in our case insulin) is already known. The cDNA can then be radioactively labelled by adding radioactive bases and hence used as a 'probe' to look for complementary sequences in genomic DNA, i.e. to search out and 'light up' the gene under study to the exclusion of all other genes. The next requirement now is to make sufficient copies of this DNA fragment to be able to handle it in the laboratory. This 'cloning' is achieved by inserting this DNA fragment into the DNA of a rapidly replicating host such as E. coli. This cloned DNA can be made single-stranded and then labelled with radioisotope; it is now called a *'DNA probe'* because it is capable of locating and 'hybridizing' with DNA of any individual that carries the complementary sequence. It is quite easy to make DNA from the nuclei of white cells obtained from a peripheral blood sample. However, because the size of the DNA probe is so much smaller than the genomic DNA, the latter can be cut up into millions of fragments by digestion with other enzymes known as restriction enzymes. These enzymes, produced from bacteria, always cleave DNA at a small number of reproducible sites. The fragments so formed can be roughly separated according to their size by electrophoresis and then, while separated, the radioactive DNA probe can be added so that it hybridizes with the fragment that contains the complementary sequence. This results in a radioactive band which can be revealed by making an autoradiograph.

Now, if the restriction enzyme cuts the DNA at always the same site, radioactive bands of the same size are expected. If, for some reason, for instance a mutation that destroys this cutting site or creates a new one, or if an extra bit of DNA (an 'insertion') is found within the cutting sites, then different sized radioactive bands are to be expected. Such variations in DNA sequence, if present in more than 2% of the population, are called *polymorphisms*. These polymorphisms are fairly common in the human genome; they may be found within a gene or in a bit of DNA that does not code for protein. They may be harmless, yet if found within the gene or sufficiently close to it, then they may affect the expression of the gene and thus result in a disease. A typical example is sickle cell disease where a polymorphism found within the ß-globin gene results in the substitution of thymine by adenine in the 6th amino acid of the gene. The most important feature of a polymorphism is its ability to be transmitted through families in a simple Mendelian fashion, and therefore, if associated with a disease, then this disease can be tracked through future generations.

The Insulin Gene

In their studies of the human insulin gene, Professor Bell and his colleagues in San Francisco were the first to discover a polymorphism just outside this gene.[2] With the use of an insulin probe and the techniques outlined above they observed a highly variable stretch of DNA which was broadly divided into a 'short' DNA insertion approximately 600 bases long and a 'long' insertion of over 2,000 bases long (Fig. 1). Individuals can inherit the same insertion from both parents (hence homozygotes), thus producing one band only on an autoradiogram, whereas heterozygotes will inherit both and display two bands (Fig. 2). Because of the close proximity of this polymorphism to the insulin gene, it was soon postulated that it might play an aetiological role in diabetes. This hypothesis was strengthened by the knowledge of mutant insulins that have resulted in this disorder.[3] Studies therefore were soon underway to seek an association with the different types of diabetes. The first study, however, by Bell's group, revealed no differences between NIDD's and controls, but these workers noted that less than 10% of the normal population were homozygous for the long insert.[2] Since then, however, three independent studies, including work in our laboratory, have revealed that subjects homozygous for this insert were indeed found to have a 4-5 times higher relative risk of concurrence of NIDD[4-6].

The situation with insulin-dependent diabetes was even more clear-cut. To date, over 150 such diabetics have been studied in two centres with the insulin gene probe and the incidence of homozygosity for the *short* insertion was found to be almost double that in controls.[7,8]

So, what can one make of these results? Certainly they offer an exciting theory that this polymorphic stretch of DNA flanking the insulin gene might be playing a causative role in diabetes. Several questions though have yet to be answered. Is the polymorphism affecting insulin gene transcription and thus leading to inappropriate insulin synthesis? Or could it simply be a genetic marker for another abnormality, hitherto undiscovered, within the insulin gene itself? Could this polymorphism have risen by random genetic drift, and the association with both types of diabetes be entirely spurious? The results so far must be considered preliminary because the number of patients studied are relatively small. The earlier results could be conflicting because of sample bias and racial differences. In support of the latter

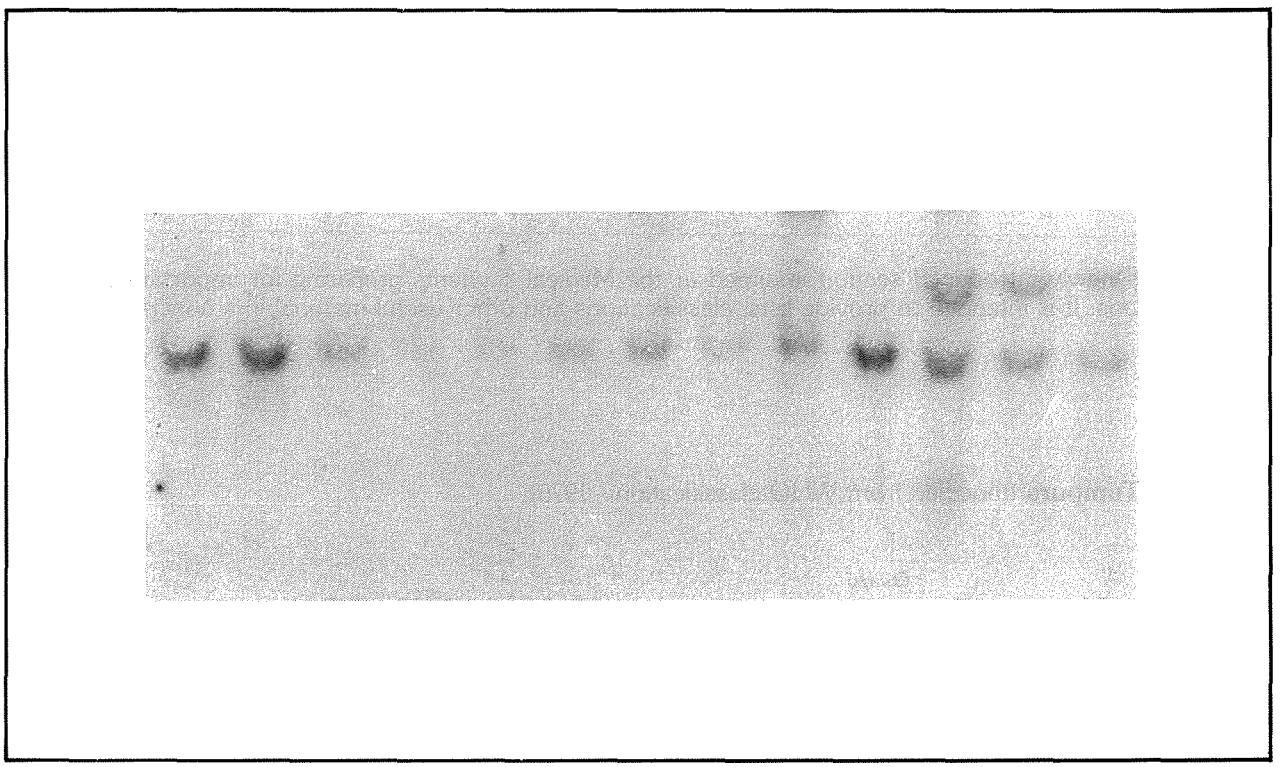

Fig. 2 This is an autoradiogram of DNA from different individuals hybridized with the insulin probe. The top band represents the large 'insertion', whereas the bottom band represents the short 'insertion'.

theory, we have studied subjects from different racial groups and observed several differences in non-Caucasian individuals, particularly in an intermediate sized insertion (1,000 bases) seen only in the Negroid race.[9] Up to now, therefore, this polymorphism can only be used in studies on the Caucasian segment. We have also attempted to see if this insulin polymorphism could be responsible for the appearance of impaired glucose tolerance in other conditions, such as gestational diabetes, acromegaly and Type III hyperlipidaemia,[10] but results have been conflicting.

Clearly, therefore, further work is required. The impact of these recombinant DNA techniques into modern medicine, however, is undisputed. For the first time, the ability to study genes themselves has become a practical proposition. Already these techniques have been applied clinically to the antenatal diagnosis of other genetic diseases, such as the haemoglobinopathies, the implications of which are enormous. Future work on the polymorphism flanking the insulin gene should hopefully elucidate the aetiology of diabetes, or at least offer a better guide to classification and understanding of this group of disorders. The next decade should see many more discoveries, and the real possibility now exists that faulty genes responsible for human disease might be replaced.

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Aides Memoires

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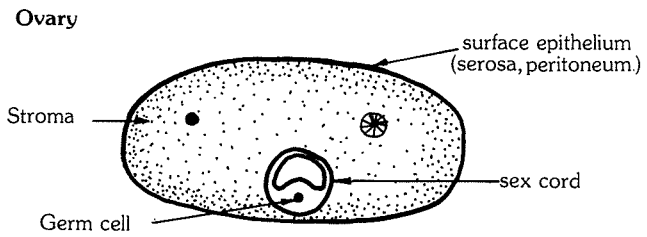
This newly introduced section is aimed at the Medical Students preparing for important tests and examinations. It is intended to provide lists, classifications and other useful material in a concise form.

Ovarian Tumours (modified from WHO classification - 1975).



1. **Surface Epithelium***

a) serous

i) benign (B)
ii) borderline (BL)
→ cystadenoma, papilloma, fibroma† → ± oestrogens (± androgens)

iii) malignant (M) → cystadenocarcinoma, papillary carcinoma, malignant change in fibroma

b) mucinous

i) B
ii) BL
→ cystadenoma, fibroma† → ± oestrogens (± androgens)

iii) M → cystadenocarcinoma, malignant change in fibroma.

c) endometrioid
d) mesonephroid (clear cell)
e) Brenner Tumour
f) Undifferentiated (M)
g) Unclassified
→ i) B, ii) BL, iii) M

2. **Sex Cord**

a) Granulosa-Stromal Cell T.
i) granulosa cell T. (m)
ii) Theca cell T. (m)
iii) Fibroma
→ oestrogens ± progestogens
→ oestrogens ± Androgens

b) Arrheno-/Androblastoma; Sertoli-Leydig cell T → Androgens ± oestrogens
c) Gynandroblastoma
d) Unclassified

3. **Germ Cell**

a) Dysgerminoma (M)
b) Endodermal Sinus (Yolk sac) T (M)→α -FP.
c) Embryonal carcinoma
d) Polyembryoma
e) Choriocarcinoma (M)→HCG
f) Teratoma
   i) Immature (M)
   ii) Mature { solid (M) / cystic (dermoid cyst) (B)
   iii) Monodermal + Highly specialized
   e.g. struma ovarii (B)→T_4
   carcinoid (M)→5.HT.

g) Mixed forms

T_4 = Thyroxine: HCG = Human Chorionic Gonadotrophin; α-FP=α-Feto Protein; 5-HT = 5-Hydroxytryptamine.

4. **Miscellaneous (1° Tumours)**

a) Lipoid cell T (B)
b) Ovarian cysts (B) i) follicular
   ii) corpus luteal
c) Endometroisis (B)
d) Haemangioma (B)
e) Leiomyoma (B)
f) Lymphoma (M)
g) Gonadoblastoma { Pure / Mixed
h) Unclassified

* Tumours of surface epithelial origin: Since the epithelial covering of the ovary and the Müllerian Duct (from which the tubal epithelium, endometrium and endocervical epithelium are derived) are both formed from coelomic epithelium, comparable metaplastic transformation into different types of epithelium is theoretically possible. According to this view, tumours with tubal (serous), endometrial (endometrioid) or endocervical (mucinous) epithelium may arise. The mesonephroid clear cell tumour is also derived from Müllerian epithelium and the Brenner Tumour may have the same origin.

5. **2° Malignant Neoplasms**

a) G.I.T. - Kruckenberg T
b) Breast
c) Uterus
→ ± Androgens

†Meig's Syndrome

FIGO classification of Staging of Ovarian Cancer.

STAGE I Growth limited to ovaries	a) one ovary b) both c) malignant ascites
STAGE II Extension within pelvis	a) uterus, other ovary, tubes b) other pelvic tissues
STAGE III Extension within abdomen	
STAGE IV Distant Metastases	

CHEMO THERAPEUTIC AGENTS

OVARIAN MALIGNANCIES
- Melphalan (Alkeran)
- Chlorambucil (Leukeran)
- Cisplatin
- Treosulphan

CHORIOCARCINOMA
- Metotrexate
- 6-Mercapto purine
- Actinomycin D
- Chlorambucil (Leukeran)
- Melphalan (Alkeran)

attach with answer 7

Clinical Diagnosis

The questions in this quiz have been set by **Mark Bugeja M.D.** The answers will be found in articles that nave appeared in past issues of Medi-Scope.

1. List the congenital heart diseases which, if not operated upon at an early stage, would result in a life expectancy less than (about) 5 years.

2. A patient weighing 75 kg. had a blood osmolality of 285 mmol/kg. Whilst in hospital, he was given 1.5 litres of isotonic saline and 1.5 litres of 5% glucose solution, in one day.

(a) What is the resultant blood osmolality?
(b) What were the changes in volume of the body fluid compartments?

3. Outline briefly the management of a patient complaining of increasingly painful and disabling pain in the knees which "crack" on moving and which show evidence of severe osteoarthrosis on radiography.

The answers must reach the *Editor* by the *30th. November 1985* together with the name, address, tel. no. and accademic year, of the participant. To be accepted, the top corner of this page **must** be stapled or glued to the answer.

The winner shall receive a prize money of **Lm10** with a **Kidney Model** kindly donated by ***Merck, Sharp and Dohme International (Aldox Ltd.)***, *25, Lighters Wharf, Marsa.*

Answers to Clinical Diagnosis 5

Case 1: Diff. Diag. • Ischaemic bowel disease • Intestinal obstruction • Acute Appendicitis **Diag.** Mesenteric Artery Occlusion by an embolus originating from a mural thrombus consequent upon myocardial infraction. **Management:** includes briefly and principally • laparotomy following stabilisation of the patient's general condition • bowel decompression • embolectomy • resection of gangrenous bowel • Antibiotics (vs gram -ve and anaerobic organisms) •
• Anticoagulants

Case 2: Diff. Diag; • Rubella (German measels) • Rheumatic fever • S.L.E. • Infectious mononucleosis (glandular fever) • Brucellosis • R.A. **Diag:** Rubella **Tests:** Serology (rising titre of antibodies against Rubella virus) **Precautions:** • Avoidance of pregnancy for 3 months • patient must avoid coming in contact with pregnant women.

Winner: *Cecil Vella M.D.*
Prize: *Doctor's Elastoplast Set* donated by ***V.J. Salomone Ltd.,*** 10, South Street, Valletta and a *Papermate Biro and Pencil Set* donated by ***George Borg Ltd.,*** 26/2 Merchants Street, Valletta.

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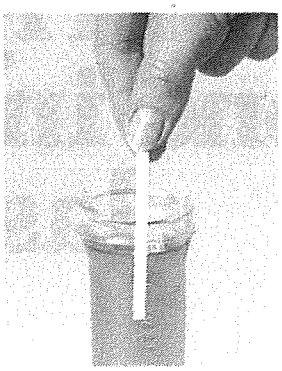
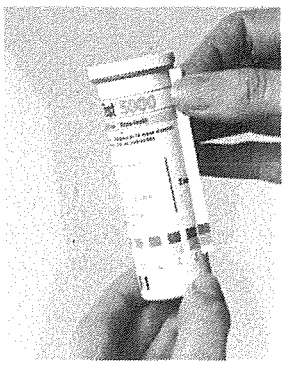


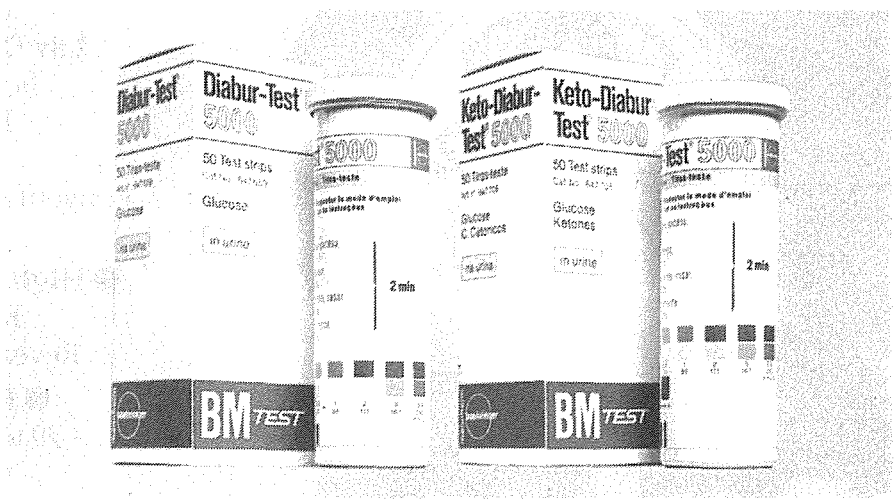
Alternatively you can hold the test areas briefly in the urine stream. Shake off excess urine.

1 Collect a urine specimen in a clean container. Briefly dip the test strip into the urine.

2 Withdraw and wipe edge along the rim of the container in order to remove excess urine.



3 After 2 min., compare the test areas with the colour scale on the label.



Diabur-Test® 5000
50 test strips, Cat. no. 647 659

Keto-Diabur-Test® 5000
50 test strips, Cat. no. 647 705

mannheim boehringer
Boehringer Mannheim GmbH
D-6800 Mannheim 31
W. Germany

Your partner in management of diabetes:

Agents: **VIVIAN COMM. CORP. LTD.**
MSIDA
TEL: 517492/3/4

Surgam 300 bd

NEW CONVENIENT PRESENTATION

High speed anti-inflammatory power within the joint

the twin benefits of surgam:
- rapidly effective against joint inflammation and particularly effective against pain
- well tolerated in both short- and long-term treatment.

INDICATIONS :
IN RHEUMATOLOGY :
- acute exacerbations of osteoarthritis (of the hip, of the knee, lumbar spondylosis, cervical arthrosis...)
- arthritis
- periarthritis of the shoulder
- rheumatoid arthritis
- ankylosing spondylitis
- cervical pain, low back pain, sciatica, cervicobrachial neuralgia
- tendinitis, bursitis.

IN TRAUMATOLOGY :
- sprains, contusions, fractures
- orthopaedic surgery
- plastic surgery.

IN E.N.T.
- tonsillitis, acute pharyngitis, acute otitis, sinusitis.

IN STOMATOLOGY AND MAXILLO-FACIAL SURGERY :
- dental extractions (germectomy), surgery for parodontopathy, alveolo-dental arthritis, cellulitis, wisdom tooth complications, facial trauma
- following tonsillectomy, rhinoplasty, plastic procedures on scars.

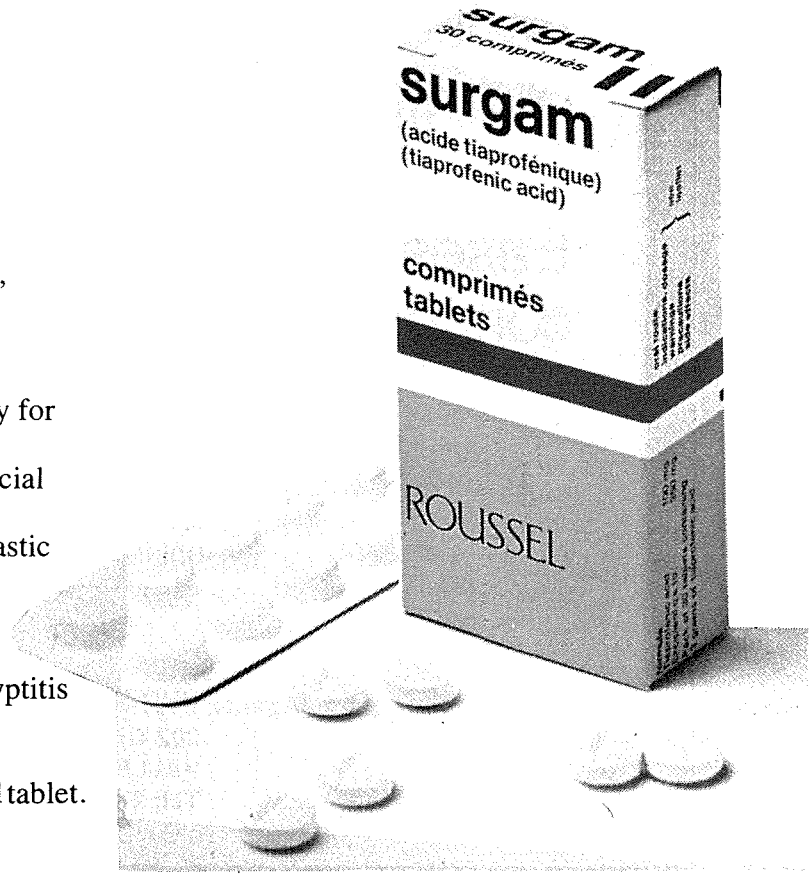
IN PROCTOLOGY :
- thrombosed haemorrhoids, following haemorrhoidectomy and fissurectomy, cryptitis and papillitis.

COMPOSITION :
- Tiaprofenic acid... 100 mg for each scored tablet.

PRESENTATION :
- Box of 30 scored tablets

DOSAGE :
- 2 tablets 3 times per day to be taken during meals. In certain cases of long term maintenance therapy, dosage levels may be reduced to 3 or 4 tablets per day in divided doses.

WARNING :
Caution should be observed in pregnant women,



Davenol*

effective 3-way cough relief

Stops irritation

Carbinoxamine maleate controls the allergic causes of cough – reduces excessive secretions of the upper respiratory passages.

Reduces frequency of cough

Pholcodine suppresses cough, at lower dosages than codeine and is virtually free from codeine side-effects such as constipation and respiratory depression.

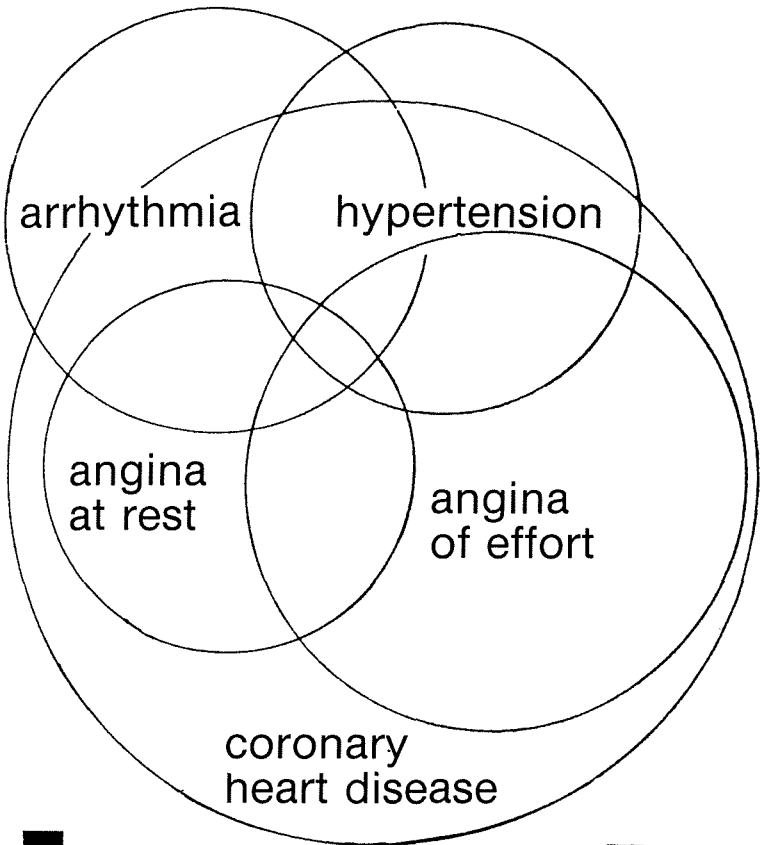
Eases congestion

Ephedrine hydrochloride is a long-acting bronchodilator with a wide safety margin. Relieves bronchospasm associated with asthma, bronchitis or whooping cough; aids effective expectoration.

Davenol tangerine-flavoured cough linctus helps the patient and the family to have a night's sleep uninterrupted by coughing.

Agents: **VIVIAN COMMERCIAL CORP. LTD.**
202 OLD BAKERY STREET,
VALLETTA.
Tel: 27446 - 26987

Comprehensive therapy of coronary heart disease



Isoptin®

antianginal
antiarrhythmic
antihypertensive

KNOLL AG CHEMICAL WORKS, LUDWIGSHAFEN-ON-RHINE, GERMANY

Agent: Joseph Cassar Ltd., 54, Melita Street, Valletta/Malta

New Zyloric-300*

once-a-day dosage in gouty arthritis

The proven advantages of ZYLORIC*

ZYLORIC, a product of Wellcome research, offers a radical approach to the treatment of disorders characterised by excess uric acid, such as gouty arthritis. By controlling the production of uric acid biochemically, it lowers both serum *and* urinary uric acid levels. Thus, apart from the more clinically obvious benefits of relief of joint discomfort, increase in joint mobility and decrease in size of tophi, ZYLORIC also significantly reduces the hazard of kidney damage and stone formation. Moreover, because of its sparing effect on the kidneys, it controls hyperuricaemia even in patients with impaired renal function.

with the benefits of simplicity and convenience

Easier to remember, less chance of missing a dose – ZYLORIC-300 combines all the established and unique benefits of ZYLORIC therapy with the simplicity and convenience of once-a-day dosage in the treatment of gouty arthritis and excess urate disorders. Continuing Wellcome research has shown that, because of its inherent long action, a single dose of ZYLORIC provides a whole day's therapy without the need for sustained release technology. Wellcome discovered that ZYLORIC is largely converted in the body to a long-acting metabolite which extends the therapeutic effect to a full day. New ZYLORIC-300, with more likelihood of maximum patient co-operation and maximum therapeutic response, adds up over the years to better control of excess uric acid.

Easier to remember – more likely to succeed!

Each ZYLORIC-300 tablet contains 300mg allopurinol
ZYLORIC is also available as tablets each containing 100mg allopurinol

Additional information is available on request

The Wellcome Foundation Ltd Berkhamsted Herts England

Wellcome

Trade mark*

GMD/M/4/74-13

DORMAX