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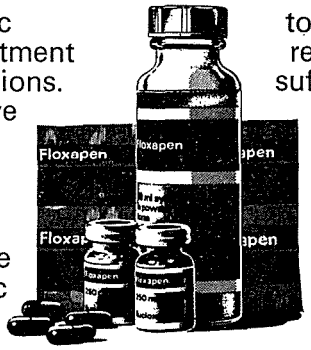

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References 1. Kales, A., *et al.*, Arch. gen. Psychiat., 1970, *23*, 226 2. Feffer, H.L., and Gibbons, B., Med. Tms (N.Y.), 1973, *101*, 130 3. Kales, J.D., *et al.*, Clin. Pharmacol. Ther., 1971, 12, 691 4. Dement, W.C., In 'The Benzodiazepines',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

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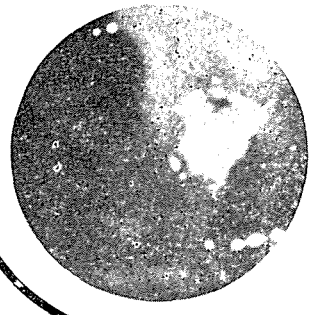

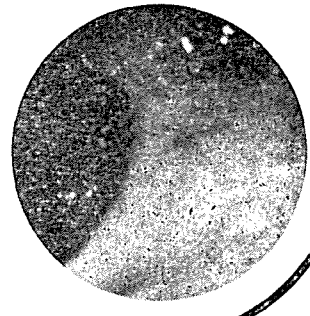

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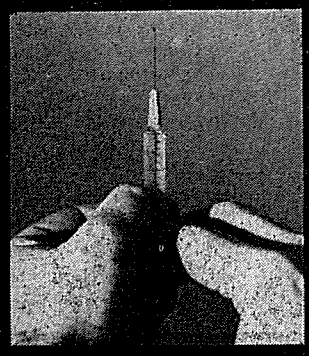

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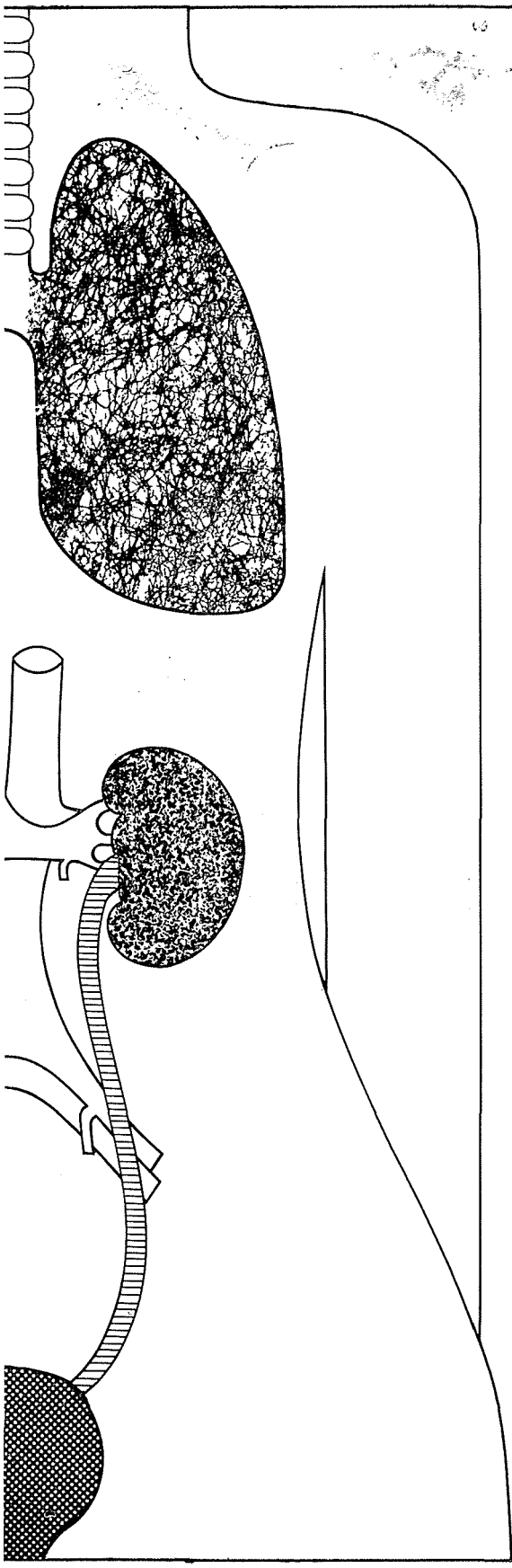

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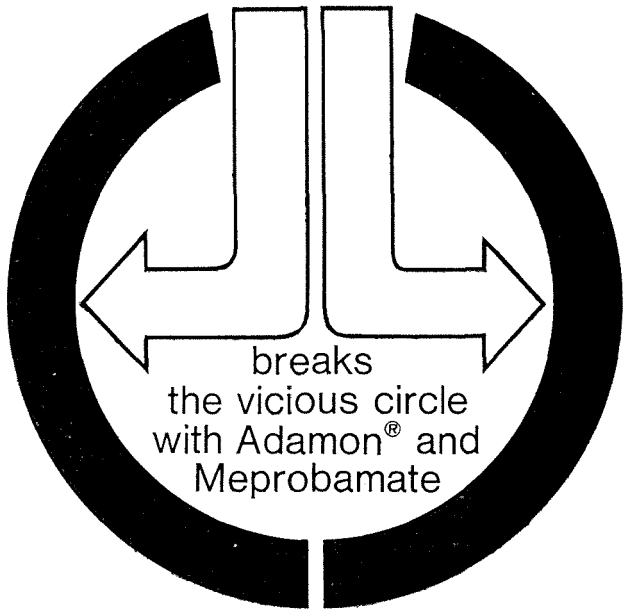

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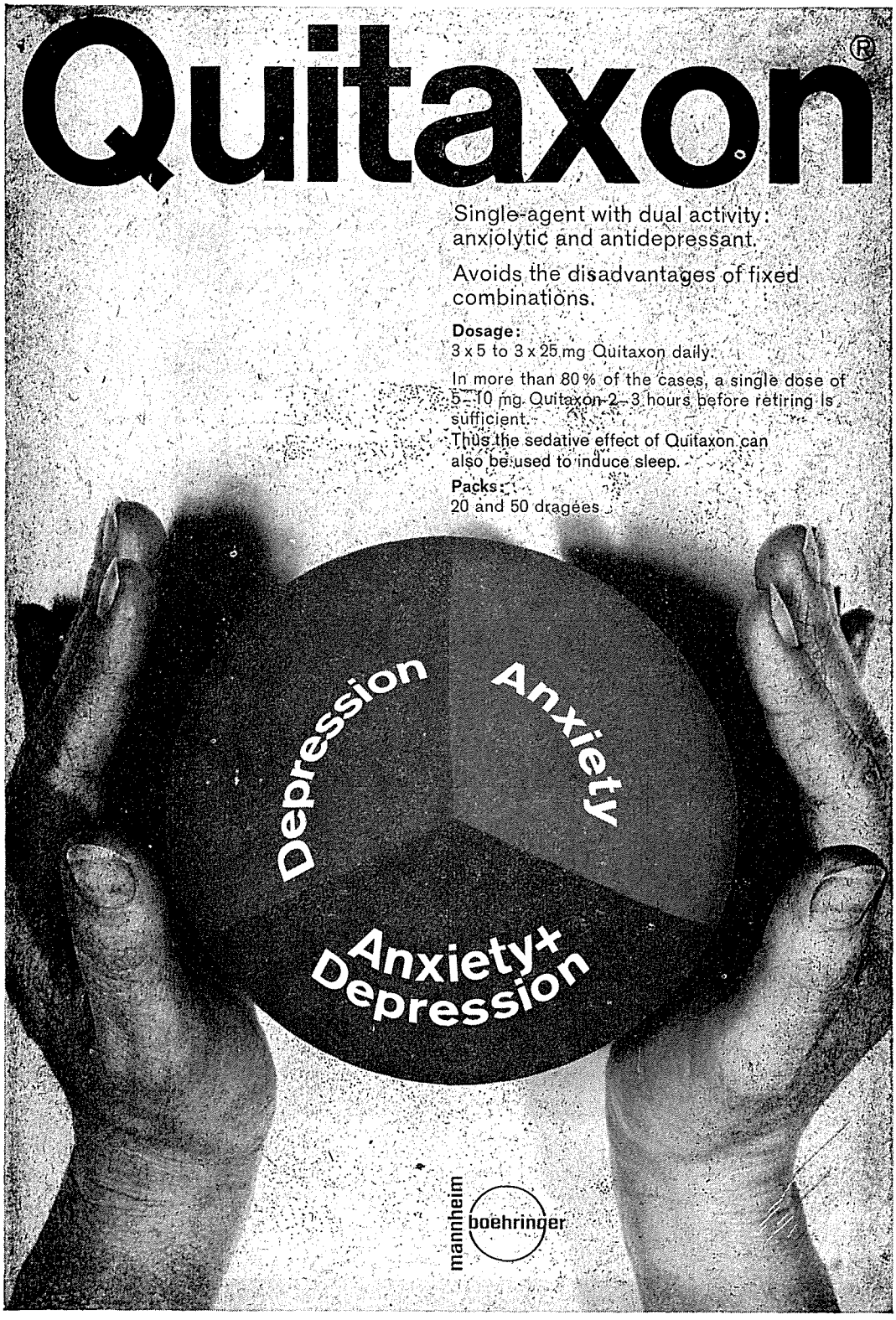

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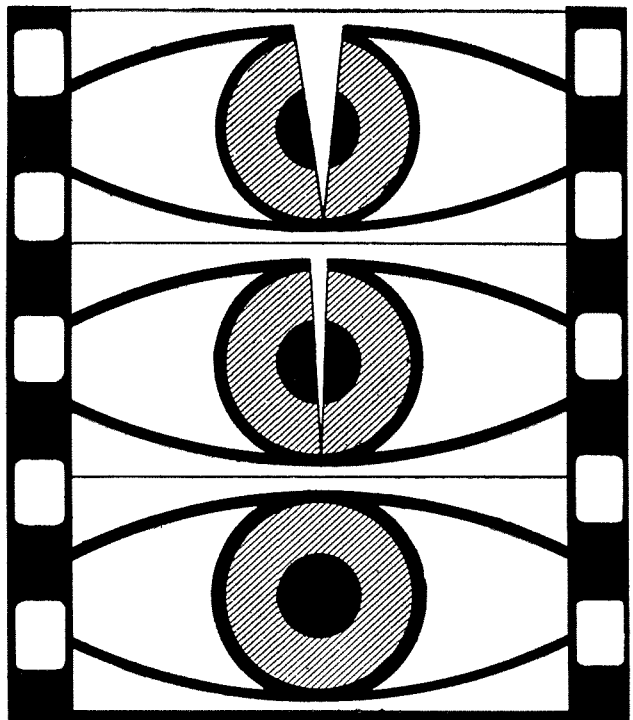

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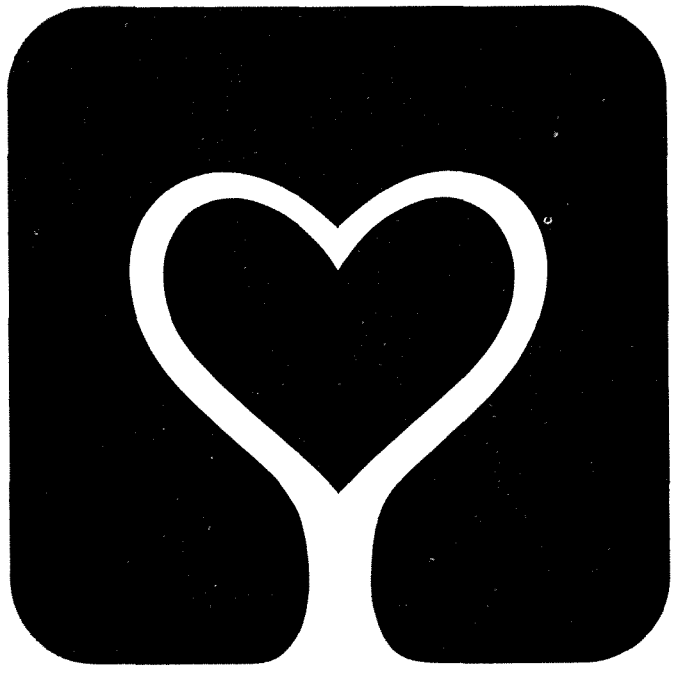

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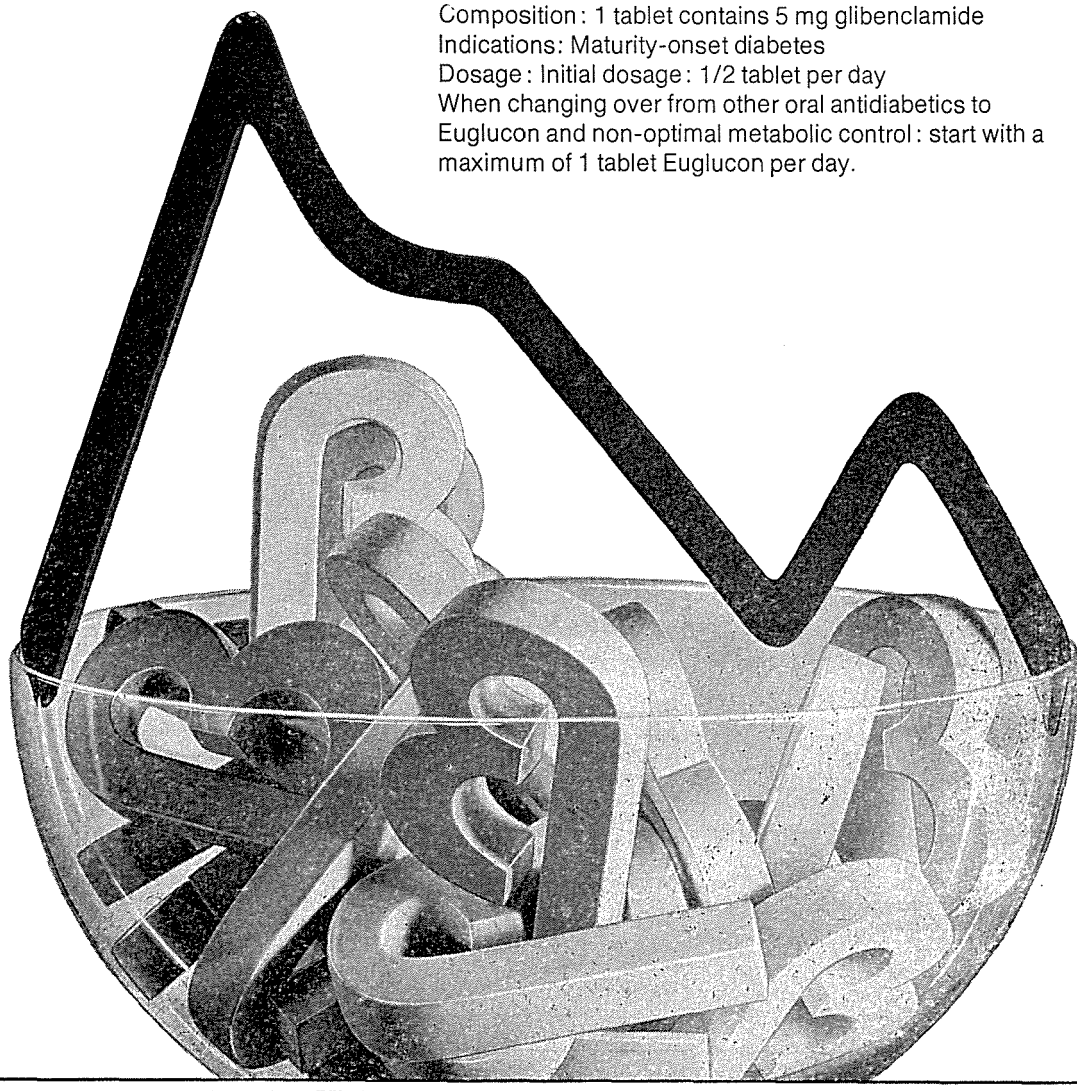

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THE ST. LUKE'S HOSPITAL GAZETTE

MALTA DECEMBER 1976 VOL XI No. 2

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CONTENTS

TERCENTENARY OF THE FOUNDATION OF OUR MEDICAL SCHOOL

Earlier on this month our Medical School celebrated the tercentenary of its foundation. Our Medical School can trace its origins to 19th December 1676 when Grand Master Nicholas Cotoner (1663-1680) founded the School of Anatomy and Surgery. Fra Giuseppe Zammit (1650-1740) was appointed to be the first Director and Teacher of this school. Zammit, who was both priest and physician, was the physician-in-chief of five successive Grand Masters. He established a garden of medicinal herbs in the ditch of Fort St. Elmo and was also responsible for the foundation of a Medical Academy in 1679. The Tercentenary Organising Committee set up by the Faculty Board of Medicine and Surgery organised a very successful series of activities. These were opened by a historical exhibition held at the National Museum, Valletta on 16th December. The exhibition was inaugurated by the Hon. Miss A. Barbara, Minister of Welfare, Labour and Culture. The exhibition was the result of the hard work and painstaking research put in by Dr. Paul Cassar. To Dr. Cassar must go the gratitude of the whole medical profession.

Through his medical historical writings he has won a justly merited international reputation not only for himself but also for our medical school. On Friday 17th December a scientific session was held which was to be chaired by Prof. J.L. Pace; due to the latter's unfortunate absence, his place was ably taken by Prof. A.P. Camillieri. An academic symposium was held in the morning of the following day. This was very successfully chaired by Prof. V.G. Griffiths. In the afternoon a plaque commemorating the Tercentenary Celebrations was unveiled by the Hon. Dr. V. Moran, Minister of Health and Environment, at the Medical School. This was followed by a historical symposium which was chaired by Dr. P. Cassar. On Saturday night a banquet was held at the Excelsior Hotel which was attended by about 150 doctors, dentists, pharmacists and their wives. On Sunday 19th December after Holy Mass by His Grace Mons. Gonzi at the University Church in Valletta the Rector delivered a tricentennial address. A plaque recording the foundation of the School of Anatomy and Surgery was unveiled later in the morning at the Holy Infirmary by the Hon. Miss A. Barbara. A reception was then held by Sir Anthony and Lady Mamo at their residence in San Anton. A final commemorative ceremony was held at the Assembly Hall of the University at Msida. This was inaugurated by the Minister of Education, the Hon. Dr. Philip Muscat. Following the Minister's speech, speeches were made by Dr. P. Cassar who spoke about the life and times of Grand Master N. Cotoner and Professor Sir Hugh Robson, Principal and Vice-Chancellor, University of Edinburgh who conveyed congratulations and best wishes both from Edinburgh as well as from other Commonwealth Universities. The Chairman of the Tercentenary Committee, Professor A.P. Camilleri, Dean of the Faculty of Medicine and Surgery delivered the closing speech.

Our medical school has continued to grow from its modest beginnings into what was described by Dr. Muscat, Minister of Education as the best faculty within the University. This is borne out by the quality of the graduates which it has turned out and its research output. Maltese doctors have a justly gained good reputation both locally and overseas and have participated with success in every sphere of society. A full twenty five per-cent of the present Parliament is made up of doctors and a similar percentage exists in the Cabinet. Members of our faculty besides their clinical work and their teaching duties have continued to publish learned articles in both the local and international medical press. This journal is proud to have published so many of these articles over the past twelve years. Some of our graduates have made it to the top of the academic tree overseas, and in this issue we are publishing two articles by two such graduates, Prof. Gilles, Profesor of Tropical Medicine at Liverpool University and Prof. Cuschieri, Professor of Surgery at Dundee University.

Our school, which has just been visited by a delegation of the General Medical Council of Great Britain, has been described as 'vigorous' in their report. They recommended that the M.D. degree of the University of Malta should continue to be recognised for the purposes of full and provisional registration in the United Kingdom. All this must however not be allowed to make us complacent. We must all strive to ensure that the standards so far acquired are not only maintained but improved upon.

Dr. R. Ellul-Micallef may be contacted at 'arc-en-ciel, San Anton Estate, Attard, Tel. 47994 or The University, Ta'-Qroqq, Msida Tel. 36451 ext. 244.
Any inconveniece to contributors to this journal due to a change in address is regretted.

SUPEROXIDE AND SUPEROXIDE DISMUTASE IN RED BLOOD CELLS

ANGELA ANASTASI, J.V. BANNISTER and W.H. BANNISTER

Department of Physiology and Biochemistry, University of Malta

Superoxide and Superoxide Dismutase

Oxygen has a propensity for one-electron reduction to superoxide radica's which are potentially harmful in biological systems. The superoxide radical exists briefly as an anion (O_2^-) at physiological pH. It decays by dismutation to molecular oxygen and hydrogen peroxide:

$$2O_2^- + 2H^+ \longrightarrow O_2 + H_2O_2$$

In 1969 a previously obscure copper protein of red blood cells, erythrocuprein, was shown to catalyse the dismutation of superoxide radicals (McCord and Fridovich, 1969). Erythrocuprein thus became superoxide dismutase and the object of intensive study.

Superoxide dismutase is typically an enzyme of aerobic organisms which utilise oxygen as the major electron acceptor. The presence of superoxide dsmutase in microorganisms has been found to parallel their tolerance for oxygen (McCord **et al.**, 1971). Thus aerobes have the highest levels of superoxide dismutase, aerotolerant anaerobes contain intermediate levels and obligate anaerobes do not possess the enzyme with the exception of some sulphate reducing bacteria and clostridia (Hewitt and Morris, 1975; Hatchikian **et al.**, 1976).

Erythrocuprein was shown to be a copper-zinc protein by Carrico and Deutsch (1970). Eurkaryotes have a copper-zinc superoxide dismutase in the cytoplasm and a manganese enzyme in the mtochondria (Weisiger and Fridovich, 1973). Prokaryotes have a manganese superoxide dismutase in the cell matrix and an iron enzyme in the periplasmic space (Keele **et al.**, 1970; Yost and Fridovich, 1973). The luminous bacterium "Photobacterium leiognathi," which is a fish symbiont, is exceptional in that i+ contains iron and copper-zinc superoxide dismutases (Puget and Michelson, 1974).

The manganese and iron superoxide dismutases of **E. coli** B have been shown by sequence homology to be related to each other and to mitochondrial manganese superoxide dismuatase from chicken liver, but they are entirely different from eukaryote cytosol copper-zinc superoxide dismutases (Steinman and Hill, 1973). This supports the idea that present day mitochondria are the descendants of prokaryotes which entered into an endocellular symbiosis with protoeukaryotes (Fridovich, 1974).

A variety of oxidation-reduction reactions have been shown to produce superoxide radicals (Fridovich, 1975). The potential sources of these radicals in the cell are of three kinds. One source is the oxidation of the reduced forms of several compounds found in biological systems including hydroquinones, leucoflavins, catechol amines, thiols, tetrahydropteridines, ferredoxin and rubredoxin. A second analogous source is the oxidation of metabolites by certain enzymes including xanthine oxidase, aldehyde oxidase, dihydroorotic dehydrogenase and some flavoprotein dehydrogenases. A third source is the dissociation or displacement of superoxide from the oxygenated adducts of haem proteins including haemoglobin and oxyperoxidase. The production of superoxide radicals during autoxidation of oxyhaemoglobin and decay of oxyperoxidase to ferric peroxidase has been demonstrated (Misra and Fridovich, 1972; Rotilio **et al.** 1975). The autoxidation of oxyhaemoglobin is discussed below.

Toxic reactions follow the reduction of oxygen to superoxide radicals or hydrogen peroxide. The oxygen molecule has two

unpaired electrons with parallel spins, one in each of two anti-bonding (π^*) molecular orbitals. This state is the one of lowest energy and reactivity for oxygen, the ground or triplet state. Two excited or energetically higher singlet states are possible with spin pairing of the two electrons in one or over the two π^* orbitals. Singlet oxygen is far more reactive than triplet oxygen although its life-time is extremely short (about one microsecond in water). Univalent reduction of oxygen to superoxide radicals is favourable because acceptance of an electron in one of the half-filled π^* orbitals does not cause a need for spin inversion.

The ubiquity of superoxide in biological systems is clear but little is known about its reactivity with biological material. Deleterious effects may be due to superoxide itself, to other oxygen reduction products derived from superoxide, or to free radicals generated by reaction of superoxide or its products with cellular components. Superoxide can mediate reductions, giving up its extra electron, or oxidations, becoming reduced to hydrogen peroxide. In general free radicals are highly reactive. They can combine with one another to form covalent bonds or they can attack bonds in other molecules. This often leads to production of new radicals, setting up a chain reaction. Superoxide has limited bond breaking ability (Sutton **et al.**, 1976).

The superoxide anion (O_2^-) is the conjugate base of a weak acid called the hydroperoxyl radical ($HO_2\cdot$) whose pK_α is 4.8. The rate constant for spontaneous dismutation of superoxide species at pH 7.0 is of the order of 10^5 $M^{-1}sec^{-1}$, whereas the dismutaton catalysed by superoxide dismutase has a rate constant of the order of 10^9 $M^{-1}sec^{-1}$ (Fridovich, 1975). The half-life of superoxide radicals can therefore be decreased by several orders of magnitude by the enzyme. Another favourable consideration is the concentration of superoxide dismutase in the cell which is estimated to be at least five orders of magnitude higher than the steady state concentration of superoxide (Fridovich, 1975). The probability of collision of a superoxide radical with enzyme is therefore much greater than that of collision with another superoxide radical.

The spontaneous reaction of superoxide with itself generates hydrogen peroxide and singlet oxygen. The dismutase reaction produces molecular oxygen of normal reactivity, i.e. triplet oxygen, which gives the enzyme an additional advantage. Hydrogen peroxide produced by the dismutation of superoxide radicals (or otherwise) can be decomposed in the cell by catalase and glutathione peroxidase. These enzymes probably act in concert with superoxide dismutase to circumvent the toxicity of oxygen by eliminating the primary products of oxygen reduction.

It has become common practice to suggest that superoxide might generate hydroxyl radicals ($OH\cdot$) in biological media **via** the Haber-Weiss reaction,

$$O_2^- + H_2O_2 \longrightarrow OH\cdot + OH^- + O_2,$$

originally postulated as a step in the breakdown of hydrogen peroxide by iron salts (Haber and Weiss, 1934). However, this ignores the fact pointed out by Fee **et al.** (1975) that even in a solution of 95% hydrogen peroxide, superoxide reacts only by dismutation (George, 1947). It is possible that where there has been strong evidence of hydroxyl radical production, as in the autoxidation of several cytotoxic agents with formation of superoxide and hydrogen peroxide (Cohen and Heikkila, 1974), hydroxyl radicals were formed by a non-Haber-Weiss reaction not involving direct decomposition of hydrogen peroxide by superoxide radicals. Cohen and Heikkila (1974) make this point in passing. It should be noted that the hydroxyl radical is a very powerful oxidant and could vastly augment deleterious effects of superoxide.

Superoxide in Red Blood Cells

The red blood cell is at increased risk of damage by superoxide and hydrogen peroxide because of the carriage of oxygen by haemoglobin. Some 3% of the haemoglobin in the erythrocytes is oxidized per day and reduced again by methaemoglobin reductase and other systems which keep methaemoglobin levels at about 1% of the total haemoglobin. Methaemoglobin

formation may either involve the loss of superoxide to leave an iron (III) complex, or the addition of an electron to bound oxygen to give an iron (III) peroxide. Misra and Fridovich (1972) showed that the autoxidation of shark oxyhaemoglobin caused the co-oxidation of adrenaline to adrenochrome. Part of this co-oxidation is due to a haemoglobin-catalysed peroxidation of adrenaline since it could be inhibited by catalase. The remainder of the co-oxidation was inhibited by superoxide dismutase, indicating that autoxidation of oxyhaemoglobin results in the generation of superoxide radicals. The production of superoxide in the process of autoxidation has been demonstrated in similar ways for bovine haemoglobin (Wever **et al.**, 1973), α and β chains of human haemoglobin (Brunori **et al.**, 1975), human haemoglobin A and unstable haemoglobins (Winterbourn **et al.**, 1976). Isolated α and β chains and unstable haemoglobins release superoxide at faster rates than Hb A.

Whether superoxide dissociates or needs to be displaced from oxyhaemoglobin depends on the electronic structure of the iron-oxygen complex. This has been considered to involve a fully developed iron (III) superoxide ion couple (Weiss, 1964) but recent studies have shown strong covalent bonding between iron and bent, end-on dioxygen, a type of bonding which precludes ready loss of superoxide from oxyhaemoglobin. For this reason Wallace **et al.** (1974) have proposed that superoxide is displaced from oxyhaemoglobin by anionic nuncleophiles in a proton-assisted reaction. The chloride ion is sufficiently active in this regard that with a normal human erythrocyte chloride concentration of about 0.1 M it could account for much, if not all, of the normal autoxidation of oxyhaemoglobin. Another feature of haemoglobin autoxidation is its catalysis by copper probably after specific binding to the haemoglobin (Rifkind, 1974). The copper-catalysed autoxidation of Hb A also involves superoxide production (Winterbourn **et al.**, 1976). Copper might facilitate the superoxide loss mechanism in the erythrocyte via the fraction in rapid exchange with serum copper.

Release of superoxide can be regarded as the initial step in the autoxidation of haemoglobin. The superoxide can then oxidize more haem in competition with dismutation producing hydrogen peroxide, which itself gives further haem oxidation. Catalase decreases the autoxidation of Hb A by about 40%. Catalase and superoxide dismutase slow it down by about 65%. Superoxide dismutase alone has only a slight effect (Winterbourn **et al.**, 1976). This is not unexpected. Reactions which produce superoxide are not generally affected by superoxide dismutase. It is rather those reactions which are dependent upon superoxide which can be inhibited by the enzyzme (Misra and Fridovich, 1972). It is possible that in reactions where catalase has an inhibitory effect augmented by superoxide dismutase, the latter could be protecting catalase from reaction with superoxide to form the enzymatically inactive oxy form or Compound III (Fee **et al.**, 1975).

Superoxide can oxidize the haem groups in oxyhaemoglobin and reduce those in methaemoglobin. The oxidation of oxyhaemoglobin has a rate constant of the order of 10^3 $M^{-1}sec^{-1}$ at pH 7. The rate constant for reduction of methaemoglobin is about 30% higher (Sutton **et al.**, 1976). In the erythrocyte the higher concentration of oxyhaemoglobin would favour the oxidation reaction but this is effectively suppressed by superoxide dismutase. The concentration of superoxide dismutase in normal erythrocytes is about 0.5 mg per g of haemiglobin or of the order of 10^{-6} M (Stansell and Deutsch, 1966). It is estimated that the erythrocyte has a molecule of superdxide dismutase for every 600 molecules of haemoglobin (Lavelle **et al.**, 1974). The concentration of the enzyme does not decrease in Wilson's disease even though serum caeruloplasmin is markedly reduced or absent (Alexander and Benson, 1975). The dismutase reaction in the erythrocyte is some 100 times faster than the oxidation of haemoglobin by superoxide taking into account the respective rate constants and the concentrations of superoxide dismutase and oxyhaemoglobin, the product of the rate con-

stant and concentration of reactant (**kC**) being about 10^4 sec^{-1} for the dismutase reaction and about 10^2 sec^{-1} for haemoglobin oxidation. The controlling or suppressing role of superoxide dismutase is therefore abundantly clear (Sutton **et al.**, 1976). Carrell **et al.** (1975) suggest that oxyhaemoglobin may act as a buffer by reaction with superoxide and hydrogen peroxide protecting sensitive components like the membrane lipids. If this is so, hypochromia would facilitate damage to the cell membrane and this might be particularly relevant in thalassaemia.

The oxidation of Hb A by superoxide does not give rise to irreversibly denatured haemoglobin derivatives in contrast to oxidation by hydrogen peroxide. There is no formation of haemichromes and precipitation. The β-93 cysteine residues are not oxidized. The unstable haemoglobins, Christchurch, Belfast and Köln react in a similar way to Hb A except for oxidation of the β-93 cysteines in Hb Köln. The methaemoglobins produced are quickly converted into haemichromes and precipitate, as expected for these haemoglobins. Haemichrome formation and precipitation is even more rapid after autoxidation of isolated α and β chains (Winterbourn **et al.**, 1976).

With normal level of superoxide dismutase in the erythrocyte only about 1% of the superoxide generated may be expected to react with haemoglobin. If other reactions occur they must either have **kC** products around 10^2 sec^{-1} in order to compete with superoxide dismutase and haemoglobin for superoxide or else take place coterminously with superoxide generation (Sutton **et al.**, 1976).

The red blood cell has an efficient system for dealing with hydrogen peroxide generated by dismutation of superoxide radicals or otherwise. It is considered that glutathione peroxidase is the primary enzyme which eliminates hydrogen peroxide in red cells although present at much lower activities than catalase (Cohen and Hochstein, 1963). Oxidized glutathione is reduced by glutathione reductase with NADPH generated by the pentose phosphate pathway. This helps to rationalize the presence of reduced glutathione in the red blood cell apart from its availability for preferential oxidation.

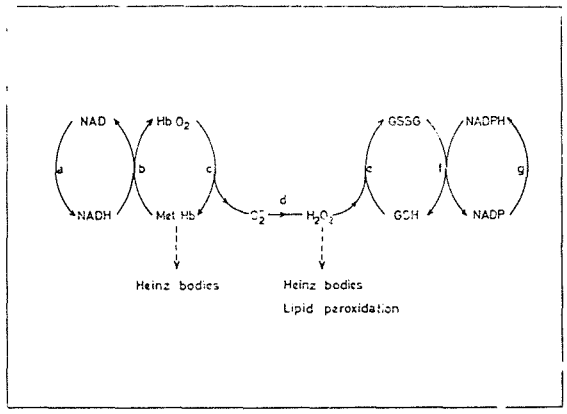

Figure 1.
Superoxide production and elimination in the red blood cell. a, Glycolysis, b, Methaemoglobin reductase; c, Oxidation of oxyhaemoglobin; d, Superoxide dismutase; e, Glutathione peroxidase; f, Glutathione reductase; g, Pentose shunt. Interrupted arrows show reactions leading to haemolysis.

A scheme of superoxide production and elimination in the red blood cell is shown in Fig. 1 after Carrell **et al.** (1975). The oxidation of oxyhaemoglobin and reduction of methaemoglobin constitutes a cycle producing a continuous supply of superoxide. Any factor that augments the production of superoxide or diminishes the elimination of hydrogen peroxide after superoxide dismutation is a potential threat to the red blood cell leading to haemolysis. Increased production of superoxide via oxidation of haemoglobin occurs with oxidative drugs, unstable haemoglobins and free α and β chains (as in thalassaemia). Build up of hydrogen peroxide can become acute in failure of reduction of oxidized glutathione through lack of NADPH generation in glucose-6-phosphate dehydrogenase deficiency. Direct toxic effects of superoxide are not shown in Fig. 1. The activity of superoxide dismutase in red blood cells in very high and superoxide dismutase deficiencies have yet to be de-

monstrated. Superoxide-dependent peroxidation of membrane lipids has been inferred from protection exerted by superoxide dismutase. A free radical or radical-like agent is involved in lipid peroxidation. Superoxide and hydrogen peroxide give rise to this agent (Zimmermann et al., 1973; Tyler, 1975).

Exposure of red blood cells to superoxide radicals does not cause haemolysis (Fee **et al.**, 1975). Dialuric acid (2,4,5 6-tetrahydroxypyrimidine), which autoxidizes rapidly to alloxan with production of superoxide and hydrogen peroxide, produces lipid peroxidation and haemolysis of erythrocytes from vitamin E-deficient rats. Catalase gives considerable protection against haemolysis if present during the brief period of oxidation of the dialuric acid. A mixture of catalase and superoxide dismutase is more effective than catalase alone. Superoxide dismutase by itself is not effective. Hydrogen peroxide in the concentration produced by oxidation of the dialuric acid has no haemolytic effect. Dialuric acid and oxygen probably react to form some highly reactive substance which either attacks the red cell membrane directly or serves as a precursor to the reactive substance. Catalase might react with the reactive species rather than hydrogen peroxide. Superoxide might block the effect of catalase by formation of Compound III and superoxide dismutase might prevent this (Fee **et al.**, 1975).

Erythrocyte Superoxide Dismutase — Erythrocuprein

The first preparation of erythrocuprein was from bovine erythrocytes (Mann and Keilin, 1939). Human erythrocuprein was first isolated by Markowitz **et al.** (1959). Thus erythrocuprein was known for several years before its superoxide dismutase activity was found by McCord and Fridovich (1969). Interestingly superoxide dismutase activity of tissue extracts or haemolysates was reported unknowingly in 1967 as tetrazolium oxidase activity. Two isozymes called A and B were found. A deviating phenotype of isozyme A was not reflected in isozyme B. This suggested that the two isozymes were under separate genetic control (Brewer, 1967). In fact isozyme A corresponded to cytosol or copper-zinc superoxide dismutase and isozyme B corresponded to mitochondrial or manganese superoxide dismutase (Beckman **et al.**, 1973).

Erythrocuprein is cytosol superoxide dismutase. This form of superoxide dismutase has a molecular weight of about 32,000 and consists of two subunits. Each subunit contains one atom of copper and one atom of zinc. The catalytic activity is due to the copper. The zinc probaly helps to stabilize the tertiary structure of the enzyme.

Knowledge of human erythrocuprein has lagged behind that of the bovine enzyme. The complete amino acid sequence of bovine erythrocuprein is known (Steinman **et al.**, 1974) and theh three-dimensional structure as revealed by X-ray diffraction analysis is known to a resolution of 3 Angströms (Richardson **et el.**, 1975). The subunits are identical. The most prominent structural feature of the enzyme is a cylinder like a barrel whose walls are composed of eight strands of the peptide chain in an antiparallel β structure. The helical content is very low. These findings have vindicated earlier predictions of the secondary structure from circular dichroism and infra-red spectra (Wood **et al.**, 1971; W.H. Bannister **et al.**, 1973). The metals share a histidine residue at position 61 of the amino acid sequence. The copper, which is more exposed than the zinc, is liganded to three other histidines. The histidine ligands of this metal had been predicted by nuclear magnetic resonance spectra (Stokes **et al.**, 1973) The zinc is liganded to two more histidines and an aspartic acid residue.

It has been suggested that the subunits might not be identical in human erythrocuprein (Hartz and Deutsch, 1972). This is at variance with the observed polymorphism of the enzyme. Human cytosol superoxide dismutase (SOD–1) is polymorphic in northern Sweden and northern Finland with genetically controlled electrophoretic variation. The common phenotype, SOD-1 1, shows one major zone

and one or two minor anodically faster moving zones in gel electrophoresis. The rare phenotype, SOD-1 2, shows a similar isozyme pattern but with an overall slower electrophoretic mobility. The phenotype, SOD-1 2-1, shows the SOD-1 1 and SOD-1 2 zones and in addition a hybrid enzyme with intermediate electrophoretic mobility. The observation of this hybrid enzyme implies that the superoxide dismutase is at least a dimer formed through free recombination between two equal polypeptide subunits (Beckman **et al.**, 1973).

Most preparations of human erythrocyte superoxide dismutase have contained a minor component with somewhat faster anordic mobility in gel electrophoresis (Bannister **et al.**, 1972) We recently described the isolation and properties of two forms of superoxide dismutase from human erythrocytes, SOD I and SOD II (Bannister **et al.**, 1976). These can be obtained from a haemolysate of red blood cells after precipitation of the haemoglobin with a mixture of ethanol and chloroform. They are separated by ion-exchange chromatography on QAE-Sephadex with buffers of low ionic strength and decreasing pH. SOD I and SOD II are homogeneous in polyacrylamide gel electrophohresis. SOD II has a slightly higher anodic mobility than SOD I. Both SOD I and SOD II contain 2 g atoms of copper and 2 g atoms of zinc per mole of protein. The rate constant for the dismutase reaction estimated with a xanthine-xanthine oxidase-cytochrome c assay system (Sawada and Yamazaki, 1973) is 1.2×10^9 M^{-1} sec^{-1} for SOD I and 1.3×10^9 M^{-1} sec^{-1} for SOD II at pH 7.8 in good agreement with the value of 1.4×10^9 M^{-1} sec^{-1} at pH 7.5 determined in a previous pulse radiolysis study on human erythrocuprein (J.V. Bannister **et al.**, 1973). The amino acid compositions of SOD I and SOD II are essentially similar. The percentages of secondary structure as computed from far-ultraviolet crcular dischroism spectra are closely simlar for SOD I and SOD II. Little helical structure (4-9%) and about 50% (47-58%) β-sheet secondary structure is indicated.

Human erythrocuprein has a well-resolved band at 322 nm in the absorption spectrum (Bannister **et al.**, 1972) which is not shown by bovine and other known cytosol superoxide dismutases. The band is optically active giving a strong positive contribution in the circular dichroism spectrum. The chromophore is present in SOD I and lacking in SOD II. We have previously shown that a persulphide group, R-S-SH, is the most likely structure for the chromophore on the basis of its chemical reactivity. Four g atoms of labile sulphur per mole of protein were found (Calabrese **et al.**, 1975). Labile sulphur may be related to some as yet unknown physiological function of human erythrocyte superoxide dismutase.

The amino acid composition of human erythrocyte sueroxide dismutase shows some difference with respect to the bovine enzyme. Tryptophan is present and methionine is notably absent. The presence of tryptophan originally inferred from ultraviolet fluorescence spectra (Bannister **et al.**, 1968), has been confirmed by magnetic circular dichroism spectra. Two residues are indicated. The catalytic or copper site is closely similar to that in bovine enzyme (Roberts **et al.**, 1974). Nuclear magnetic resonance spectra indicate a histidine ligand field for the copper as in the superoxide dismutase of bovine erythrocytes.

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PROSPECTS FOR THE CHILDLESS

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Over the past three hundred years the population of the Maltese Islands has multiplied four-fold. In the year 1676, when the beginnings of our Medical School were instituted, an estimate of the population would have been in the region of 80,000 persons (Camilleri, 1954); today it exceeds 320,000. Indeed our Islands to-day are among the most densely populated places in the world.

Much concern has been voiced about over-population. To decry high birth-rates has become the fashionable slogan of most Governments. Conversely it is almost unthinkable to waste time and money on the plight of the childless. It is ever so much easier to obtain financial support for research into the limitation of fertility than into the cure of infertility. The number of couples involved in relation to fertility is proportionally small, and hence numerically weak. Moreover, it is often alleged that the duration of treatment tends to be distressingly long and that the ultimate results are hardly more successful than in the untreated.

The sorry plight of infertile couples has attracted my interest for several years. My experience leaves no shred of doubt that their silent suffering deserves to be shared and if possible relieved. I believe, too, that with perserverance the success rate can reach satisying proportions. And I envisage that the prospects are becoming brighter.

In private practice between 1969 and 1975 I have had 332 couples who sought advice about their infertility, an average of 47 per year. Yet so many of them seemed to become readily disheartened, in some cases because they expected "miracle" pills or injections, in others because the husband would not countenance the idea that he should be investigated, and in many cases for no clear reason at all. In my series there were 53 couples who attended only once (17.5 per cent) and another 58 couples only twice; so that more than one-third of the initial couples (actually 35 per cent) failed to persevere beyond the second visit. This failure of perseverance accounts, in my view, for the commonest single factor that prolongs the childless state of infertile couples. It seems so difficult for the doctor at the couple's first attendance to steer an honest course between a fervent encouragement for investigation and treatment and a truthful declaration of their probable chances for a pregnancy.

In considering further this factor of perseverance, I found that out of the remaining 216 couples there were 88 who stopped attending before the lapse of 2 years, and another 24 couples ceased attendance after 2 years or more. These 112 patients had a mean duration of attendance of 17,25 months. If we aggregate the couples who only gave up after 2 or more years together with the couples who are still attending or have achieved a pregnancy or were provisionally discharged (usually due to resistant azoospermia) then we reach a total of 128 couples whom I wish to classify as the Perseverers. These amount to 38.5 per cent of the original number in my series.

In this series there were 86 couples who achieved one or more pregnancies. All 86 of them now have at least one live child. The resultant pregnancy rate is depicted in Table I in relation to the degree of perseverance as already discussed. It is pointed out that a pregnancy resulted in a quarter of the entire series, and in no less than two-thirds of the persevering couples.

These figures, I submit, justfy my belief that with perseverance the success rate in the management of infertility can reach satisfying proportions.

I have also expressed the belief that the prospects for success are becoming brighter. This belief I think, can be justi-

Attendance	Number of Couples	Per cent of intial series	Pregnancy Rate
All couples	332	100%	25.9%
Excluding one or two visits only	216	65%	39.8%
Perseverers	128	39%	67.2%

fied on several counts. And I propose to illustrate some of the clearer indications of progress in this regard.

In the first instance there is a greater awareness and acceptance of the fact that the husband quite often carries a substantial part of the blame for the couple's infertility. More men are expecting to be examined and treated in cases of infertility. The concept of Meaker's Index is helpful: it asserts that the fertility of a couple is a product of the fertility of both husband and wife. In other words if the wife's fertility is half the normal and the husband's is also half the normal, then their combined fertility is only a quarter of the normal ($0.5 \times 0.5 = 0.25$); whereas if the wife has a normal fertility and the husband's is half the normal, their fertility remains half the normal ($1.0 \times 0.5 = 0.5$). A deficient semen is a case in point. In my series of 332 couples there were 83 men who did not undergo a semen analysis; of the remainder no less than 173 had a deficient semen, including 36 who had absolute azoospermia or only a few non-motile spermatozoa.

The treatment of male infertility is attracting greater scientific attention, and slow but steady progress is being registered. In a way it is unfortunate that there are few specialist Andrologists for the husband in the sense that there are Gynaecologisits for the wife. For instance the investigation of deficient sperm still leaves much to be desired, and the treatment is often somewhat arbitrary. On the other hand some drugs do prove effective in certain cases, such as some androgens (especially when they do not materially inhibit the pituitary) as well as the gonadotrophic hormones and more recently the pituitary gonadotrophin releasing factors.

In the case of the wife the investigation and treatment are more realistic, although established misconceptions are difficult to eradicate or modify.

Many women keep a basal temperature record very faithfully, and they continue to believe that they must wait for the mid-cycle rise in temperature before having intercourse! Surely this practice is a mis-use of the onset of the Safe Period. I have had several couples who overcame their infertility apparently only on adopting more correct advice than they had previously been given.

Another disquieting practice from the point of view of subsequent infertility is the use of the Pill in certain cases. Elsewhere (Camilleri, 1970a and 1972a) I have emphasized that adolescent girls who have been given the Pill for longer than 6 months (for such purposes as physiological amenorrhoea of puberty, or menorrhagia, or dysmenorrhoea) run a real risk subsequently of failing to ovulate regularly, and consequently of being infertile; their anovulant infertility is also rather resistant to treatment.

Ovarian dysfunction is in fact a common contribution to a couple's infertility. Two deficiencies may be high-lighted; on the one hand ovulation may be absent or merely occasional, and on the other hand the luteal phase in each cycle may be too short (hence not allowing enough time for the endometrial development that permits proper implantation). The basal temperature record is very helpful in identifying these two faults. And their correction

can often be achieved by modern drugs (clomiphene, cyclofenil, gonadotrophic hormones, bromocriptine). I might emphasize that in some women the principal defect lies in the marked shortness of the luteal phase, and that in such cases the exhibition of ovulatory therapy is indicated from the earliest day possible in each menstrual cycle. I have increasingly adopting this regimen in my practice; there have been 52 such cases in this series (mostly in the last 4 years), and 16 of them became pregnant.

As the physiological mechanisms and processes entailed in ovulation, fertilization and implantation (Camilleri, 1972b) continue to be studied in earnest, it is inevitable that further advances will follow in the management of infertility. The effect of certain antibiotics at the time of ovulation, the influence of aspirin and other anti-inflammatory drugs on prostaglandin levels and hence on fertility in men and in women, the intricacies of spermatozoal capacitation, observations of this kind will command attention and eventually lead to practical and effective measures.

It may be, however, that some women will remain resistant to all treatment aimed at inducing their ovaries to ovulate. Much research is proceeding apace to achieve in-vitro fertilization and, after early cleavage of the fertized human ovum, to transfer the embryo to the woman's womb. We are ourselves looking into a different approach, namely that of homograft transplantation of the ovary (Camilleri et al., 1976). We believe that for women with absent or non-ovulant ovaries a successful ovarian orhotopic homograft would probably be more acceptable than test-tube fertilization and subsequent inovulation. The former procedure would carry several advantages over the latter: it involves less surgery, it is technically easier, it may prove more lasting, it appears more natural, and it is probably genetically safer.

Finally one might recall that the childless may indeed be quite fertile (Camilleri, 1968). Here one has particularly in mind the couples faced with recurrent abortions. I have no doubt that the most rewarding single factor in the management of these women is the patient imposition of absolute rest in bed from the earliest stage possible in the pregnancy to at least 15 weeks gestation. This measure is essential whatever the underlying cause for the recurrent miscarriages; in other words, even in patients who require a Shirodkar suture for cervical incompetence. This measure, in fact, may itself prove effective enough in some women with congenital malformations of the uterine cavity, thereby obviating the need for the hysteroplasty operation which might otherwise become indicated (Camilleri, 1969). Concerning the use of progesterone depot preparations I cannot refrain from stressing their probable uselessness and their unwarranted hazards: whereas we have shown that progesterone is worse than ineffective in the management of threatened abortion (Camilleri and Montanaro Gauci, 1971) and others have found no evidence that progesterone increases foetal salvage in preventing recurrent abortion, yet it is well established that certain progestagens may exert a virilizing effect on a female foetus and it is becoming clear that sex steroids taken by the mother during pregnancy may influence the adult sex behaviour and fertility of her offspring by the manner that the brain becomes programmed (Camilleri, 1970b). It is disconcerting that such iatrogenic risks should persist without any commensurate basis for the effectiveness of the therapy.

Undoubtedly many a childless couple is an unhappy couple. Within the limits of genetic and developmental well-being, their lot deserves every attempt at amelioration. With perseverance many of them should be confident in achieving a child of their own.

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HEALING BY SORCERY IN 17th AND 18th CENTURY MALTA*

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The type of medical care available in Malta from the 16th to the 18th century ranged from that provided by the academically trained doctor, usually a graduate of the medical schools of Salerno and of Montpellier, and by his auxiliaries the surgeon and the barber-surgeon to that obtainable from his rivals, i.e. the lay healers without any medical background. These were elderly Maltese women and Moslem slaves.

I propose to deal with these lay healers because this aspect of our medical history has not been adequately dealt with and because its documentation does not form part of conventional medical sources and, therefore, it is bound to escape the notice of the researcher who restricts his investigations to exclusively medical archives. In fact, the information about this topic is to be found among the records of the trials of the Tribunal of the Inquisition which was set up in Malta in 1575 and remained in action until 1798 when it was abolished by Napoleon on his taking over possession of the Maltese Islands.

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The Tribunal of the Inquisition took cognizance of all issues touching the religious beliefs of Catholics which ranged from blasphemy and heresy to reading and keeping prohibited books, engaging in magical practices to treat illness, believing in the effects of spells as causes of diseases and holding communication with the devil (AIM 79a).

The most notorious healer that persistently occupies the centre of the stage is the Moslem slave. The existence of Moslem slavery is one of the most salient features of Maltese history between 1530 and 1798 when Moslem slaves formed an important component of the population of our Islands during the rule of the Order of St. John. They were owned by wealthy private individuals or by the Order. Besides being engaged as rowers in the galleys, slaves were employed in the building and repairs of the fortifications, in public works, as labourers in workshops and as domestic servants with knights and Maltese families. In 1630 there were some three thousand of them in Malta (population about 60,000) who, because of their occupations came in daily contact with all sections of Maltese society (Mallia Milanes, 1975). In contrast to that of the galley-slave, the life of the land-slave was

not rigorous. It is true that his liberty of movement was restricted but he was protected by law against ill treatment so much so that penalties were laid down for Christians who insulted, molested or beat him. When sick he was treated either at the Holy Infirmary or at the Prison Infirmary at Valletta (Cassar, 1965a; Cassar, 1968).

The slave-healers were either picked up at random from the streets or else they were recommended for their reputation of expertise at treating the sick. There was, for instance, the so-called "barberotto" or barber-surgeon of the Slave Prison who, inspite of his title, does not seem to have received any surgical training at all; the "Papasso" or Mohammedan priest of the same Prison who claimed to be able to "read and write Arabic" and who treated sickness by writing excerpts from the Koran on slips of paper which were handed to the patient (AIM 108a); Stephen Abdalla, to whom "many went to be cured" in the second decade of the eighteenth century (AIM 108b); Gaetano Schembri, a baptised slave, who had been employed for nine years in the Holy Infirmary in the inunction of venereal patients with mercury (AIM 137a); and another slave, who earned his living by repairing shoes (1636) but was renowned for his ability to treat epilepsy (AIM 51a).

The consultation and treatment were usually held in the patient's home, the slave charging from four "tari (one "tari" = 5 mils) to three "scudi" (one "scudo" = 10 cents) for a visit (1636) but sometimes as much as six "scudi" were asked for, two of which to be paid before the initiation of treatment (1720) (AIM 51b; AIM 108c).

Besides slaves there were elderly Maltese women who undertook the treatment of diseases by instructing members of their families or their neighbours in the application of the traditional remedies that they themselves had learned from their ancestors, or from their own personal experience. Thus a woman from Zebbug (Malta) told the Tribunal how she came to acquire her reputation of treating jaundice. She said that she had suffered from this disease when she was ten years old and was cured by a man from Attard who treated her with fumigations of burnt blessed oil and candles and with recitation of prayers. Years later she again developed jaundice and treated herself in the same manner with recovery. She then taught others how to treat themselves for this ailment but they preferred to go to her rather than carry out the treatment themselves. Indeed it was public knowledge that patients visited her daily to be cured of their jaundice (AIM 135a).

Sometimes these healers gained their experience from treating sick animals by the casting of spells. Thus in March 1722 a woman from Valletta undertook to treat human beings after having successfully treated sick pigs and dogs struck by the evil eye by fumigating them (AIM 108d).

By the end of the eighteenth century there were no less than five women living at Zebbug (Malta), Qormi and Lija known for these activities. In 1792 a family of three—father, mother and daughter—were similarly engaged (AIM 135b).

Occasionally one comes across priests as healers of bewitched patients. A Sicilian friar at the Carmelite Convent in Valletta was active in 1635. Having diagnosed illness as due to a spell, he prescribed the rubbing of joints with oil and the ingestion of a syrup concocted by himself. He received fees (AIM 51c).

In April 1722 a priest was approached by a sick man who believed that his illness was the result of a spell. The priest tried to persuade him that it was not a question of bewitchment and recommended that he should bathe himself with white wine containing "various herbs and aromatic substances". The man, however, persisted in his belief and went back to the priest. The latter then wrote the name of the person, who the sick man believed to have cast the spell, on a slip of paper and told the patient to burn it while pronouncing these words:— "May the person who is seeking to harm my body and my soul be burned like this paper" (AIM 108e).

Very rarely a priest became involved unwittingly by being asked to bless water

or oil which was subsequently used in a magical ritual as happened in a case in 1720 (AIM 108f).

Finally there was the swindler who undertook to provide the client with the necessary herbs and ingredents but actually supplied counterfeit ones. Thus in 1636 a man confessed to the Tribunal of the Inquisition that he had given powdered tobacco and St. Paul's Earth to a woman who had instead requested powered "vinca" plant ("Vinca major" and "V minor." "Gis'min ahmar") and a piece of loadstone to bind her paramour by a spell (AIM 51d).

In February 1722, a slave who had diagnosed illness in a woman as being due to the influence of the evil eye, admitted to the Tribunal that he had undertaken to treat the woman because she was rich and he grasped the opportunity to earn some money which he had to share with the pharmacist who had acted as a go-between (AIM 108g). In September 1794 another slave made a similar confession stating that he had no experience of sorcery and that he did not even know how to read or write but that he pretended to be a sorcerer "only to earn some money to feed himself and his wife" as they were starving (AIM 137b).

Nature of Illness

The nature of the malady is very vaguely stated (1636)). It is referred to in such generic terms as a "long standing illness", "illness of seven months duration" "indisposition"; sometimes the sufferer mentions more specific complaints such as "headache", "eye disease", "blindness', "continued fevers", "terzana" and "jaundice"; and occasionally such nosological entities as "epilepsy" and "madness" (AIM 51e; AIM 108h; AIM 135c).

Although it was then a wide-spread belief that illness could be brought about by the harmful influence of the evil eye or by bewitchment or spells, the existence of "natural disease" was not excluded. It was, therefore, important to distinguish between the two types of illness.

The following procedure was adopted by a Moslem slave in August 1722. The patient was given a piece of paper with a script. After fumigating it with a given "profumo", it was placed under his pillow. If his illness was a natural one, he was not expected to dream at all but if he was smitten by a spell, he would dream how the spell was cast upon him (AIM 108i). It was important to make this distinction because if the disease was a "natural" one, it called for "natural" remedies but if it was due to a spell this could only be removed by the casting of a counter-spell. Thus a bewitched patient was told by a slave to eat some flour made into a paste with the saliva of the person who had cast the spell (AIM 108j). In the same year another slave claimed to recognise the nature of the disease by observing the urine of the patient in a glass vial (AIM 108k). In 1792 a woman-healer made the differential diagnosis between natural illness and disease due to bewitchment by placing some salt and water in a plate and floating a few drops of oil on the surface. If the oil spread, the sickness was attributed to a spell; but if not, the ailment was a natural one (AIM 135d).

Typical Case Histories

To illustrate the procedure followed by the patient and healer and the background against which it was carried out, I am reproducing two typical case histories. They are translated from the Italian as found in the files of the Tribunal of the Inquisition.

On the 15th November 1636 John Paul Grima of Luqa was accused of obtaining the services of a Moslim slave for the treatment of his niece by witchcraft. "I have a niece", he said, "called Maria, wife of Peter Caruana, who is always ill. I went to the Slave Prison in Valletta to talk to a lame slave, known as the barber-surgeon ("barberotto"), with the intention of asking him to undertake to treat her. After seeing her, he said that he was sorry that he was not in a position to cure her because he did not possess certain herbs that were needed for her treatment. However, he referred me to another slave from the same prison who, he said, would cure her as he was a better "doctor" ("medi-

co") than him. I, therefore, sought out this slave and after giving him an account of her illness he came to visit her at home in Luqa. In the presence of her husband, myself and others, he passed several small pieces of paper containing some writing over a fire and then fumigated them with a perfume which he had brought with him. Then he asked for a receptacle with water which he covered with a bed-sheet. He told us to put our hands in the water and stir it. He next passed a live hen over the head of my niece and later put the already mentioned pieces of paper in a mortar which he pounded into a paste with the "ruta" plant ("Ruta bracteosa. Fejgel) while muttering some words in a low voice. He then instructed us to annoint the legs of my niece with the resulting juice. Finally he told us to melt a lead ball and throw it into a vase of water which the patient had to place over her head. The slave charged us four "tari" and took the bed-sheet saying that it was of no further use for us (AIM 51f).

Here is a summary of another case that was dealt with in the same year. After seeking orthodox therapy at the hands of several physicians, a woman of twenty-two years consulted a Sicilian Carmelite friar at Valletta who ascribed her ailments to a spell and who promised that he would cure her. He gave her some oil with which to rub her eye-brows, ears, nose and upper lip and her knees and feet for four nights. He also prescribed a mixture by mouth which the patient declined to drink as she had heard that the friar had caused the death of several persons who took it. She did not improve and in despair she went to a slave who confirmed that she was under a spell and proceeded to remove it. He took a hen, cut its head, placed it in a bowl and asked the patient to urinate on it. He then divided the hen's head in two and buried the halves under the threshold of two different houses. The following day he gave the woman a mixture to drink consisting of incense and musk in white wine. He then wrote some words on a piece of paper with saffron instead of ink, placed the paper on her chest and afterwards burned it. He instructed the patient to scatter the ashes on the floor of the church of Porto Salvo at Valletta to remove the spell because, he said, it was in that church that her enemies had bewitched her (AIM 51g).

Social Strata

These beliefs and activities were not restricted to the untutored populace but infiltrated also the higher social strata of the community including members of the Order of St. John and of the priesthood.

In April 1635 the Italian Knight Vittorio Scaglia appeared before the Tribunal of the Inquisition where he accused himself of reading books on necromancy; of having bewitched three persons and indulged in magical practices to find hidden treasure; and of having gone to the extent of invoking the aid of the devil in carnal matters (AIM 51th).

In March 1676 we read of Antonia, wife of the physician Dr. Fabrizio Gauci, resorting to the most repulsive and weird spells to re-kindle her husband's amorous passion for her. As, however, the means adopted by her proved unsuccessful her love turned to hate and she decided to procure his death. She, therefore, invoked the devil and pleaded with him to destroy her husband promising the devil that if he destroyed her husband she would surrender herself to him and allow him to have sexual intercourse with her (AIM 79b).

According to evidence submitted in another case in 1635, the Rev. Pietro Cutajar, who had been sick in bed for four months, believed that his illness had been brought about by a spell cast upon him by another priest, the Rev. Santoro dello Piscopo. Cutajar was convinced that unless Santoro visited him and removed the spell he would not get well. Eventually Santoro did so and Cutajar recovered from his illness so much so that while previously Cutajar "shouted and was agitated he now became calm and restful" (AIM 51i).

At this period a Franciscan friar availed himself of the therapeutic services of a Greek who treated him for a disease of the spleen by placing the patient's foot on the succulent leaf of the prickly pear and then cutting the leaf round the contour of the

foot (Bonnici, 1967).

It is also on record that a lame priest sought treatment from a slave for his disability in 1722 while another one confessed before the Tribunal in the same year that he had fallen "under the influence of a slave to such an extent that he blindly carried out everything that the slave suggested" (AIM 108 l).

Some patients, after the treatment failed ,regretted having been so gullible. Thus a woman who was treated by a slave for an ocular ailment in January 1636 not only declared her loss of confidence in her healer but insisted that he should return the fees she had paid him for two visits (AIM 51j). Another sick woman (1636) suspended the remedies ordered by a slave on becoming aware that she was being hoodwinked (AIM 51k). The relative of a patient declared before the Tribunal of the Inquisition in 1792 that the patient recovered from his illness not because of the treatment he had received at the hands of a Turkish slave but because the illness was a reversible one (AIM 135e).

Why did people seek lay healers?

1. Some patients went to the slave or other lay healer because of the reputation he or she enjoyed as a healer; or because they believed themselves to be sick because of a spell cast upon them by an ill-wisher. Other misfortunes were also ascribed to bewitchment, as failure in business affairs, and the course to take was to seek a sorcerer to remove the spell by casting a counter-spell (AIM 37).

2. Others (1636) sought treatment from a slave because they thought that the remedies prescribed were "natural" ones and not magical practices (AIM 51l); or else that the slave had learned them from some medical practitioner (AIM 137c).

3. A number of sufferers decided to seek the help of slaves after they became disillusioned with the treatment of the orthodox physician from whom they did not obtain the relief they craved. Such was the case dealt with by the Tribunal in 1636 of a woman of twenty-two years from Valletta who had been sick for seven months and who after having had "recourse to prayers and to the physicians" went for treatment to a Sicilian friar and finally to a slave. "I became so confused and so depressed on account of my affliction", she told the Tribunal, "that I did not care by what means the slave would treat me as long as I obtained the desired cure" (AIM 51m). A similar confession was made in 1677 by another woman aged twenty-three years who had been subject to continuous fever for four months and had been unsuccessfully treated with "all the remedies ordered by the doctors". In despair she went to a slave and asked him to prescribe her "the remedies in use in his country" (AIM 79c).

In 1792 a patient suffering from jaundice sought the ministrations of an old woman-healer from Zebbug (Malta) because she felt "so tormented" by her illness that she did not care whether she acted sinfully or not in seeking a sorceress. Another woman with ocular disease and "a pannus in one of her eyes" was induced to resort to magical therapy by the fear of losing her eyesight (AIM 135f).

Methods of Treatment

1. The standard treatment was the fumigation of the patient (1636) with burnt ingredients. In March 1636 a Maltese elderly woman prescribed the fumigation of a sick child with the smoke of a mixture consisting of oil blessed in honour of St. Peter the Martyr, a laurel leaf and a small piece of wood removed from the house door. This method, used in the treatment of three children, cured two of them but failed in the third child who died (AIM 51 n).

Sometimes the material to be burnt consisted in pieces of paper containing some writing which the patient could not decipher (1636) (AIM 51o). This is how a youth of 17 years was treated for epilepsy in 1636. In 1677 a woman suffering from a long standing fever was advised to burn a written piece of paper over lighted coal in a jar and then fumigate herself with the smoke. She was also given a similar slip of paper and told to immerse it in water and drink this water. In 1678 a

patient was fumigated with the smoke of a burnt mixture made of a written paper, saffron and musk. A separate piece of written paper was soaked in water and the patient directed to have three mouthfuls of the liquid and wash the affected parts of the body with the rest (AIM 79d).

Occasionally the fumigation was combined with far more complex ritual. In October 1631 a Maltese woman advised the smoking of the patient's head with the fumes of the resin from "Dorema ammoniacum"; then mixing the ashes with water and, after pounding them, make the sign of the cross over the body joints and finally throwing away the remainder of the mixture from the window saying:— "May the spell be removed as this mixture is being scattered" (AIM 51p). In 1792 a woman treated eye diseases by fumigation with burnt oil and candles while pronouncing the following verses:—

Jekk il ghajn hia kahla
tmur mal berqa
u jekk l-ghajn hia zerqa
tmur bhan-nahla (AIM 135g).
If the eye is blue,
Let it go with lightning.
And if the eye is azure
Let it go like a bee.

In ancient times, fumigation, consisting in the burning of such odoriferous substances as incense, formed part of the pagan religious ceremonial of the Egyptians, Greeks and Hindus and, in more recent times, of the Catholic Church as a symbol of the ascent of prayers to Heaven. It acquired its medical usage through this mystic association with the godhead. Hippocratic writers recommended fumigations with burnt herbs for gynaecological disorders, the smoke being directed into the vagina by means of a reed emerging from the vessels containing the smouldering herbs (Mathison, 1958a). Fumigation also constituted the standard preventive method against the plague by the Maltese sanitary authorities at the Lazzaretto as late as 1810 for passengers and the 1880s for letters (Cassar, 1965b).

2. Although written papers as already mentioned were mainly employed in conjunction with other remedies, their use by themselves was deemed sufficient to effect a cure. Thus in September 1720 a slave pretended to treat a mentally sick woman by giving her husband three slips of paper with writings on them and telling him to tie one of them to a tree; to let another one to be blown away by the wind and to tear the third one.

The script on these papers appears to have been in Arabic though it is possible that in many instances it was only a pseudo one. In fact one of these papers submitted to the Tribunal of the Inquisition in September 1720 although apparently written in Arabic characters "could not be read as it was made of syllables that made no sense at all"; another paper was described as having a Turkish script. In another instance the wording was genuine and consisted of quotations from the Koran. One of the slaves summoned by the Tribunal in July 1720 stated that what he wrote "were all prayers which we offer to our saints to intercede with God to cure the patient's illness and restore him to good health... They are all taken from the Koran" (AIM 108m).

It is of interest to know that it is customary among Arabian women to-day to wear amulets round their neck in the shape of silver cases containing texts of the Koran written with ink in which myrrh and saffron have been mixed (Mathison, 1958b).

3. The laying of hands figures in some cases. In May 1636 a young man with jaundice was taken to the wife of a baker at Mosta. She treated him by laying her hands on his head and muttering some words which he did not understand (AIM 51q). An old woman from Senglea treated ailments of the spleen in 1635 by laying her hands on the patient's abdomen while reciting prayers and invoking the names of St. Peter and St. Nicholas of Bari.

One may recall that healing by touch has a biblical tradition. Paul raised a dead man to life at Troas by laying himself upon him (Luke, The Acts, Chap. 20, v 10). In Malta Paul healed Publius' father by praying and laying his hands on the ailing man (Luke, The Acts, Chap 28, v 8). In later

Christian times, the saints healed the sick by the same process, i.e., the transference, through their hands, of invisible miraculous forces from themselves to the patient. The possession of a similar supernatural power was attributed to the Kings of France and England to whom patients suffering from scrofula were brought for the "Royal Touch". It is to be noted that the last recorded instances of such treatments occurred as recently as the accession to the throne of Charles X of France in 1825 (Bloch, 1973).

4. Bathing parts of the body was prescribed for various ailments. In 1636 a slave treated a woman suffering from headaches and pains in her arms and eyes by washing her eyes with cotton wool soaked in a solution of rose water containing the white and yellow of an egg. As there was no improvement the patient was told to throw some salt in the street.

In January 1636 a woman of seventy years from Mosta told the mother of a sick child to wash him with water containing the goose-foot plant ("Chenopodium vulvaria." "Nittiena") but had to be careful not to mention the name of Jesus or make the sign of the cross during the bath as it was said that the devil had washed himself with water containing that herb (AIM 51r).

5. Reading from a book over the patient was the method adopted by a slave in 1677 (AIM 79e). The same procedure was used in 1794-97 by priests who believed that a man, diagnosed by doctors as suffering from mental disorder, was really a case of Satanic possession (AIM 137d).

6. The idea was current that evil spirits possessed the power to substitute healthy children by sick ones, hence the term changeling ("mibdul") given to sick children. In 1678 the mother of an ill child was adivsed to bathe her child in water containing a "certain herb" and then repeat three times the formula:— "Take your child and give me my own" (AIM 79f).

7. In 1636 a sick woman, whose illness was diagnosed as being due to bewitchment, was given two wax dolls by a slave and told to bury one of them in her house and to melt the other one over a fire (AIM 51s). This procedure was inspired by the concept of transference of disease, i.e., the belief that sickness could be removed from a patient by passing it on to others or their substitutes by means of objects that have come in contact with the patient. In this particular instance the dolls represented substitute human beings to whom the disease was transferred through touch with the patient; the destruction of the dolls through burial and melting symbolised the annihilation of the human beings to whom the disease had been transferred.

8. Sometimes the religious element predominated in therapy. An elderly woman from Zebbug (Malta) was treating sufferers from jaundice between 1789 and 1792 by smoking them with a burnt mixture of oil and candles blessed on the Day of Purification of Our Lady and making the sign of the cross over the head eyes and joints and reciting prayers to the Holy Trinity and the Madonna. She explained that she expected the patients to get well only if "they had the necessary faith and if they prayed with devotion... I firmly believed that God, by means of prayer, fumigation and the symbol of the cross, would free them from jaundice" (AIM 135h). She was obviously relying on a well-known psychological trait — the suggestibility of the patient — to obtain the desired therapeutic effects.

9. Very rarely, rational methods devoid of magical significance, were employed. A slave ordered venesection from the arm for a patient suffering from headache and the application of ice on the head and hot baths for the feet. He used the same treatment, with minor variations, for a mental case (AIM 137e).

10. These lay healers occasionally practised a sort of preventive medicine by the distribution of amulets. A slave gave one such charm to a man to guard him from getting injured by weapons. It consisted of a piece of paper with a Latin script and the cabalistic knot of King Solomon and the words "Deus meus". Belief in these protective amulets was still current a century later when we come across a priest who carried on him pieces of paper with

extracts of the Gospel of St. John and of the "Miserere" psalm to guard him against being wounded (AIM 108n).

Plague was a dreaded disease in the 17th century not only in Europe but also in Malta. A woman, to protect herself from infection, wore a gilded silver ring on the inside of which were engraved a number of crosses and these letters:— Z+Dia+ Bir+Sab+Z+HGF+BFRS+ (AIM 51t).

Penalties

The offence of treating sick persons by sorcery, though not countenanced by the state, did not constitute a breach of the lay criminal code but of the laws of the church which condemned superstitious beliefs and witchcraft as being attempts to alter life's events by thwarting Divine will. That is why these cases were dealt with by the Tribunal of the Inquisition and not by the law courts of the state.

Many of the patients tried by the Tribunal had denounced themselves spontaneously "to clear their conscience" when they learned that the practices they had followed were sinful ones; or else they applied to appear before the Tribunal on the advice of their confessor.

The penalties awarded by this ecclesiastical court were of two kinds — corporal punishment for the convicted Moslem slave who was condemned to be publicly whipped through the streets of Birgu, Senglea and Bormla (1720 and 1722) (AIM 108o); and spiritual penance for the Catholic patient seeking cure by sorcery. This penance usually consisted in renunciating all heretical and superstitious beliefs; undertaking not to incur again in the same errors; and promising to fast on Saturdays and to recite set prayers for a period of two years and going to confession and receiving Holy Communion four times a year (AIM 51 u). The patient was then absolved from the excommunication in which he had incurred by his acts (AIM 135i).

In the case of a baptised slave convicted of sorcery in 1797, the penalty consisted in exposing him at the entrance of a church, during the celebration of Mass, with a placard over his chest on which was written the nature of his offence. This punishment, however, instead of humbling him served as an advertisement of his reputation as a sorcerer. In fact, when asked by passers-by whether he was really a sorcerer he took advantage of their eagerness and readily admitted being so to entice them as clients and exploit their credulity for financial gain (AIM 137f).

Tribunals of the Inquisition abroad have acquired a notorious reputation for their appalling record of witch hunting and burnings of heretics (Sprenger & Kramer, 1968). By contrast the Maltese Tribunal of the Inquisition, although it did not shirk from burning at the stake a Francesco Gesualdo for spreading Lutheranism in 1545 (Vella, 1964) and although it made use of torture to extract information from reluctant witnesses (AIM T. 13), showed great restraint in the penalties it awarded to offenders. Indirectly it exercised a salutary check on illicit medical practice in the Island by deterring patients from seeking the superstitious ministrations and so-called magical remedies of lay healers.

Comment

The activities here described were opposed to the tenets of the Catholic Church and were considered to pose a serious threat to the dominant faith of the island. In spite, however, of the efforts of the church to suppress them they remained alive and constant for many years reflecting the remarkable credulity of the Maltese people of those days in the supernatural. They thus illustrate the paradox or dichotomy, of how the Maltese Catholic, instead of trusting blindly in divine help when faced with adversity, in conformity with the teachings of his church, did not shrink from seeking the assistance of prohibited intermediaries when labouring under the stress of illness.

The influence of Moslem slave-healers, though infiltrating all strata of Maltese society, made itself felt particularly among the humbler people of low socio-economic status. This phenomenon affords an instanct of cultural hybridazation whereby an alien group, hostile to the national interests and to the established religion of the com-

munity, is actively utilised for its supposed knowledge of magical practices and its alleged ability to harness recondite supernatural forces in an attempt to combat the effects of illness.

A factor which, apart from the pain and fear engendered by physical disease, might have neutralised the polarity between Catholic and Moslem and facilitated communication between the two groups, was the fact that there was hardly any language barrier between them owing to the existance of a common vocabulary between Arabic and Maltese.

Indeed there is nowhere any hint. in the documents examined, of the need of an interpreter between the Moslem healer and the Maltese patient; on the contrary the fact that the Arabic and the Maltese languages are so much akin to each other served as a bridge to span over the traditional religious enmity between the two groups.

Although from the medical angle these healers may be dismissed on the ground that their type of medicine was scientifically unsound and therapeutically sterile, they occupy a place, however humble, in the social history of Maltese medicine; indeed they are a mirror of the social and religious context that flourished in our island during the 17th and 18th centuries; they also show how this context moulded the people's beliefs and behaviour and how it left its impact on the medical matrix of those days by the emergence of lay healers at a time when academic medicine and surgery had very little to offer by way of relief and cure. Indeed it must be recalled in this respect that it was only in the late 19th century that medicine and surgery began to emerge as scientific desciplines and to provide some effective treatment.

The remedies applied by lay healers now look absurd; they fitted into the uninformed and illiterate world of the time and into the contemporary attitude towards the supernatural. After all, even to-day, in spite of the profound changes that have occurred in the educational and medical fields, there are people that still believe in the sinister influence supposedly exercised by the evil eye. It is not uncommon to see a big red "coral" hanging on the inside of the windscreen of cars or to meet women wearing a silver horn on a necklace round their neck, sometimes combined with a religious medal; or a gold horned hand with other charms on a bracelet to ward off the harmful effects of the evil eye. This attitude is encouraged by newspapers that advertise the sale of amulets and publish horoscopes, etc.

Lay medicine appealed also because it seemed to offer a quick solution to problems which contemporary medical thought failed to provide. This attitude still exists and we are all familiar with the patient of to-day who resorts to fads and folk remedies as a protest against formal medicine when this is unable to allay his pains and anxieties. After all, as doctors we are quite aware that there are many situations with which we are unable to deal effectively because of lack of therapeutic knowledge or because the aetiology of disease is still beyond our comprehension. In this regard, therefore, we are not such a long way from the 17th and 18th centuries and we must not be surprised when our patients, faced with the riddle of disease and the impotence of modern medicine and surgery, seek therapeutic assistance from anyone — be it a human or a divine agency — and by all means — whether it be the offering of a votive candle to their protective saint or the wearing of a copper bracelet against rheumatism; for the emotions of anxiety and fear still constitute a universal and perennial trait of human psychology.

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AM 108e, fol. 922.
108f, fol. 122.
108g, fol. 501 et seq.
108h, fols. 501, 646, 687 & 958.
108i, fol. 100.
108j, fols. 387 & 772.
108k, fol. 501.
1081, fol. 558.
108m, fols. 122, 646, 719 & 772.
108n, fol. 616.
108o, fols. 122 & 501.
AIM 135a, fols. 322 & 409.
135b, fols. 306 & 409.
135c, fol. 306.
135d, fol. 306 et seq.
135e, fol. 721.
135f, fols. 306 & 443.
135g, fol. 443.
135h, fols. 306, 322 & 443.
135i, fol. 306.
AIM 137a, fol. 274 et seq.
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THE PRIEST-PHYSICIAN IN MALTA AND ABROAD

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The association of healing with the deity and the combination of healer and priest in the same person are as old as the emergence of organised religion in the history of mankind. This derives from the fact that early man ascribed disease from within — physical and psychological — to a supernatural agency, as the possession of the body by an evil spirit or demon, and to punishment for sins committed both by the individual and by the community. The priest who was in the privileged position of being in contact with the supernatural was, therefore, the only person that could effectively exorcise the devil and induce the gods to grant a cure from illness. Even right down to historical times, biblical accounts frequently refer to the problem of sin in terms of disease and equates the healing of the body with pardon from sin.

In ancient Egypt, medicine, as all Egyptian wisdom, was closely linked with religion. Imhotep was venerated as the god of health and as long as 1400 BC incubation or temple sleep was practised as a therapeutic measure by his priests in temples dedicated to him (Saunders, 1963).

Among the Jews, both in the biblical and the later Talmudic periods (AD 200-600), various aspects of the healing art were applied not only to control the spread of dermatological diseases and to foster

the maintenance of personal and communal hygiene, but also to many legal and ritual ordinances of Judaism; hence the union of the medical and the religious functions in the person of the Rabbi (Snowman, 1929).

In Greek mythology the god Apollo, and later Asklepios (c 1250 BC), were associated with medical practice and the management of disease. The temples of Asklepios in Greece and Asia Minor were the focal points for sick people who sought deliverance from illness through divine intercession. These temples, where prayer, bathing, exercise and dieting were prescribed, formed the germ of the first crude hospitals and nursing homes.

The surgeon and the lay medical practitioner began to emerge by the side of the priest-doctor in Babylon at the time of King Hammurabi (1948-1905 BC) but the first man who tried to free the theory and exercise of medicine from the priesthood was the Greek physician Hippocrates (BC 460-355) who was himself born in a sacerdotal family in the service of the temple of Asklepios in Cos. With the Graeco-Roman Claudius Galen (c AD 131-200) the gap between rational medicine and religion became wider but not complete for Galen himself still regarded the body as the mere vehicle of the soul (Guthrie, 1946a). In spite of these pioneering efforts, therefore, medicine remained embodded in the matrix of religious ritual and belief.

Not only the ancient pagans but also the early Christians equated illness with sin and healing with pardon from guilt. Indeed, we find the apostles being given power to cure "all manner of diseases and all manner of infirmities" (St. Matthew, Chap 10, v 1). This merging of minister of religion and healer persisted far into the Christian era when the health of the soul was regarded as being more valuable than that of the body and when it was held that disease was God-sent, serving the purpose of punishing the sinner to make him a better man. Remedies against disease were despised but it was believed that their success depended entirely upon the will of God (Kudlien, 1974). A close link between the realm of the spiritual and the art of healing is to be found in the figures of such early saints as Luke, who is reputed to have been a physician; the two brother saints, Cosmas and Damian, who were also medical men; in the veneration, right down to the later Middle Ages, of the saint protectors against the plague as St. Roche and St. Sebastian; and in the foundation of monastic orders such as that of St. Benedict where apart from his purely sacerdotal duties the monk or friar was engaged in the care and nursing of the sick and infirm and in the transmission, through copyinig and translating, of the learning of Greek medical authors.

The separation of medicine from religion became definite with the lay foundation, about the ninth century, of the medical school of Salerno which reached its zenith in the eleventh century. No one was admitted to the course of medicine before he had reached the age of 21 years and had studied logic for three years. The medical course lasted five years with an additional year of practice under the supervision of an older practitioner. Having passed successfully the prescribed examinations, the candidate became entitled to call himself a doctor and to practice medicine. Through the influence of Salerno, the lay medical schools of Padua, Pisa and Bologna in Italy, and Montpellier and Paris in France, eventualy came into being. Medicine thus assumed a distinct identity, separate and independent from the eccesiastical function; this is not to underestimate the influence which the Christian church contineud to exert on the moral and scientific thought of all forms of academic learning in succeeding centuries; or to overlook the fact that the secularisation of medicine did not preclude the same individual from following theological and medical courses at universities and from graduating in both these disciplines. Thus one recalls that King William I (1027-1087) was attended in his last illness in Normandy by Archdeacon Gilbert who is said to have been one of the most skilful physicians of his time (Dobson, 1970). Arnold of Villanova (1235-1312) was a graduate in theology and law as well as in medicine from the University of Montpel-

lier; Petrus Hispanus (c 1277) was another theologian who was also a physician and who ultimately was raised to the Papal Chair as John XXI; Theodoric of Lucca (1205-98) was a theologian and a medical man who eventually became bishop of Cervia (Guthrie, 1946b); Thomas Linacre (1460-1524), medical founder of the College of Physicians of London, was ordained priest in 1509; Simon Ludford, originally a Franciscan friar, was a doctor in medicine of the University of Oxford (d 1574) and William Delaune (d 1610), a French Protestant clergyman, was admitted a Licentiate of the College of Physicians of London (Munk, 1878); while Niels Stensen (1638-86), the discoverer of the parotid salivary duct, studied both medicine and theology and became Bishop of the Catholic Church (Poynter, 1963; Quattrin, 1961). In England members of the clergy sought to take degrees in medicine after losing their ecclesiastical benefices in the period of the Civil War (Medical History, 1969).

Yet, in spite of the occasional emergence of men like these with a double qualification, a point had been reached where the theological and the medical disciplines were no longer combined in the same person, in other words the kinship between the priest and physician came to an end.

A parallel cycle of events evolved in the Maltese Islands where since prehistoric times the beginnings of medicine are inextricably interwoven with the rise and growth of religious belief and ritual. In fact, the earliest evidence of primitive medical practice in our Islands is associated with the neolithic temples of Mnaidra, Hagar Qim and Hal Saflieni Hypogeum that date back to about 2400 BC. This testimony takes the form of a number of "ex-votos" representing parts of the human body, such as legs and torsos, that were excavated from Mnaidra temple where the sick are believed to have gathered to pray for deliverance from sickness. Modern counterparts of these votive offerings are still to be seen in our Christian churches where they have been deposited by devotees in thanksgiving for recovery from disease.

There are strong indications that the hypogeum at Hal Saflieni was a temple-hospital where incubation or temple-sleep was practised. In these underground chambers the sick were put to sleep by the priests after praying to the deity. While in the hypnotic state the god inspired the patient, by means of dreams, with the kind of therapy to be followed. This is how archeologists have interpreted the significance of the two clay statuettes found in the Hypogeum showing women reclining or sleeping peacefully on a litter or couch (Cassar, 1964). The so-called Oracular Chamber that forms part of this underground complex may also have played a part in these procedures. The oracular voice — proceeding from one of the priests may have provided the patient with a prognosis and prescribed the reward or fee due to the temple.

The healer-priest comes into a sharper focus during the Roman occupation of Malta. In fact, the first written record concerning the medical state of Malta in AD 60 comes from the physician St. Luke in the Acts (Chapter 27 & 28) and the healer is no less a personage than Paul of Tarsus, the apostle, who following his shipwreck on Malta, healed the father of Publius, the Roman delegate of the Praetor of Sicily, from fever and a "bloody flux". Other miraculous cures were effected by Paul for Luke informs us that "those that had diseases in the Island came and were healed" by the Apostle.

After the Roman period there is a very long gap in our medical history but it has been alleged that about 200 AD a certain Don Pietro, who was a physician, was consacrated Bishop of Malta by Pope Victor I and died in Valencia (Cassar, 1965a).

The foundation of the earliest hospital known to have been established in Malta, under the title of "Santo Spirito", is linked with the Order of the Minor Conventuals of St. Francis. It was set up in close proximity to the convent and church of this Order at Rabat in the early fourteenth century and the Francsicans continued to hold its rectorship until 1506. There is no evidence, however, that the friars, apart from their administrative duties, exercised

any clinical or therapeutic functions.

In the fifteenth century the Jews formed an important element of the Maltese community. Besides engaging in commerce they appear to have monopolised the profession of medicine. Some of these physicians, such as Braccone Safaradi ("floruit" 1446) and Abraham Safaradi ("floruit" 1485), combined the practice of medicine with the religious duties of Rabbi who was the spiritual head of the Jewish group in the Island (Cassar, 1965b).

The religious and chivalric Order of St. John of Jerusalem, founded as a nursing order in the eleventh century came to Malta in 1530 and founded the Holy Infirmary of Valletta In 1574 but the Order's outstanding contribution to Maltese medicine was the creation of the Chair of Anatomy and Surgery at this infirmary in 1676. This Chair was entrusted to a priest-physician, Dr. Fra Giuseppe Zammit, Chaplain of Obedience in the Aragonese Langue, physician to several Grand Masters and Chief Government Medical Officer of the Island.

In the eighteenth century we come across "Dr fisico e sacerdote" Fra Antonio Grana, likewise member of the Order of St. John, who flourished about 1703 ("Arch" 647). Anther contemporary physician (1709), who was in addition a Doctor of Theology, was Dr. Filippo Giacomo Gauci whose tombstone is still extant in St. Dominic's Church at Rabat ("Ms" 142E; "Ms" 721).

Dr. Bartolomeo Mifsud (1708-1781) from Żebbuġ qualified as Doctor of Laws and Doctor of Medicine, probably at Rome, and subsequently joined the Capuchin Order of St. Francis under the name of "Padre Pelagio" (1742). It is not known whether he continued to practice medicine after he became a friar (Mifsud-Bonnici, 1960-68a; "Ms" 147; Ciappara 1882).

Two priests-physicians — Dr. Joseph Briffa and Dr. Joseph Ellul — were in practice at Hal Luqa in the first three decades of the eighteenth century. I am unaware where Dr. Briffa pursued his medical studies but it is likely that he did so in Italy like his brother Dr. Jacob Briffa who studied medicine at Naples. Dr. Joseph Briffa died at Luqa at 33 years of age on the 15th June 1734.

Dr. Joseph Ellul left Malta in 1711 for Naples where he followed courses in medicine and theology being ordained priest in 1703. He continued his medical training in Rome. He was back in Malta and practising as a physician at Luqa in 1715. He appears to have been very much in demand in neighbouring villages but the people complained that he charged fees to both rich and poor though the parish priest of Luqa declared that Dr. Ellul did treat poor patients gratis. He died at 49 years of age on the 17th April 1737 (Micallef, 1975).

A contemporary member of the clergy and of the medical profession was Dr. Francesco Mamo who on the 21st April 1742 applied for the post of physician at "Santo Spirito" Hospital at Rabat where he was eventually appointed "Secundus medicus" ("Arch" 1188).

Dr. Fra Luigi Pisani, born on the 12th July 1776, was the last medical man who was also a priest and a member of the Order of St. John. He was the brother of Dr. Salvatore Pisani, who died of the plague in 1813, and the uncle of Dr. Aloisio Pisani (1806-65), who subsequently became Chief Government Medical Officer. Dr. Fra Luigi Pisani had joined the government service as "Medical Practitioner for the Poor" at Birgu on the 1st January 1808. He was still active as a physician in 1850 (Mifsud Bonnici, 1960-68b; "Libr 19).

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CURRENT VIEWS ON THE TREATMENT OF PORTAL HYPERTENSION

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There is no established treatment protocol for bleeding oesophageal varices on which there is universal agreement between surgeons and physicians with special interest in the subject of portal hypertension. In general, the outlook for these patients is poor irrespective of treatment and the single most important factor in determining the prognosis in the individual case, is the nature and progress of the underlying liver disease with the attendant overall hepatocyte function. This article attempts to review current views on the subject of therapy for portal hypertension and proposes a rational programme of management for these patients whch is influenced by the author's personal experience.

Classificaton of Portal Hypertension.

The various disorders associated with portal hypertension have been recently reclassified by Malt (1976) into pre-parenchymal, parenchymal and post-parenchymal blocks. The pre-parenchymal group comprises most of the entities often referred to as extra-hepatic blocks such as congenital or adult thrombosis of the portal vein. The parenchymal group includes a number of disorders which produce obstruction without hepatocellular dysfunction (Schistosomiasis, congenital hepatic fibrosis and cysts) and cirrhosis where, in addition to a parenchymal block to the liver blood flow, a varying but usually progressive state of hepatocellular decompensation is present. Cases of chronic hepatic vein obstruction (thrombosis, veno-occlusive disease, congenital diaphragm in the vena cava or heart disease) constitute the post-parenchymal group.

Emergency Treatment of Bleeding Oesophageal Varices

The essential steps necessary for these patients are — diagnosis of the bleeding site, cessation of the haemorrhage and the institution of supportive measures followed by a period of assesment of the patient once the situation is under control.

It is important to stress that not all patients with portal hypertension bleed from their varices. In some of the patients, the sources of the bleeding is a chronic duodenal ulcer and indeed the incidence of

peptic ulceration in cirrhotic patients is higher than that of the general population. Barium meal studies and, in particular, fibreoptic endoscopy are therefore required in order to establish with certainty the bleeding site. The methods available for the control of the bleeding include the administration of Pitressin, balloon tamponade and the direct injection of the bleeding varices with Sclerosant solutions.

The value of Pitressin is now established. In the author's experience, Pitressin administered intravenously in a dose of 20 units in 200 ml of saline over a period of twenty minutes, resulted in the cessation of the bleeding in 75 per cent of cases. More recently, Pitressin has been administered as an intraarterial infusion via a catheter introduced into the superior mesenteric artery using the Seldinger technique (Nusbaum **et al.**, 1968). The advantage of this method lies in the much lower dose of Pitressin required and therefore a potential reduction of possible side effects especially on the myocardium. On the other hand, it is a rather complicated technique which necessitates an in-dwelling Seldinger catheter and pump perfusion and it is therefore not without certain arterial and infective risks, which may contribute to the demise of the patient (Berardi, 1974). Indeed a recent study showed distinct disadvantages with this technique of administering Pitressin (Murray-Lyon, **et al.**, 1973) and the author has abandoned its use. It is important that the biological activity of Pitressin is assessed by the occurrence of a massive bowel action which should follow within a few minutes of its administration and which is of therapeutic benefit as the resultant melaena reduces the protein load in the intestinal lumen. Intravenous Pitressin acts by lowering the portal venous pressure and, in the author's opinion, it is still an extremely useful first-line measure in the immediate management of bleeding oesophageal varices.

Balloon tamponade is certainly effective in controlling bleeding but carries certain hazards (Bauer, 1974; Pitcher, 1971). The most commonly used tube is the Sengstaken-Blakemore tube which is best inserted lubricated, via the nasal route down to 50 centimetres. The gastric balloon is inflated with 200 mls of air and slight traction is applied after which the tube is strapped to the forehead. Only if bleeding is not controlled in this way is the oesophageal balloon inflated to about 4 millimetres of mercury. In this situation, a small nasogastric tube is also inserted into the oesphagus proximal to the inflated oesophageal balloon to prevent aspiration. The complications of balloon tamponade include erosion and further bleeding, airway occlusion and aspiration pneumonitis. With strict vigilance, the complication rate and morality from its use can be kept at acceptable low levels (10-12 per cent). In any event, deflation of the balloon should be carried out at 24 hours and, if the bleeding recurs, then emergency surgery should be seriously contemplated.

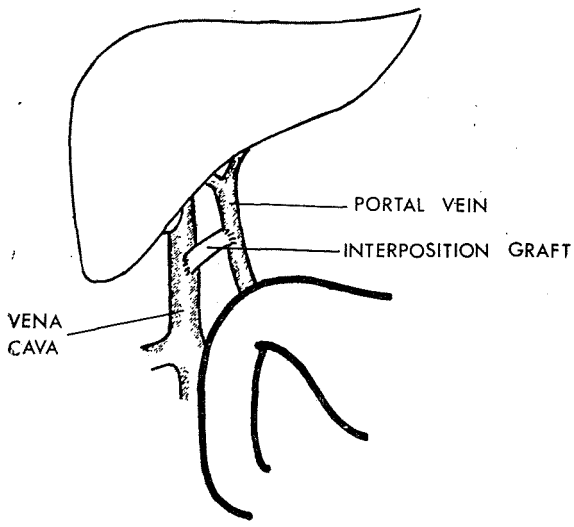

Fig. 1: Synthetic graft (Gore-Tex) between the portal vein and the inferior vena cava.

There has been a revival in recent years of the procedure of sclerosant injection of the oesphageal varices. The author has no practical experience of the technique but the best results have been reported when the technique is used after the bleeding has been controlled by gastric balloon tamponade.

TABLE 1
CLASSIFICATION OF PATIENTS WITH CIRRHOSIS (Child, 1964)

Group	A	B	C
Serum bilirubin (mg/100 ml)	<2.0	2.0—3.0	>3.0
Serum albumin (g/100 ml)	>3.5	3.0—3.5	<3.0
Ascites	None	Easily controlled	Poorly controlled
Neurological disorder	None	Minimal	Advanced "coma"
Nutrition	Excellent	Good	Poor "wasting"

Correction of hypovolaemia is best achieved by the administration of fresh blood and should be carried out with central venous pressure monitoring. In addition, these patients usually have coagulation defects due to multifactorial deficiencies which require correction by the administration of clotting factor concentrates in addition to parenteral Vitamin K.

Measures designed to prevent portosystemic encephalopathy such as the administration of neomycin or lactulose together with magnesium sulphate enemata, correction of fluid and electrolyte abnormalities (in particular hypokalaemia) and the administration of intravenous Dextrose (10 per cent) should be commenced forthwith. The level of coma is best assessed by E.E.G. monitoring.

The cessation of the bleeding episode either by vasopressin or by balloon tamponade allows of time for evaluation of the patient, with regard to his general condition, the state of his liver function and histology, the patency of his portal venous system and his blood clotting status. A decision is thereby reached using Child's criteria shown in Table 1 as to whether the patient comes into Child's category A, B or C. All Child A and some B cases are suitable for shunting should bleeding recur, whereas Child C patients are not, as their advanced liver disease imposes a prohibitive immediate post-operative mortality in excess of 50 per cent (Malt, 1976). All Child C patients should therefore have non-shunting procedures if surgery is contemplated because of continued haemorrhage. Liver histology when available, may have an important bearing on the type of surgical intervention as patients with acute hyaline change have a poor prognosis after shunting as do patients with chronic active hepatitis.

Shunt Surgery versus Long Term Conservative Medcal Treatment

In the past, a strong argument has been made for the use of prophylactic shunt operation i.e. operations performed in patients with portal hypertension and oesophageal varices before any bleeding episodes, in order to prevent the occurrence of variceal haemorrhage. However, there has now been a number of prospective randomised controlled clinical trials (Jackson et al, 1968; Resnick et al, 1969; Conn and Lindenmuth, 1965; Conn et al, 1972) which have shown that prophylactic shunt operations do not impart any real benefit to these patients but alter the cause of death from variceal haemorrhage to liver failure. Moreover, prophylactic shunt operations in fact result in a decreased survival time. These clinical trials have conclusively proved that there is no indication for prophylactic shunt surgery.

The question of a therapeutic shunt is still highly controversial. Recent controlled clinical studies comparing therapeutic shunts i.e. a shunt operation carried out after bleeding has occurred versus conservative treatment (Jackson et al, 1971; Resnick et al, 1974) have indiciated no signifi-

cant differences in survival between these two approaches. However, in these trials patients with liver disease of varying severities were lumped together and indeed in some of the studies, some of the patients that were originally allocated to the conservative treatment group were subsequently shunted. Since it is known that only patients with Child group A and some cases of Child group B do well after shunt surgery, a more valid comparison is between shunt surgery and continued conservative medical treatment in patients with good liver function. The preliminary report of Mikkelsen (1974) of patients who had bled at least once from varices and who were under 60 years of age and classified as Child Group A, has shown that medical treatment (38 patients) results in a 10 per cent five-year survival as opposed to 60 per cent five-year survival following shunt operation (37 patients).

Non-Shunting Procedures

There are a number of these operations. They include Boerema-Crile transoesophageal ligation, oesophageal transection, porto-azygous disconnection of Tanner, splenectomy and devascularisation, the Boerema-Crile button, oesophagogastrectomy etc. The one main advantage of all these procedures is the retention of a high pressure venous zone adjacent to a low pressure one and this ultimately leads to the recurrence of the varices and therefore to recurrent haemorrhage. Nevertheless, they are the operations of choice in patients with normal hepatocytes and a high portal blood flow such as patients with Schistosomiasis cavernous transformation of the portal vein if and when conservative treatment fails. The operation most favoured in this group of patients in view of the good results obtained is splenectomy and devascularisation. For patients with advanced liver disease (Child C) who continue to bleed, the author favours the oesophageal transection procedure of Walker. The immediate mortality in this group is high, and the prognosis for those that survive the operation is extremely poor. It is therefore debatable whether surgical intervention is indicated even in the presence of continued or recurrent bleeding. In the final analysis, the decision of whether or not to operate is based chiefly on moral grounds.

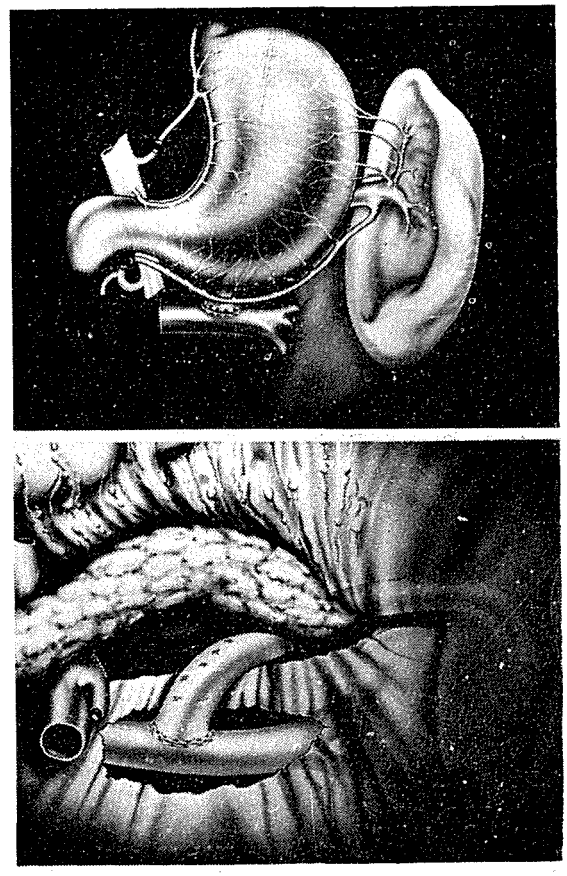

Fig. 2: Warrent Shunt. (Top) shows the completed procedure with the relevant anatomy. (Bottom) Details the anastomosis between the splenic vein and the renal vein.

Shunt Operations

The various types of shunt operations are shown in Table 2. The most established operation and the one that is often used as the yardstick against which all other shunt procedures are compared, is the portacaval shunt. The end-to-side portacaval shunt has been favoured by most surgeons in preference to the side-to-side variety largely because of technical considerations. On haemodynamic grounds of course the side-to-side portacaval shunt is a better procedure and is the operation

TABLE 2
SOME OF THE MORE POPULAR SHUNT OPERATIONS

I. Portasystemic shunts —
   A. Portacaval: end-to-side
      side-to-side
      interposition (H) graft
   B. Splenorenal.
   C. Mesocaval: end-to-side
      interposition (H) graft
   D. "Makeshift".

II. Shunts causing selective decompression.
   A. Warren's trans-splenic decompression.
   B. Left gastric — vena caval shunt.

of choice in the presence of ascites and reversed portal blood flow. However, it is technically very difficult and has a higher thrombosis rate than the end-to-side portacaval shunt. The more recent inter-position graft procedure between either the portal vein and the vena cava (author's preference) or between the superior mesenteric vein and the vena cava is, in fact, a type of side-to-side anastomosis which can be performed with relative ease and avoids the risk of tenting of the vessels and therefore of late thrombosis of the shunt. The author now tends to favour a portacaval shunt using an interposed synthetic (Gore-Tex) graft anastomosed end-to-side to the inferior vena cava and the portal vein as shown in Figure 1.

The concept of selective decompression of the portal venous system whereby the pressure at the site of the offending oesophageal varices is reduced but the portal blood flow is not affected to any great extent is an attractive one. However, it is not based on any scientifically proven premise that retention of the portal venous blood in such patients is the important factor in determining whether or not deterioration of liver function and encephalopathy occur after shunt surgery. Not infrequently, in patients with portal hypertension, effective portal flow through the liver is greatly reduced and in some the flow in the portal vein is reversed. The operation that has been most extensively investigated as a selective decompression procedure is that described by Warren et al (1974) and shown in Figure 2. Another type of selective shunt is that described by Japanese workers (Inokuchi et al, 1975) which consists of an anastomosis between the left gastric coronary vein and the inferior vena cava using an interposed saphenous vein graft. The author has obtained good results with the Warren procedure but the operation is technically very difficult and had to be abandoned in 3 out of 12 patients. It is also highly debatable whether one needs to devascularise the stomach after the completion of the distal splenorenal shunt as recommended by Warren et al.

In patients with portal hypertension in whom hepatocyte function is normal, e.g. Schistosomiasis and cavernous transformation of the portal vein, non-shunting operations should be performed in the first instance. Severe encephalopathy will almost certainly develop after any form of portacaval shunt but is less likely after a splenorenal shunt; so that this becomes the shunt operation of choice in these patients should bleeding recur after a non-shunting procedure.

The complications of shunt operations include recurrence of haemorrhage and encephalopathy. Recurrence of haemorrhage after shunt operation is the result of thrombosis of the shunt; and, in general, the recurrent haemorrhage rate after a portacaval shunt is of the order of three to five per cent. Encephalopathy is a problem. A recent randomised but not blind study has shown that the incidence of encephalopathy in patients with alcoholic cirrhosis is doubled in little over four years even without a shunt, whereas after portacaval shunt, the incidence during the same period increased from 20 to 53 per cent. The difference between these two groups was not significant (Mutchnick et al, 1974). However, the incidence of acute encephalopathy after shunting is more than twice as common as in the non-shunted group and the difference was significant. In general, the incidence and severity of encephalopathy is less after a splenorenal than a portacaval shunt. The incidence of encephalopathy is also low after the selective decompression procedures.

Conclusion

It is now generally accepted that patients with pre-parenchymal blocks and parenchymal blocks with normal hepatocyte function are best treated in the first instance by non-surgical measures. Cirrhotic patients with varices who have not bled should not be treated surgically. In the presence of bleeding varices in these patients, the choice of treatment is dictated by the overall general condition and the liver funcion together with the details of the histology of the liver. In good risk patients (Child A and some Child B) the evidence available suggests that a therapeutic shunt is probably the best form of treatment in that it is accompanied by a low immediate mortality and a five-year survival rate of about 60 per cent. On the other hand, the patients with more advanced liver disease and with poor general condition should not, in the first instance, be treated surgically. In the presence of recurrence or continuance of the haemorrhage in this group of patients, then a difficult decision has to be made. On moral grounds alone, very often one has to resort to emergency surgery which should take the form of a non-shunting procedure. The ultimate prognosis of these patients is of course extremely poor.

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FUNCTIONAL ANATOMY OF OLFACTORY SENSE ORGANS

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The olfactory organ is the most primitive of the organs of special sense and the one with the simplest structural organization, and yet it has defied a clear exposition of the way in which it perceives and distinguishes between different odours. Undoubtedly one of the main reasons for this has been the greater interest which scientists have taken in other aspects of sensory physiology, particularly sight and hearing, impairment of which produces severe handicap, and is positively detrimental to the independant survival of an affected indivdual. The sense of smell is not so indispensable for Man; its loss is a more tolerable burden depriving him only of the emotional experiences aroused by odours.

Yet the olfactory organ in Man is endowed with a remarkable degree of sensitivity and a finesse of its dicriminatory powers. The sensitivity of the human olfactory mucosa is more than one hundred times better than that of the best gas chromatograph, and its discriminatory powers enable Man to distinguish between an immense variety of odours and to identify specifically those with which he is familiar. For example almost anyone can distinguish between water, gin, eau-de-cologne, kerosone, acetone and other substances, all of which look very much alike, by their distinctive odours. An experienced perfumer can do very much better and is frequently capable not only of distinguishing between a large variety of lavender oils but also of naming their country of origin.

The significance of odours to man is mainly psychological and emotional. In most other animals, including mammals odours have a more profound signficance in terms of survival. In fact most animals rely on their sense of smell for the detection and recognition of prey for feeding, for escaping from predators and for selecting their mates for reproduction. However in animals it is much more difficult than in man to estimate the sensitivity and the range of discriminatory capacity of their olfactory organs. Certainly many animals are much more keenly scented than Man as can be appreciated for example from the ability of dogs to follow a trial and to distinguish the odour complex of a particular individual from all other extraneous odours.

Not all animals share the same degree of olfactory acuity and it is customary to categorize them roughly as macrosmatic and microsmatic. Attempts to identify an anatomical basis for this difference have shown that there is no simple relationship between the degree of development of the sense of smell and the size of the olfactory area or its density of receptors.

Olfaction is the most primitive of the special senses, the first to be developed in the evolutionary scale and the first sense which enabled perception of objects from a distance without the necessity of actual physical contact. The olfactory organ also has a simple structural organization consisting of receptor cells surrounded by supporting cells and overlying a layer of basal cells. Besides, the receptor cells are themselves primary sensory neurons the cell bodies of which lie close to the sensory surface, a common feature in invertebrates but unique in the vertebrate series. Their axons proceed directly to the cerebral cortex without any complicating synapses; the olfactory bulb in which they terminate is developmentally a forward extension of the cerebral hemisphere and histologically has the structure of a cortex. It is pertinent to point out that this direct connection of the receptors with the

cerebral cortex is considered to be an expression of the fact that, from an evolutionary point of view, the cerebral hemispheres were initially developed as correlation centres for the olfactory sense.

In spite of this apparent simplicity in structural organization, the mechanisms underlying olfactory perception and discrimination pose serious and far reaching problems; and when we attempt to interpret the electrical responses of the olfactory epithelium to odour stimulation it becomes clear that we are dealing with a far more complex system than was orginally supposed. Apart from the receptors there are other factors in the olfactory epithelium and its environment which must be considered, such as the structure and function of the supporting and basal cells, and the chemical composition and properties of the surface fluid which bathes the receptor endings and which is secreted by Bowman's glands underlying the epithelium.

The nature of the olfactory stimulus itself present a number of problems. Unlike visual and auditory stimuli, namely light and sound waves whose physical properties and variables are accurately understood, the physical and chemical properties of odoriferous molecules which constitute the olfactory stimulus are still the subject of considerable controversy and much speculation.

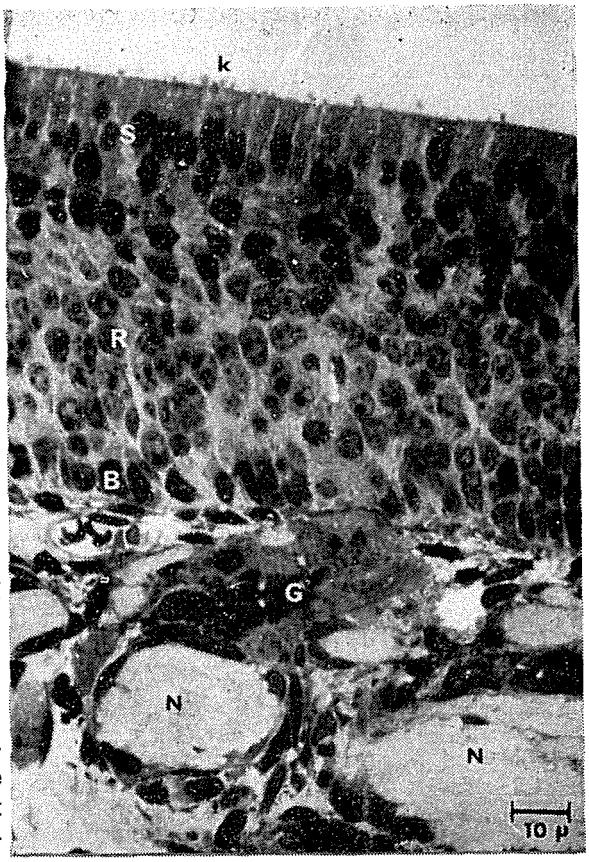

Fig. 1: Vertical section through the olfactory mucosa of an adult mouse. The supporting cell nuclei (S), the receptor nuclei (R) and the basal cell nuclei (B) form three distinct zones. Olfactory knobs (K) can be seen at the surface of the epithelium. Olfactory nerve bundles (N) and a Bowman's gland (G) are present deep to the epithelium 1um epoxyresin section stained with toluidine blue.

The Fine Structure of the Olfactory Mucosa

It is remarkable that the olfactory epithelium is very similar in all vertebrates from cyclostomes to mammals. It is a pseudostratified epithelium, much thicker than the surroundng non-sensory respiratory epithelium of the nasal cavity. The classification of the component cells into three distinct types namely receptor cells, supporting cells and basal cells was first established by Schultze in 1856 and is still valid today. Histologically the three cell types are recognizable from the position of their nuclei (Fig. 1 and 2). Deep to the epithelium are situated the olfactory fasciculi of unmyelinated axons and the distinctive Bowman's glands whose ducts extend vertically to the surface of the epithelium. Here the secretions of Bowman's glands form an adherent film of fluid. Further details which have been added on to this basic picture have been obtained from various lines of research. A considerable amount of knowledge regarding the ultrastructure of the component cells has been gained from numerous electron microscope studies of the olfactory mucosa amongst which are those in

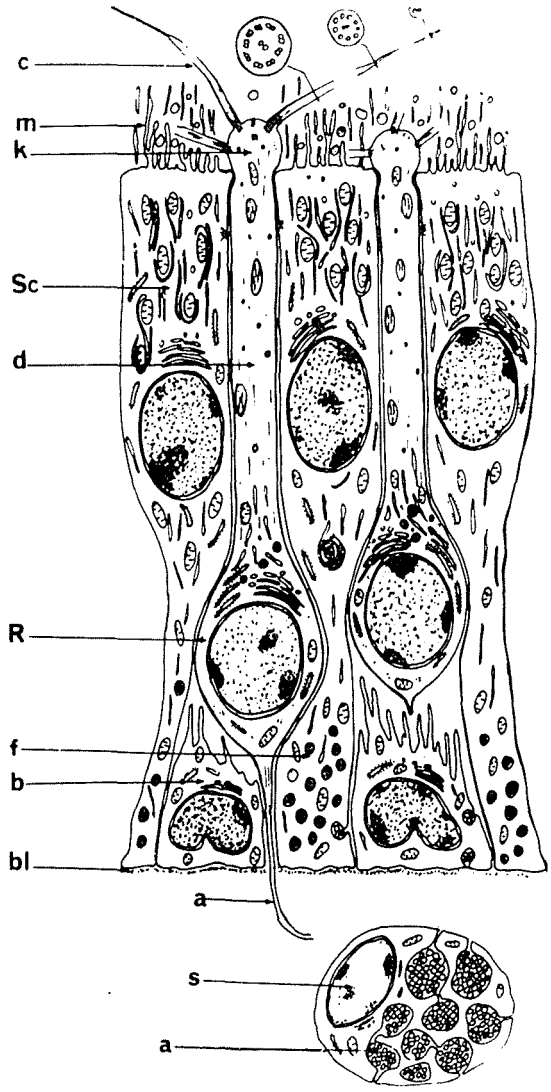

Fig. 2: Diagram illustrating the structure of the olfactory epithelium. C — cilia; m — microvilli; K — olfactory knobs; — Sc — supporting cells; d — distal process of receptor cell bodies; f — foot process of supporting cell; b — basal cell; bl — basal lamina; a — olfactory axon; s — schwann cell.

the frog (Reese, 1965), rabbit (de Lorenzo 1957), mouse (Frish, 1967), primates and Man (de Lorenzo, 1970). More recently attention has also been turned to the fine structural development of the olfactory mucosa (Briephol et al 1973; Cuschieri and Bannister 1975) contributing to a better understanding of certain ultrastructural features and their functional signficance.

A few histochemical studies (Baradi and Bourne 1953; Bronshtein 1965; Shantha and Nakajima, 1970; Shapiro, 1970; Cuschieri and Bannister, 1974) have described the location and distribution of various enzymes and other substances in the olfactory mucosa. Such histochemical studies are potentially useful in elucidatnig some aspects of the metabolism and functions of the various cells but the interpretation of the precise metabolic role of the enzymes demonstrated has been complicated by the existence of variations amongst the different animals studied and by the inherent limitations of the histochemical techniques employed.

Of direct relevance to the study of olfaction is the vomeronasal organ, a paired structure present in the nasal cavity of many animals, being particularly well developed in reptiles and some mammals but vestigial or absent in primates and birds. It usually takes the form of a diverticulum lined in its greater part by a sensory epithelium similar in basic structure to the olfactory epithelium, and also sensitive to odours. Although it shows some minor differences from the olfactory epithelium both in structure and in its electrophysiological responses to odours it has provided useful information on the sense organs of smell.

The following account of the detailed structure of the component cells of the olfactory mucosa will attempt to correlate the results obtained from these various lines of research. In this way a better evaluation of the current status of knowledge of the anatomy of the olfactory organ will be possible.

The Olfactory Receptors

The olfactory receptors are biploar neurons. A thick "distal process" is directed towards the surface of the epithelium where it is expanded into a terminal knob projecting for about 2μm beyond the surface. The distal process, sometimes inaccurately named the olfactory dendrite,

contains longitudinally oriented microtubules, vesicles and mitochrondria. The terminal knob bears a variable number of cilia (usually not exceeding 20) which arise from basal bodies within its cytoplasm. They also contain free contrioles and an abundance of mitochondria indicating a high level of metabolic activity as is to be expected in sensory nerve endings.

"The cilia" are the parts of the olfactory receptors which are most readily accessible to odoriferous molecules. It has therefore been generally assumed that the odour receptor sites, where the initial events in olfactory stimulation occur, lie on their surface membrane but there is no conclusive evidence for this. It should be noted that modified cilia are also found in other sensory organs, notably the rods and cones in the retina, and appear to be the initial transducing elements (Sleigh, 1962). 1962).

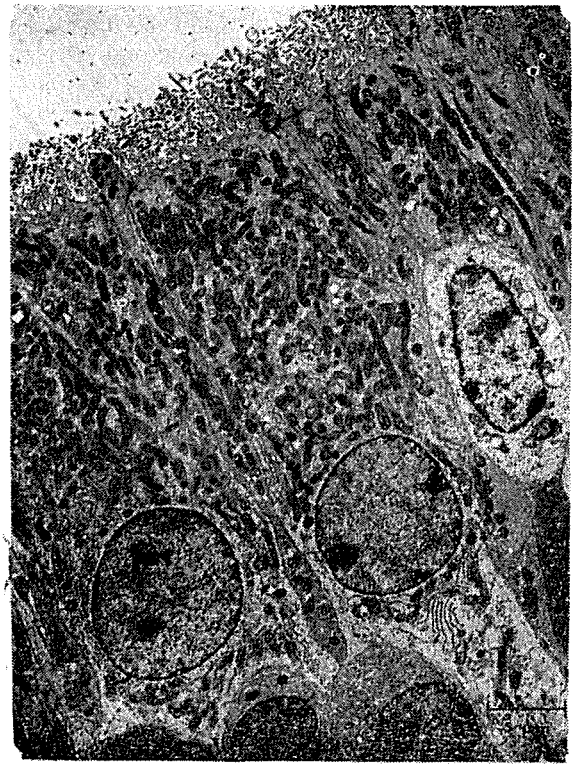

Fig. 3: Electron micrograph of superficial part of the olfactory epithelium. Note the abundance of mitochondria in the supra nuclear parts of the supporting cells.

The olfactory cilia possess in their proximal parts an array of nine pairs of microtubules surrounding one central pair, an arrangement typical of motile cilia. The modified cilia of other sense organs typically lack the central pair of microtubules. The olfactory cilia show a modified structure only in their distal part which tapers into a long thin segment containing decreasing numbers of microtubules (Reese, 1965) (Fig 2). The ciliary structure does not, however, appear to be indespenable for olfactory function since receptor endings having microvilli, instead of cilia are found in certain species of fish (Bannister, 1965) and in the vomeronasal organs of reptiles and mammals (Altner and Muller, 1968; Bannister 1968).

The length and motility of cilia have been subjects of much disagreement. The ciliary movements which have been observed were slow, irregular and asynchronous and it has been suggested that such movement may have been stimulated by breakage of their delicate, thin distal parts (Reese, 1965). Even if ciliary movement does normally occur it is unlikely to have any mechanical signficance in wafting odoriforous particles to and from the receptor sites or in the movement of the olfactory surface fluid. It would be more reasonable to suppose that the olfactory cilia simply provide an increased receptive area for the cell.

The technical difficulties involved in measuring the lengths of cilia have cast doubts on the validity of the reported measurements which have varied from 1 to 200 μm. The question of ciliary length is significant in so far as it determines whether the cilia are completely covered by the olfactory surface fluid which odour molecules would have to penetrate before reaching the receptor sites; or whether they are long enough to lie at the air-fluid interface directly accessible to air borne odours. In most electron micrographs the former appears to be the case.

The "cell body" of the receptor neuron is small, being only about 8 μm in diameter and is largely occupied by its vesicular nucleus. The scantly cytoplasm it contains is occupied by a lammellar system of

smooth-surfaced and granular endoplasmic reticulum and a well developed Golgi apparatus, (both indicative of synthetic activity), as well as large numbers of lysosomes some of which contain membranous remanants indicative of autophagic activity. Histochemical studies have shown that acid phosphatase is present in high concentration and is located mainly within the lysosomes and partly within the Golgi apparatus. The internal organization of the receptor cells suggests the occurrence of a continuous process of synethetic and degradative activity possibly providing a mechanism for cellular maintenance. Presumably a significant part of this process is renewal of the delicate exposed surface membrane of the receptor endings, whch is prone to physical damage and to exhaustion by repeated stimulation.

The "proximal processes" of the receptors cells form the unmyelinated olfactory axons. These are amongst the smallest of axons having a diameter of 0.2 μm. Within the epithelium they are enclosed in small invaginations of the supporting and basal cells. In the sub-epithelial tissues large numbers of axons are clustered together and collectively are enclosed within single invaginations of the surrounding Schwann cells. This arrangement is unique for olfactory nerves since unmyelinated axons elsewhere, such as those in the sympathetic grey rami, are enclosed singly in Schwann cell invaginations. It may also have functional implications possibly allowing for axonal interaction to occur although synaptic contacts between the axons have not been observed.

Are There Morphologically Distinct Types Of Receptors?

In an attempt to find some anatomical basis for olfactory discrimination several workers have claimed that they could distinguish different types of receptors and classified them according to such criteria as differences in shape, size and number of cilia. None of these classifications appears to be justified since differences in shapes and size of the receptors are to be expected from the close packing of the cells in the epithelium. Electron microscope studies have also failed to detect any differences which would not be expected as a result of random variation and the idea that differences in receptor function may be reflected in their gross morphology is now tending to be discredited.

The Supporting Cells

The supporting cells surround the individual receptor cells and isolate them from one another. Each supporting cells extends from the surface to the basal lamina. From the free surface project long branched microvilli which extend beyond and enmesh most of the olfactory cilia. The part of the cell above the oval nucleus contains most of the cell cytoplasm, the most characteristic feature of which is the abdundance of mitochondria surrounded by an elaborate system of smooth surfaced endoplasmic reticulum. This region of cytoplasm also contains an abdunance of enzymes including dehydrogenases, cytochrome oxidase, adenosine triphosphatase and esterase all of which are present in concentrations far greater than in any other part of the olfactory epithelium. The supporting cells, therefore, far from being passive supporting elements are highly active metabolically and may have important functions.

In amphibians and reptiles secretion granules containing mucosubstances are present within the supporting cells indicating that these have a secretory function contributing to the formation of the olfactory surface fluid. In mammals and birds, however, the supporting cells show no evidence of secretory activity.

The way in which the supporting cells ensheath the receptors suggests that there may be a relationship between these two cells in a manner analogous to that between neuroglia and neurons. The supporting cells may be responsible for maintaining the chemical composition and, in particular, the ionic balance in the intercellular fluid which forms the immediate environment of the receptor cells. Molecular and ionic transport may also occur between the supporting and receptor cells.

It has been shown (Cuschieri 1972) that at the junctonal complexes between these two cells alkaline phosphatase activity is present, an enzyme which would favour the occurrence of such transport processes at these sites. There could even be, as a result of such ionic interchange, some degree of electrical coupling between the receptor and supporting cells.

In the olfactory epithelium of mammals almost all the receptors are completely isolated from one another by the supporting cells. However, adjacent receptors are common in the vomeronasal organ and are also found in the olfactory epithelium of lower verbetrates. The degree of receptor cell isolation may be of functional importance since interaction might occur between adjacent receptors. Studies in the olfactory epithelum during development have shown that when the receptors are first formed they are grouped together in clusters and that they become separated from one another by the supporting cells during later stages of development (Cuschieri and Bannister, 1975). It would therefore appear that any close proximity of receptors in adult olfactory epithelia is the result of incomplete separation rather than of any specific functional association of receptors.

The Basal Cells

Like the supporting cells, the basal cells also show evidence of high metabolic activity and contain a variety of enzymes including succinic dehydrognase, cytochrome oxidase and adenosine triphosphatase. Alkaline phosphatase is present in particularly high concentration and is located on the plasma membrane which is thrown into finger like processes extending between the receptor cells and also enclosing olfactory axons. This enzyme indicates that the basal cells are active in molecular transport across the base of the epthelium. This may be important for meeting the nutritional requirements of the olfactory epithelium which is much thicker than any other epithelium and yet is supplied only by a sub-epithelial vascular plexus. It is perhaps significant that during embryonic development, before the basal cells have been differentated, the olfactory epithelium is supplied by capillary loops invaginating deeply into the epithelium. A similar situation occurs in the adult vomeronasal organ which also lacks basal cells but is suppled by intra-epithelial capillary loops.

A further function which has been attributed to the basal cells is that of providing a blastema for the continuous regeneration of receptor and supporting cells. Autoradiographic studies (Moulton et al 1970) have shown that continuous cell proliferation occurs within the olfactory epithelium and that initial uptake of tritiated thymidine occurrs mainly in clusters of nuclei close to the base of the epithelium. It is, however, unlikely that this is the only function of the basal cells, since they do not resemble undifferentiated cells in their structure or enzyme complement.

Bowman's glands and the Olfactory Surface Fluid

The surface of the olfactory epithelium is continually bathed by a highly tenacious film of fluid. In mammals it is derived from Bowman's glands only but in amphibians and reptiles the supporting cells also contribute their secretions (Graziadei, 1971).

The chemical composition of the olfactory surface fluid is only poorly known. A few enzymes such as acid phosphatase and succinic dehydrogenase have been demonstrated histochemically in the surface fluid and in the Bowman's glands of mammals (Baradi and Bourne, 1953; Cuschieri, (1974b).

The secretion of Bowman's glands have been reported to contain acid mucosubstances in some animals and neutral mucosubstances in others. The supporting cells of amphibians and reptiles also contain neutral or acid mucosubstances. The histochemical composition of the mucosubstances secreted by Bowman's glands have been analysed in some detail in mice. It has been shown that they differ from all the other secretions in the nasal cavity in that they contain sulphated mucosub-

stances, (Cuschieri 1974 a), a finding which has been confirmed by autoradiographic studies with the isotope sulphur-35 (Dodson et al, 1976). Similar findings have also been obtained in other mammals (unpublished results).

Functions of the Surface Fluid

Undoubtedly the olfactory surface fluid is important for protection against drying, osmotic damage, infection and mechanical abrasion, functions common to secretions covering most other mucous membranes. In addition it is to be expected that this surface fluid will influence the access of odour molecules to the receptor sites and their subsequent removal. This may be affected by such factors as solublity of the odour molecules in the surface fluid, the air/fluid partition coeficient and physical interactions between polar groups on the odour molecule and in the surface fluid. Chemical interactions may also occur and it is possible that certain odour molecules may be altered by enzymic action.

It is also likely that the surface fluid forms a reservoir for inorganic ions, which are necessary for the electrical events associated with sensory transduction, and a conduction pathway for the flow of ions at the olfactory surface. It is interesting that sulphated mucosubstances occur in the olfactory surface fluid of mammals since similar mucosubstances have also been demonstrated in the central nervous system (Saigo and Egami, 1970) and in the extracellular fluid at the nodes of Ranvier (Langley and Landon, 1967). These polyanions are known to bind inorganic cations strongly.

The Olfactory Pigment

It had long been noted that in many animals the olfactory mucosa had a yellowish or brownish colour. It had also been assumed that the pigment involved was important in olfaction. This belief was supported by the observation that certain albino animals, which were presumed to lack pigment in their olfactory mucosa, died from eating poisonous plants (e.g. St. John's wort, 'Hypericum crispum') because it was thought that they had a poor sense of smell and were unable to recognise them. Experimental evidence has not supported these assumptions. In fact it has been shown that albino animals do not lack olfactory pigment (Moulton, 1962) and that albino rats had lower thresholds for certain odours than pigmented rats (Moulton, 1960). The death of albino animals from eating St. John's wort is almost certainly the result of photodynamic sensitisation from exposure of unpigmented skin (Horsley, 1934). Pigmented animals are unharmed by eating the plant.

The olfactory pigment has been found to be located in the supporting cells and in Bowman's glands; and has never been demonstrated in receptors. It is thought that the pigment which is a complex of carotenoids and non-carotinoid phospholipids is a metabolic by product which is stored in the basal parts of the supporting cells. There is no definite evidence which might suggest that the pigment has any functional significance.

Electrophysiology of the Olfactory Mucosa

Recordings of the electrical responses of the olfactory mucosa to odour stimuli provide quantitative data regarding its sensitivity and differential responses to various odours. Most electrophysiological studies have been carried out on frogs for technical convenience but studies on other animals have shown that there is no essential difference in response in the different species. Most recordings have been made from an electrode placed on the sur-

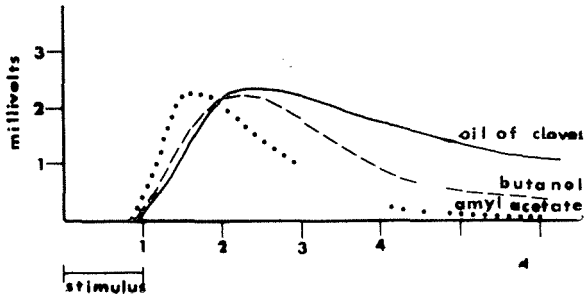

Fig. 4: Electro-olfactogram (E.O.G.) responses to three different odours. The duration of the stimulus was 1 second in each case (after Ottoson).

face of the olfactory mucosa. When a puff of odourised air is directed towards the region being studied a slow, negative, purely monophasic potential develops. This is the electro-olfactogram (E.O.G.). The E.O.G. response to various odours shows differences in the time course of the potential change. Some odours show a faster rising phase than others; and some show a longer falling phase than others (Fig. 4). Compared with corresponding potentials from other sense organs, the E.O.G. response is very slow. A puff of air containing a low concentration of an odour and lasting one second produces a response lasting about 5 seconds or longer. The slow response would not be surprising if the odour molecules have to diffuse through a layer of fluid before reaching the receptors. The time course of the response depends on the number of molecules reaching the receptors per unit time and its duration on the time it takes for odour molecules to be removed or inactivated.

Increasing odour concentration results in a logarithmic increase in amplitude of the E.O.G. potential. Continuous stimulation results in a sustained potential which remains throughout the duration of the stimulus, indicating that the olfactory receptors adapt extremely slowly. This finding conflicts with the common observation that the sensation of a smell rapidly weakens and soon becomes imperceptible.

Fig. 5: Spike activity of olfactory axons. Spikes of three different amplitudes arising from 3 separate receptors can be distinguished (a) resting state; (b) response to stimulation with tetraethyl tin (after Gestland).

The E.O.G. is only obtained by recording from the surface and it declines progressively as the electrode is inserted into the epithelium. It reflects the summated electrical activities at the olfactory surface but it is still uncertain how it is related to the 'generator potential' elicited in the receptors. It could also be a composite potential caused not only by potentials arising in the receptors but also by potentials arising in other cells.

Recordings from single receptors was made possible by the use of special glass microelectrodes, which were pushed into the mucosa until the spike activity from the receptor axons could be recorded (Gestland, 1965).

The spikes arising from different axons could be distinguished from one another by their amplitude — the spikes arising from one axon are constant in amplitude. The response of one receptor could therefore be distinguished from that of other receptors (Fig 5). Using this method of single unit recording three important facts emerged: (1) a single receptor can be excited, inhibited or remain unaffected by an odour; (2) one unit responds differently to different odours; and (3) no two receptors respond in the same way to a variety of odours. The responses could also be measured quantitatvely. These results, which have been considerably amplified by further research, have provided a basis for understanding the differential sensitivity of olfactory receptors to odours, which is of considerable importance in olfactory discrimination.

Theories of Olfaction

Perhaps the greatest paradox in olfactory research is that we still do not know the nature of the essential stimulus that constitutes a smell. The original idea that the chemical configuration of an odoriferous molecule determined its smell was soon discarded since no correlation between the two could be found. Numerous

alternative theories were therefore advanced attempting to explain which physical or chemical characteristics of molecules determined their particular odour, how these characteristics could account for the specificity of odour sensations, and in what way the stimulating molecules altered the receptor cell so as to generate an impulse.

The molecular characteristics which have been implicated in formulating these theories have included such features as the polarity of molecules, their over-all shape or profile, the chemical nature of their end groups and intra-molecular vibrations, or various combinations of these. Some theories have even suggested that odorant substances emit waves which stimulate the receptors.

It is not intended to review the numerous and varied theories which have been proposed but merely to point out that they testify to the lack of adequate experimental evidence which has given way to considerable imagination. The theories of olfaction have therefore been based mainly on theoretical consideration. However, theories are important for the researcher in designing critical experiments which may throw light on the fundamental problems of olfaction, but the difficulties encountered in doing this have so far been quite formidable.

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DIABETIC RETINOPATHY

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Diabetic Retinopathy is well described by Duke Elder and Debree (1967) as: "One of the major tragedies of Ophthalmology of our generation; always common and rapidly becoming still more common, affecting the young as well as the aged; predictable but not preventable, chronic and progressive in its course and leading to blindness in a distressing number of cases."

Diabetic Retinopathy is responsible for about 10% of new cases of blindness at all ages and almost 20% of new cases of blindness between 45 and 75 years. Because it is assocated with a much higher mortality than most other causes of blindness, these proportions are halved if persons who are blind from diabetic retinopathy are compared to the total existing population of blind persons. (Kahn & Heller, 1974). In a survery of the causes and incidence of blindness in the Maltese Islands carried out in 1958, it was found that Diabetic Retinopathy was the cause of 17% of cases of blindness (Damato 1958). Diabetes is rapidly becoming a major Public Health problem in many nations in the world. There is every reason to believe that within the next five to ten years, it will be the leading cause of new adult blindness in many countries in Europe and the U.S.A. (Kupper, 1971). If Diabetes is diagnosed at the age of 20, the risk of blindness at the age of 30 is only 0.1%. It increases to 3.5% at the age of 50 (35 times). For the general population, the risk of blindness from all causes at

age 30 is 0.09%
at age 50 is 0.15 i.e. 1.6 times.

At the age of 50, the diabetic is about 23 times more likely to be blind than his non-diabetic counterpart. (Goldberg, 1971).

Visual disability in Diabetes can be caused by Cataract, Refractive changes, retinopathy, and rubeosis iridis ending in secondary glaucoma.

The preponderance of evidence suggests that a chemical aberration of the carbohydrate metabolism is the common aetiological forerunner of diabetic retinopathy. The intervening pathogenesis responsible for the conversion of carbohydrate intolerance to diabetic retinopathy remains obscure.

Certain conclusions regarding the natural history of this serious retinal disease can be drawn. 2% of all diabetics become blind from Retinopathy alone. This is 10% greater than that of blindness from all causes in the general population. Duration of Diabetes appears to be the primary factor affecting the frequency of retinopathy.

Diagnosis before 30:

after 5 to 9 years	10%
after 15 years	50%
after 25 years	80 to 90%

Ageing makes the retinal vasculature more vulnerable to the diabetic process and makes the older patient more likely than the younger one to develop retinopathy within a given period of time (Goldger, 1971). Caird and Knowles in 1969 summarized evidence showing that the frequency of retinopathy may be reduced and the age of onset raised if control of diabetes is particularly strict during the first five years following the discovery of the disease. However, once most retinal lesions are established, metabolic control has little if any influence on the retinopathy.

This point is controversial. Irregularities of the retinal veins (dilatations, tortuosity, beading) may be reversible with ap-

propriate therapeutic management such as diet and insulin. Permanent lesions such as neovascular and fibrovascular proliferations appear to be minimally influenced by the systematic effects of dietary management and metabolic control.

Regression has been observed in approximatively 10% of cases having neovascular tissue but no vitreous contraction. Instead of following the course of vitreous contraction and associated haemorrhages, neovascular tissue simply regresses and atrophies, so that major extravasations are rare. The factors responsible for this phenomenon are currently unknown. They are obviously important in devising a successful treatment for diabetic retinopathy (Ashton, 1963).

The initial vascular changes in Diabetes occur in the capillary bed. There is a thickening of the capillary membrane which is associated with increased permeability. Its pathological significance, however, is not known. The electron microscope has contributed important information on changes in the basement membrane of the capillaries and other ultra-microscopic structures.

The initial vascular change in the retinal circulation of the diabetic is a venous engorgement which may last for several years. The first sign of retinopathy is the appearance of small punctate haemorrhages usually around the posterior pole on the temporal side. Pathological changes occur in the basement membrane of the capillaries in one suffering from vascular decompensation as a result of venous obstruction. This is a fundamental condition. Whether it results from decompensation of the vascular circulation and partial anoxia, or as a direct result of toxaemia due to diabetes. is not known.

The basement membrane undergoes thickening and vascularization, especially that between the mural cells and the outer border of the capillary. The mural cells (intramural pericyte) undergoes eosinophilic degeneration. This area of the capillary wall is weakened and gives way under intracapillary blood pressure, leading to the sacculated outpouching seen ophthal moscopically as minute pin-point haemorrhages or capillary aneurisms. Serum and blood cells exude through weakened capillary walls and lipid substances are deposited in the retina. Since the circulation is poor, these substances remain as retinal exudates and haemorrhages. Still another and more malignant phase of diabetic retinopathy is the formation of new vessels usually at the disc margin and also in the retina proper.

This is an attempt to re-establish the circulation in area of venous obstruction and compensate for the anoxia of the retinal tissue (Kornweig, 1971).

Photocoagulation is useful where localized areas of newly formed blood vessels can be seen and treated. The study of the results of such treatment suggests the interesting and exciting hypothesis that the progress of diabetic neovascular proliferating retinopathy can be altered by reducing the amount of functioning retina.

The retinochoroidal metabolic or haemodynamic balance can be altered by producing numerous harmless, nonfunctioning choroid retinal scars.

When photocoagulation is applied before the stage of vessel proliferation, the symptoms of diabetic retinopatly are almost always reversible. By treatment in the early stage, late sequelae with proliferations, hemmorhages and retinal detachment can be prevented. If however, vessel proliferation and fibrous changes are already present at the time treatment is started, photocoagulation is too late to stop the progress of the disease (Waubke 1971).

The way in which photocoagulation acts in diabetic angiopathy of the retina is unknown. It has been suggested that changes in the intravascular pressure or an improvement in the oxygen supply to the remaining undestroyed retina may play an important role:

1 — Improvement in the disturbed permeability. The regression of impaired permeability indicates that after photo-coagulation, a functioning blood tissue barrier may be re-established.

2 — Occurrence of a new capillary pattern. The angiogram before light coagulation shows typical findings in capillary

dilatation, micro-aneurysms, haemorr hages, and leakage of dye.

The angiogram taken a year after coagulation shows a pattern of rather large capillaries extending quite regularly over the whole posterior fundus. Some of the microaneurysms are still visible but the leakage o fthe dye has been considerable reduced.

This new pattern is not a temporary effect of the treatment but a long lasting change in the whole capillary network.

This is not found in untreated eyes. The newly formed capillary pattern which develops after photocoagulation seems to demonstrate a new adaptation in both the haemodynamics and metabolism of the retina (Waubke 1971).

In April 1974, an assessment of cases suffering from Diabetic Retinopathy with a view to treatment by light coagulation, was carried out at the O.P.D. along with Dr Duncan and Dr. Cullen of Edinburgh University. Three hundred and thirty one cases were examined: 226 females and 105 males. The fundi of both eyes of every patient were examined under full pupillary dilatation. Visual acuity was also recorded. According to the changes found in the fundi, cases were divided into 5 groups (Table 1):

1 — Exudative
2 — Haemorhagic
3 — Mixed (Haemorhagic and Exudative)
4 — Background retinopathy. Early microaneurysms and scattered exudates.
5 — Proliferative retinopathy.

In the "exudative group" (Table 2) extensive lipoid deposits were found on the macula and around it all over the fundi. Most of the cases were in the 60-69 age group. There were five cases in the 40-49 age group. There was a preponderance of female patients over males. Visual acuity was found to be considerably impaired, and varied from 6/12 to counting fingers.

Haemorrhages varying in size were the main findings in the group 3 (Table 3). There were 3 cases in the 40-49 age group. The largest number of cases was in the 50-59 age group. Visual acuity was better than in the exudative group. A considerable number of these cases were considered suitable for light coagulation.

"In the mixed group", (Table 4) more or less equal changes of the haemorrhagic and exudative varieties were found. The most numerous age group was the 60-69 age group. Vision varied from 6/12 to 6/60. There were some cases suitable for light coagulation. As usual, there were more females than males.

Table 1
Diabetic Retinopathy in Malta

	Females	Males
Exudative	58	21
Haemorrhagic	17	12
Mixed	18	4
Proliferative	60	29
Background	73	39

Table 2
Exudative Retinopathy

Age	Females	Males
40-49	1	4
50-59	7	5
60-69	34	8
70-79	16	4

Table 3
Haemorrhagic Retinopathy

Age	Females	Males
40-49	2	1
50-59	6	6
60-69	5	2
70-79	3	3
80	1	-

Table 4
Mixed Retinopathy

Age	Females	Males
40-49	-	-
50-59	3	2
60-69	10	2
70-79	5	-
80-89	-	-

"Background group", (Table 5) this is by far the most numerous group. There were many more females than males. The main changes are minute micro-aneurysms, pinpoint haemorrhages, minute lipoid deposits and macular oedema. These changes are usually found at the posterior pole. Other areas however showed changes. Vision varied from 6/6 to 6/60.

Most cases are found in the 60-69 age group. There was one case in the 20-29 age group, and another one in the 80-89 age group.

"Proliferative diabetic retinopathy" (Table 6). In this group, there were extensive changes varying from large retinal haemorrhages, lipoid deposits, fibrotic changes, retinal detachment and glaucoma. Vision was very much impaired. As many as 78 cases could be considered as practically blind. The was one case in the 20-29 age group and 2 cases in the 30-39 age group. The numerous age group was the 60-69 age group. Fifty six cases were considered to benefit from treatment by light coagulation. Another group of forty patients required constant watching for possible treatment by light coagulation. There were no indications for pituitary ablation.

The aim of treatment by light coagulation is to seal off the new vessels in order to prevent or at least delay the bleeding sequelae of neovascularization, leading to recurrent vitreous haemorrhages, fibrous tissue formation, retinal detachment and haemorrhagic glaucoma (Guinan 1968). It is known that, in some cases, new vessels regress spontaneously without these severe effects. But this is the exception (Beetham, 1963; Bobree, 1964). Sometimes, too, the new vessels remain almost stationary for long periods. In general, the usual course is one of proliferation. Beetham has shown that the average deterioration time from slight to extreme proliferaive retinopathy is 5 years.

It is mainly in the early stages that treatment by light coagulation seems to show obvious improvement both anatomically and functionally. One may claim that blocking of the progress of the disease and even improvement could be achieved by photocoagulation. Therapeutic results can best be interpreted by considering the morphological details.

Here, comparative fundus photography is the most useful method. Since one can analyse microstructure changes over a long period of time.

Table 5

Background Retinopathy

Age	Females	Males
20-29	1	-
30-39	-	-
40-49	8	5
50-59	11	7
60-69	41	20
70-79	11	7
80-89	1	-

Table 6

Proliferative Diabetic Retinopathy

Age	Females	Males
20-29	-	1
30-39	1	1
40-49	3	2
50-59	21	6
60-69	27	18
70-79	8	1

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ALTERED PULMONARY FUNCTION IN BRONCHIAL ASTHMA

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Asthma has attracted a great deal of attention over the centuries both because it is common and because of its frequent dramatic manner of presentation (Ellul-Micallef, 1976). Up to comparatively recently, knowledge of physiological changes occurring in asthmatic patients, both during an attack and following therapy has been scanty. Over the past few years various tests have been developed enabling the clinical pulmonary physiologist and the chest physician to measure a number of different variables. It is only by considering all the changes in pulmonary function which take place in this condition that a reasonably clear picture can be obtained and a rational approach to therapy instituted. In this article discussion of altered pulmonary function in asthma includes changes in:

(i) Airway resistance.
(ii) Lung volumes.
(iii) Lung elastic recoil pressure.
(iv) Pulmonary diffusing capacity.
(v) Arterial blood gas tensions and pulmonary gas exchange.

(i) Airway resistance in asthma

Increased and variable airway resistance may be said to be the physiological hallmark of bronchial asthma. In general the forced expired volume in one second (FEV_1), the maximum mid-expiratory flow rate (MMFR) and the peak expiratory flow rate (PEFR) are found to be decreased from the predicted values and are likely to be related to the severity of symptoms. The ratio of the forced expired volume in one second to the forced vital capacity is also found to be reduced. Subjective improvement in the patient's condition is not always reflected in a proportional change in these tests. Clinical improvement may occur while some spirometric tests such as the FEV_1, remain unaltered. The improvement may be reflected by a decrease in lung volumes (Woolcock & Read 1966; Weng and Levinson, 1969).

Airway resistance (Raw) as measured by body plethysmography is believed to provide a direct measurement of the resistance to the flow of air. The Raw is always increased, frequently very considerably, and the specific conductance (SGaw), that is, the conductance divided by the thoracic gas volume at which the airway resistance is measured, correspondingly decreased during the acute phase, both indices returning towards normal values as the patient's condition improves (Lapp Le Roy and Hyatt 1697; McFadden & Lyons 1968, 1969; Pelzer & Thomson 1969; Fisher et al 1970; Daly 1971). An increased Raw has also been found in some symptom free asthmatic patients (Ruth & Andrews 1959; Bernstein & Kreindler 1963). Cade et al (1971) provoked bronchoconstriction in symptom free asthmatic subjects with nebulized metacholine. They found that pulmonary resistance increased within one breath of the metacholine inhalation and was the measurement of lung function which changed most in response to drug when it was compared with changes in FEV_1 and lung volumes obtained by helium dilution. Airway resistance is of course also increased in chronic bronchial asthma; it has been shown to decrease on corticosteroid adminitration (Ellul-Micallef et al, 1971, 1972, 1974).

(ii) Lung Volumes

The vital capacity is generally decreased in asthma and is usually more severely

diminished the greater the degree of airway obstruction. A decrease in vital capacity commonly persists during the symptom free phase of bronchial asthma (Levine et al 1970). Lowell et al (1955) used the vital capacity to follow changes in asthmatic patients, but it proved to be a less sensitive index than the dynamic ventilatory tests. A number of reports have appeared in which measurements of the total lung capacity (TLC), functional residual capacity (FRC) and residual volume (RV) in asthmatics were found to be elevated, thus reflecting the presence of a certain degree of hyperinflation. A reversible increase in TLC was first documented in asthma as early as 1934, when Hurtado and Kaltreider observed a decrease in TLC following the administration of adrenaline to patients with acute asthma. Since then a considerable number of papers reporting the changes in lung volumes that occur during acute asthma and the period of recovery have been published (Woolcock and Read, 1965; 1966; 1968; Meissner and Hugh-Jones 1968; Weng and Levison 1969; Palmer and Diament 1969; Stanescu and Tetulescu 1970; Mayfield et al, 1971; Freedman et al, 1975). Lung volumes have also been reported to be elevated in chronic asthma returning towards predicted normal values after corticosteroid therapy (Ellul-Micallef et al 1971, 1974).

In general, the more severe the degree of airway obstruction the greater the amount of hyperinflation present, shown by an elevated TLC, FRC and RV; all indices tending to decrease following successful treatment. In some of the patients reported by Woolcock and Read (1965) the FRC during acute asthma was greater than the TLC after recovery. In these patients tidal breathing during severe obstruction must have been taking place at a higher level than the point of maximal inspiration after recovery. Mead, Milic-Emili and Turner (1963) claim that inhibiting reflexes normally limit the degree of voluntary lung inflation; if this is true, then one must presume that such reflexes are modified in asthma. Palmer and Diament (1969) similarly found that in asthma as the airway obstruction increased there is a progressive hyperinflation of the lung and that when the obstruction is reduced by a bronchodilator, hyperinflation becomes less. Of the indices of hyperinflation they found that only RV/TLC% correlated consistently with the dynamic lung volumes and regard it as the best single measurement of hyperinflation in this condition.

Various studies have now been reported in which serial measurements of FRC by a helium dilution method and thoracic gas volume by body plethysmography have been carried out in asthmatics during the acute attack and the subsequent recovery period (Meisner and Hugh-Jones 1968; Stanescu and Teculescu 1970). In general, plethysmography yielded signficantly larger FRC values than did the helium method. The differences were greatest when the asthma was most severe and decreased during clinical recovery. As the helium dilution method reflects the volume of ventilating parts of the lung, there appear to be portions of the lung which fail to ventilate during the time involved in helium equilibration.

Hyperinflation may persist in the asthmatic patient even in the symptom free phase (Beale et al 1952; Gold et al 1967; Levine et al 1970). An increase in FRC may be compensatory to the decreased bronchial calibre found in asthma and to a certain extent this may have a guy-rope effect in helping to maintain the patency of the airways. This is not obtained without a disadvantage to the patient, for as the lung volume increases, compliance diminishes progressively so that the further inhalation of a given volume of air requires the production of a higher transpulmonary pressure difference because the patient is breathing on a flatter part of the Pressure-Volume (P-V) curve. The elastic work of inspiration will be greatly increased and presumably must make considerable contribution to the patient's sensation of dyspnoea. Asthmatic patients thus often find as much difficulty with inspiration as with expiration.

(iii) The Lung elastic recoil pressure in Asthma

In 1963, in two separate studies, Macklem and Becklake, and Ting and Williams both reported mean inspiratory static pressure-volume (P-V) curves in normal subjects, in patients with asthma and in those with emphysema. In both studies the P-V curves for symptom free asthmatics were shifted upwards and to the left as compared with the mean curve for normal subjects; i.e. it appeared that the lung elastic recol pressure, Pst(l), was reduced. Macklem and Becklake (1963) corrected for the increased lung volume seen in some of their subjects by calculating the "over-all compliance' (Mead et al 1955), i.e. the ratio of TLC to the maximum negative intrapleural pressure. This correction reduced the difference between the normal group and the group of asthmatics but accentuated the loss of elastic recoil in the group with emphysema. Work by Tooley and his associates (1965) provides supporting evidence.

Several workers have since measured Pst(l) in asthmatics both during exacerbations as well as in symptom free phases to try and establish whether it is indeed reduced in asthma (Gold, Kaufman and Nadel 1967; Woolcock and Read 1968; Finucane and Colebatch 1969). Gold and his associates showed that the Pst(l) was decreased at all lung volumes in seven of their twelve asthmatic subjects. After a week's treatment with corticosteroids and bronchodilators, the increase in airway resistance and in lung volume reverted to normal and their P-V curves moved back to the normal range, in all the patients but one. In the latter, a further week of treatment finally reversed all abnormalities. Gold also induced bronchoconstriction in four asthmatics who had normal P-V curves and in one normal subject, with a 0.03% histamine phosphate inhalation. Although this resulted in a mean airway resistance of 320% of the pre-inhalation value, the Pst(l) remained normal. Acute hyperinflation of the chest in a normal subject for an hour also resulted in insignificant changes in Pst(l). It thus appears that loss of lung elastic recoil pressure is slow to develop. Woolcock and Read (1968), reported a decreased Pst(l) in six out of their ten asthmatic subjects, during an exacerbation of symptoms. Unlike Gold's patients, after intensive therapy, although the airway resistance returned to normal in almost all the patients, the loss of lung elastic recoil and hyperinflation persisted in five subjects.

Finuncane and Colebatch (1969) assessed the elastic properties of the lung in patients with asthma, emphysema and in normals, by measuring the static P-V curves of the lung during deflation from TLC after a standard volume history. The P-V characteristics of this study thus reflect mainly the elastic properties of lung tissue since the pulmonary retractive pressure was measured during deflation from TLC when lung surface forces contribute least (Radford, 1946) In three of the four asthmatic patients studied there was a persistent reduction of pulmonary elastic recoil pressure despite relief of airway obstruction for six weeks or longer. This finding agrees with that of Woolcock and Read (1968) and it seems likely that some patients with severe asthma might have a more or less permanent reduction of Pst(l).

The cause of the loss of elastic recoil of the lungs in asthmatic subjects is unknown. According to Mead (1961), the static P-V curve is dependent on two factors: the tension exerted by surfactant and the elastic properties of pulmonary tissue. The tissue component of the elastic retraction of the lung resides in the close association and architectural arrangement of collagen and elastin fibres in the respiratory bronchioles, alveolar ducts and alveoli (Pierce and Ebert 1969). In emphysema this fibre network is disrupted (Wright 1961) and elastic retraction of the lung would be expected to be and is in fact reduced. In asthma the fibre network is intact (Gough 1955) and hence other factors must be responsible for the loss of elastic recoil. Gold et al (1967) have suggested that prolonged distension of the connective tissue of the lungs causing temporary structural deformation is a

possible explanation. Other alternatives that must be considered are that the changes could be related to the forces exerted by surfactant; or the changes may be due indirectly to a reduction in perfusion to some alveoli, which affects their producton of surfactant or of another product important to the normal retractile forces.

Finucane and Colebatch (1969) suggested that the loss of elastic recoil could be the result of a reduction of tissue forces due to tissue stress-relaxation (Marshall & Wi dicombe, 1961). In asthma, stress-relaxation may occur in those parts of the lung held inflated by airway closure. Theoretically, the reduced retractive pressure in asthma could also involve increased recruitment of surface active molecules consequent upon prolonged over-expansion of the lung (Tierney & Johnson 1965). It is known that the surface tension of a liquid is inversely related to the concentration of surface-active molecules in the surface (Davies & Rideal 1961).

Woolcock and Read (1969) suggested that hyperinflation of the lung, may itself, cause a reduction in lung elastic recoil in a manner in which they could not explain fully. They looked at the problem from the opposite point of view from that of Gold and his associates. The latter considered the loss of elastic recoil to be responsible for the hyperinflation in asthma. If hyperinflation of the lungs itself causes a reduction in elastic recoil, then a residual abnormality in the airways sufficient to maintain a degree of hyperinflation could account for the apparent loss of lung elasticity in symptom free asthmatics. This could possibly account for the differences in results reported by Gold et al (1967) and Woolcock and Read (1968). All the patients reported on by Gold and his coworkers had normal lung volumes when the lung elastic recoil was measured after a week's therapy, whilst those reported on in the other two studies had persistent hyperinflation.

In a recent paper, Peress et al (1976) reported findings which indicate that the increase in Total Lung Capacity in acute asthma results from a combination of loss of lung elastic recoil, increased outward recoil of the chest wall and increased strength of contraction of the inspiratory muscles. They suggest that this may be the result of a rapid change in the elastic properties of lung and chest wall. Such properties have up to now been regarded as fixed and immutable.

(iv) The pulmonary diffusing capacity in Asthma

The measurement of the pulmonary diffusing capacity (DLco) in asthma has produced discordant results. Some workers have claimed that diffusing capacity values remain remarkably normal but others have shown that a considerable reduction may be present. Among the first to report normal values were Bates (1958) and Macklem and Becklake (1960) who used a steady state method to measure DLco Macklem and Becklake reported that both DLco and elastic recoil were well preserved in asthma and contrasted this with the decrease in both variables that occurred in the emphysematous patients they studied. They found, that at equivalent values of pulmonary conductance, emphysema is characterized by a considerably lower DLco than asthma. Normal values for diffusing capacity have also been reported when this was measured by the single breath method (Burrows et al 1961; Kanagami et al 1961; McFadden and Lyons 1968: Meissner and Hugh-Jones 1968; Daly 1971). The diffusing capacity was found to be normal even when the FEV_1 was markedly decreased (Bedell and Ostiguy 1967; McFadden and Lyons 1968; Ogilvie 1968; Meissner and Hugh-Jones 1968).

On the other hand, Palmer and Diament (1969, 1970) using the single breath method measured the diffusing capacity in all grades of severity of asthma and found that it fell signficantly as the degree of asthma became more severe. They reported a mean value for DLco of 16.2 + 7.3 ml/min/mmHg when the FEV% was less than 40% (the predicted being 26.1 ± 2.70 ml/min/mmHg); this value improved when salbutamol was administered. Weng and Levinson (1969) measured the diffus-

ing capacity by the steady state method in thirty asthmatic children during an acute attack and repeated the measurements when they were in a symptom-free status. They found that it was significantly reduced during an acute attack but returned to the normal range during the symptom free period. The indices DLco/TLC and DLco/FRC which were markedly reduced during the attack remained significantly lower than normal during the symptom free period. These findings have been supported by the work of Levine et al (1970) who using a steady state method report a lower than predicted value in a group of six symptom free asthmatcs.

Pecora, Bernstein and Feldman (1966) measured the diffusing capacity by the single method in twenty six children with intractable asthma. They reported that in sixteen children with hyperinflated lungs the diffusing capacity was greater than predicted, whilst in the ten children who had no pulmonary hyperinflation the diffusing capacity was normal. They suggested that this increase is due to a moderate increase in surface area of the lung and a greater decrease in the thickness of the alveolar membrane. Ogilvie (1968), too, reports higher than predicted values in a number of asthmatics, and points out that an imbalance between ventilation and perfusion can sometimes result in erroneously high values.

Forster (1957) in his classical review of the processes of pulmonary diffusion and their assessment refers to the errors which may be introduced by non-uniformity of various variables. Although the concept of a diffusing capacity is not a difficult one to envisage, the details of its measurement and the interpretation of the results obtained by the various techniques are far from straightforward, especially in clinical conditions in which there is inhomogeneous distribution of alveolar gas. Bates, Macklem and Christie (1971) have ascribed the difficulty in sorting out the apparent discrepancy of the diffusing capacity values in asthma obtained by various workers to four main factors — patient selection, variation in degree of airway obstruction, differences in technique and the uncertain interpretation of results obtained from induced bronchoconstriction. Difficulty often arises, when selecting patients, in differentiating between those suffering from asthma and those with chronic bronchitis with a degree of emphysema.

However, the interpretation of reports on diffusing capacity in bronchial asthma is perhaps most seriously hampered by the variety of methods used in its determination. It is obvious that each method measures something different and probably none measures the true diffusing capacity of the 'pulmonary membrane'. The accuracy of each method for measuring this index of pulmonary function depends on certain critical assumptions about the relative uniformity of blood flow, ventilation and alveolar volume and if one of these assumptions is incorrect the measurement becomes biased. Since the assumptions are different for each method of measurement, a given type of non-uniformity in the lung is bound to bias the diffusing capacity measured by one method more than by another. This possibly accounts for most of the discrepancy between the various reports. Ohman et al (1972) measured the diffusing capacity in ten symptomatic asthmatics by both the single breath and steady state methods before and after treatment. The diffusing capacity measured by the single breath method was greater than predicted on both occasions. The mean pre-treatment value obtained by the steady state method was 51% of the predicted and it went up to 66% of the predicted following therapy.

The severity of the disease during which the measurement is made is another important factor to keep in mind when assessing results. Tests of diffusing capacity must be to a greater or lesser extent influenced by ventilation-perfusion abnormalities (Apthorp and Marshall 1961). Thus although the single breath method is said to be less sensitive to ventilation-perfusion (V/Q) abnormalities, in severe cases an impaired distribution of inspired air, regional V/Q variations and the DI/Q ratio can decrease the value of the transfer factor obtained by the single breath method

(Piiper and Sikand 1966). The transfer of gas in bronchial asthma thus appears to be more impeded by failure to deliver inspired gas to the alveolar surface than by interference with diffusion through the 'pulmonary membrane'.

(v) Arterial blood gas tensions and pulmonary gas exchange.

Very little attention was paid to the changes that occur in blood gases during asthma until comparatively recently. Bates and Christie (1964) stated that, "the patient with moderately severe bronchospasm but not in status asthmaticus only rarely shows any significant abnormality of arterial oxygen saturation or CO_2 tension". It had been generally assumed that the $PaCO_2$ is usually normal or low, due to hyperventilation until the terminal stages of status asthmaticus, when the $PaCO_2$ rises rapidly and respiratory failure supervenes (Marchand and van Hasselt 1966). Before the important paper of Tai and Read in 1967 there had only been occasional reports of blood gas disturbances in bronchial asthma (Herschfus et al 1953; Williams and Zohman 1960; Feldman 1962).

Tai and Read (1967) were the first to report carbon dioxide retention and marked respiratory acidosis in twelve patients admitted to their care in status asthmaticus. Their data showed that in other patients with only moderate clinical severity considerable hypoxaemia could also be present. Similar results have now been reported by a number of different workers (Rees, Miller and Donald 1968; McFadden and Lyons 1968; Meissner and Hugh-Jones 1968; Miyamoto et al 1970; Rebuck and Read 1971). Arterial PO_2 levels belows 60 mmHg may be associated with PCO_2 levels varying between 30 and 80 mmHg; such a level of PaO_2 is commonly seen when airway obstruction is severe, with an FEV_1 below 30% of the predicted normal value.

Flenley (1971) states that if milder cases are included the fall in PaO_2 seems to bear a roughly linear relation to the FEV_1; normal PaO_2 values being usual when the FEV_1 is above 2 litres. Tai and Read (1967) found a general correlation between the degree of reduction of the FEV_1 and the extent of disturbance of blood gas tensions in their study of sixty four patients with moderately severe asthma. They pointed out that FEV_1 levels of less than a litre were especially associated with a significant reduction of arterial PO_2. However, it should be stressed that the correlation is not good enough to make FEV_1 levels greater than a litre a reliable index of a fairly normal arterial oxygen tension. Palmer and Diament (1968, 1969) reported a correlation between PaO_2 and the RV/TLC%, hypoxaemia becoming progressively more severe as hyperinflation develops.

Rees, Millar and Donald (1968) following the clinical course and arterial blood gas tensions of twenty four patients in status asthmaticus, found that hypoxaemia was invariably present, was frequently quite marked and persisted despite extensive therapy sometimes for weeks. Most patients were normocapnic or even hypocapnic. When severe hypercapnia was present the patients generally died. They found that changes in $PaCO_2$ were inversely related to changes in pH, and patients with severe hypercapnia also had metabolic acidosis. The pulse rate correlated well with PaO_2 and in the severely hypoxaemic patients the frequency exceeded 130 beats/min. McFadden and Lyons (1968) studied ninety one patients during an acute asthmatic attack. All their patients had hypoxaemia but hypercapnia was only present in eleven patients, and was not found till the FEV_1 fell to below 20% of the predicted value. Hence despite the fact that CO_2 retention is a prominent feature in some asthmatics with marked airway obstruction, low PCO_2 values indicating hyperventilation are frequently encountered. Hypocapnia and respiratory alkalosis was present in about 80% of the patients studied by McFadden and Lyons. These studies have now established the fact that hypoxaemia, often of a dangerous degree may be present in asthmatic patients, and that severe hypercapnia is not usually present except terminally. Feldman (1962) pointed out the grave prognostic signifi-

cance of an increase in $PaCO_2$ in adults with severe asthma.

The accompanying disturbance in the acid-base balance as reflected in the arterial blood, shows that the hypercapnia in most of these patients probably develops acutely. Flenley (1971) analysing the data from various authors (Mithoefer et al 1968; Tabb and Guerrant 1968; Tai and Read 1967; Downes et al 1968; Simpson et al 1968) concluded that chronic elevation of PCO_2 is relatively uncommon is asthma. The increased renal reabsorption of bicarbonate which is an important defence against respiratory acidosis would appear to be too slow a mechanism to be of great importance in acute asthma, where dangerous hypercapnia may develop very acutely. Mithoefer et al (1968) have found that correction of the respiratory acidosis by infusion of sodium bicarbonate was valuable in treating intractable asthma, but others seem to have had less success with this approach (Flenley 1971).

Hypoxaemia, with or without CO_2 retention, implies a maldistribution of ventilation and perfusion in the lungs which is shown by increased alveolar — arterial tension differences for oxygen (A-a) DO_2 and higher ratios of physiological dead space to tidal volume (VD/VT). A higher than normal (A-a)DO_2 and VD/VT has been shown to be present both during the acute attack (Field 1967; Meisner and Hugh-Jones 1968; Valabhiji 1968), in chronic asthma (Ellul-Micallef et al, 1972), as well as during the symptom free phase (Levine et al 1970; Waddell et al 1967). Although uneven distribution of pulmonary ventilation in asthma has been recognised for a long time in both the acute phase (Bates 1952; Fowler et al 1952; Herschfus et al 1953; Malmberg et al 1963; Bates et al 1968) and in the symptom free period, (Beale et al 1952), the effect of this on the distribution of pulmonary blood and the ventilation-perfusion relationships had until comparatively recently received less attention. Single cases of asthma with V/Q disturbances had been reported by Donald et al (1952) and by West et al (1957). Ledbetter et al (1964) in a study of asthmatic children reported that an abnormally high percentage of the cardiac output perfused the 'slow' or poorly ventilated compartments in the lungs.

The presence of adaptive mechanisms to divert blood flow away from poorly ventilated regions of the lung were postulated by Barcroft (1930), Anthony (1930), and Haldane (1935). The observation that hypoxia causes an elevation of pulmonary artery pressure probably secondary to pulmonary vasoconstriction led von Euler and Liljestrand (1946) to suggest that pulmonary hypoxia might play a role in controlling the distribution of pulmonary blood flow. Recent work has in general confirmed these suppositions. It is now generally accepted that the concentration of gases in the alveoli determine the resistance to blood flow in the adjacent vessels, and that the chemical stimuli for this local vasomotor control are hypoxia and to a lesser extent acidosis (Liljestrand 1958; Fishman 1961; Fishman 1969). Other workers (Severinghaus and Stupfel 1957; Arborelius 1965) have also shown that a decrease in bronchiolar PCO_2 will redirect ventilation away from poorly perfused areas of the lung.

Although it seems unlikely that local alterations in perfusion could possibly compensate for the unevenness of ventilation in bronchial asthma, there is a lot of evidence to suggest that such homeostatic mechanisms do exist in asthma, and that they tend to reduce the V/Q defect by decreasing the blood flow of underventilated lung units. Factors disturbing these homeostatic mechanisms would be expected to result in an increased V/Q abnormality. Thus, the administration of oxygen, presumably, by abolishing pulmonary vasoconstriction in hypoxic regions, resulted in a worsening of the ventilation-perfusion imbalance in asthmatics as shown by an increase in the (A-a)DO_2 and VD/VT ratio. Breathing pure oxygen has been shown to have no effect on the pattern of V/Q inequality in normal subjects or in patients with chronic lung disease (Riley, Cournand and Donald 1951; Larson and Severinghaus, 1962; Cole and Bishop, 1963). Such a deterioration occurred not only in the acute phase of their illness

(Field 1967) but also in the symptom free period (Valabhji 1968); suggesting that during the latter phase a compensatory reduction of blood flow to underventilated parts of the lung might still be present. Supporting evidence for the existence of pulmonary vasocontriction in asthmatics when symptom free has been produced by Irnell and Noredgren (1966) who infused acetylcholine into the pulmonary artery of nineteen asthmatics and observed a reduction in arterial oxygen saturation in all but one. Valabhji (1968) reports a very small contribution of veno-arterial shunt of 3.7 $\pm$ 1.4% to the hypoxaemia present in their acute asthmatic patients. This is perhaps surprising in view of the widespread mucus plugging of the small airways that has been reported in asthma. The absence of a significant veno-arterial shunt could perhaps be explained on the basis of a diversion of blood flow from non-ventilated areas of the lungs as a result of pulmonary vasoconstriction.

A large number of studies on regional pulmonary ventilation and perfusion in asthmatics using lung scanning following the inhalation of radioactive gases such as Xe^{133}, the intravenous injection of I^{131} macroaggregated albumin, as well as the inhalation of an aerosol containing Tc^{99m} — iron complex, have now been carried out both during the acute attack and in remission (Woolcock et al 1966; Mishkin & Wagner 1967; Mishkin et al 1968; Hechscher et al 1968; Wilson et al 1970; Despas et al 1970). Most measurements showed well demarcated local ventilation and perfusion defects. Although the areas of hypoventilation generally showed decreased perfusion, it has been reported (Wilson et al 1970) that the perfusion was frequently less effected than ventilation. Lung scans showed that the V/Q imbalance frequently appears to be widespread in asthma. In general, repeated studies during improvement of symptoms showed normalisation of ventilation-perfusion patterns in areas which were previously involved; however, defects arising in new areas have also been observed (Mishkin et al 1968; Heckscher et al 1968).

Novey and his associates (1970) have studied early ventilation-perfusion changes following the induction of asthma by means of pollen, metacholine and exercise. They reported multiple focal V/Q abnormalities appearing within minutes of induction of asthma. The regional ventilatory abnormalities were greater than those of perfusion although similar in distribution. Although hypoxia is generally accepted as being mainly responsible for local pulmonary vasoconstriction, other mechanisms may also be involved in the causation of regional blood flow defects. These include mechanical occlusion of the capillaries by high intra-alveolar pressure at sites of regional hyperinflation. (Despas et al 1970).

Conclusion

Although no agreement has yet been reached on a definition of asthma (Working Group on the Definition of Asthma 1971), none would contest that the main pathophysiological hallmark of this disease is a variable increase in airway resistance to the flow air due to widespread narrowing of the airways. The actual site of such narrowing is still a matter of some controversy. Evidence for obstruction at both a peripheral level (Cade et al, 1971; Chan-Yeung; 1973) as well as in the large airways (Dulfano, 1966; Mildon et al, 1974) has been produced. It is probable that narrowing is present in both the large as well as in the small airways (Ellul-Micallef, 1974); small airways narrowing being the determining feature in acute asthma. Hyperinflation frequently occurs and it has now become widely recognized that this may be present when the more common spirometric indices used for detecting airway narrowing are normal; indicating an attempt on the part of the asthmatic patient to overcome the obstruction present by breathing at a higher lung volume. Further research is necessary to elucidate the precise nature of the changes in lung elastic recoil and pulmonary diffusing capacity that have been reported in asthma. Blood gas changes in the disease, often of a severe nature, are now an established fact and appear to be mainly due to V/Q abnormalities.

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THE INTRADERMAL LEISHMANIN TEST AS AN EPIDEMIOLOGICAL TOOL

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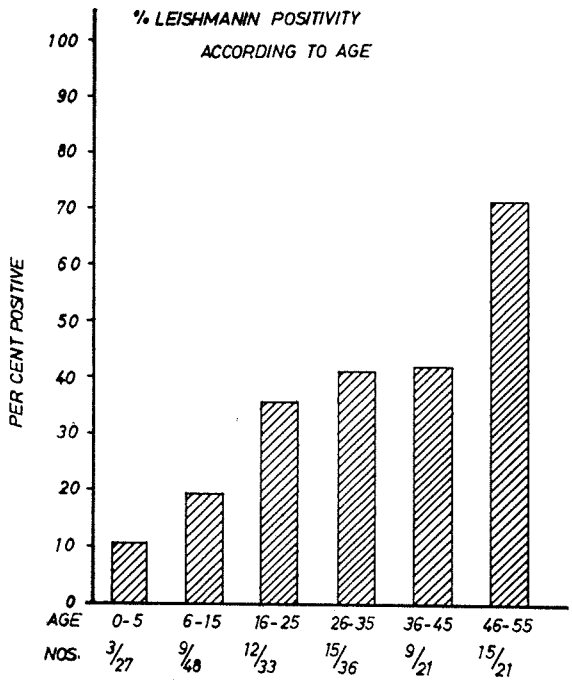
Malta had been an endemic area for Kala-azar long before Critien made the diagnosis of the first case of infantile leishmaniasis in 1911. There is no doubt that the dramatic drop in the incidence which has occurred since 1948 must be related to the general improvement in sanitation and the standard of housing as well as to such other measures as the suppression of the insect vectors and elimination of the animal reservior (Cachia and Fenech, 1964). Between 1970 and 1974, the average annual incidence was six cases; however, in 1975, there were 20 cases of Kala-azar, an incidence similar to the 1960 figures. Recent studies by Pampiglione et al (1975) in Italy, have provided further evidence that clinically obvious cases of Kala-azar represent a minority of infected people, the majority developing no symptoms at all or only a few symptoms and a spontaneous recovery. This is not surprising as this state of affairs occurs in other infectious diseases. Manson-Bahr (1961) used the intradermal leishmanin test successfully as an epidemiological tool in his studies on leishmaniasis in Kenya. It is worth noting that the leishmanin test bears a similar relationship to leishmaniasis as does the tuberculin test to tuberculosis. Pampaglione et al (1975) also demonstrated its usefulness in Mediterranean Kala-azar. The purpose of this preliminary study was to confirm the hypothesis that actual cases of Kala-azar are a microfocus of infection in the community as well as to assess the usefulness of this skin test in epidemiological work.

Material and Results

The household contacts of the 40 cases of Leishmaniasis reported in the years 1972 to 1975 were invted to take part in the study; however, only 28 families agreed to participate. 186 household contacts as well as 28 recovered cases were tested with a leishmanin preparation provided by Professor Pampiglione of Bologna, Italy. The antigen was injected intradermally into the forearm in a dose of 0-1ml. The size of the reaction was read after 48 hours and an area of induraton over 5mm in diameter was considered as positive. A control injection in the opposite forearm was not used.



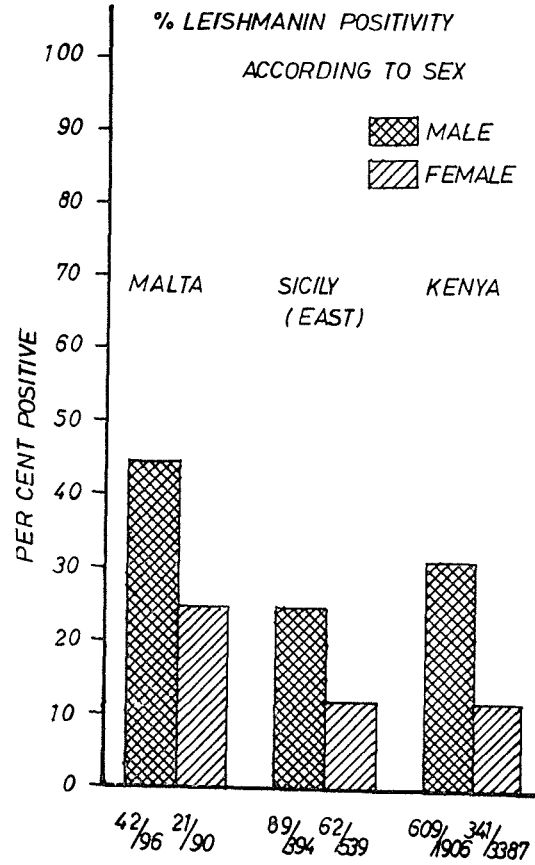
Discussion

The leishmanin skin test, like the tuberculin test, becomes positive when cell mediated immunity develops. An essential prerequisite for such an event is the presence of leishmania in the body irrespec-

tive of whether or not clinical manifestations have appeared. The percentage of positivity in the various age groups provides information of the degree of distribution of the disease in the community. Figure I shows that there is a steady increase in positivity with age, reaching a level of 73% in those over 45 years. The gradual increase in positivity with age does suggest that there has not been a sudden change from a high to a low. level of transmission. In such a situation, the development of certain environmental changes such as an increase in the vector or reservoir population could explain the relatively high incidence of Kala-azar in 1975 as compared to the previous years. It is also interesting that the disease is also affecting older patients; in fact, patients over the age of 10 years accounted for 23% of a total of 61 patients in the years 1970 to 1976 as compared to less than 3% in the period 1947 to 1962 (Cachia and Fenech, 1964) It is likely that, whilst in the past most of the adult patients were immune due to subclinical infection, it is less so now.. This is borne out by the high leishmanin positivity rate in the over-45-years group as compared to the younger age groups.

Another interesting feature is that whilst the sex of patients does not appear to influence the incidence of the disease (Cachia and Fenech, 1964), there was a definite higher leishmanin positivity rate in male household contacts as compared to females (Figure II). This is similar to what has been found in other studies in Eastern Sicily (Pampiglione et al, 1975) and Kenya (Southgate and Oriedo, 1967).

It is likely that the leishmanin skin test can prove as useful in the study of the epidemiology of leishmaniases as the tuberculin test in tuberculosis. Moreover, Pampiglione et al (1976) have also suggested a more practical use for it. As leishmanin posivity develops in asymptomatic cases early and practically at the same time as patients presenting with the clinical illness, the presence of a positive leishmanin test in household contacts associated with a negative test in the ill patient might suggest the diagnosis of



Kala-azar in the affected individual. This observation, if confirmed, has useful diagnostic implications epecially when Kala-azar affects adult patients as, in this group, the clinical presentation is very often atypical (Fenech, 1976).

I would like to thank Professor S. Pampglione for supplying the leishmanin antigen and Professor H. Gilles for helpful advice. My thanks are also due to Drs. R. Ellul-Micallef, A. Caruana Galizia and C. Mallia for all their help.

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MALARIAL NEHPROSIS

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EPIDEMIOLOGICAL DATA

Convincing evidence of an association between "Plasmodium malariae" and the nephrotic syndrome in children has accumulated over the years. The epidemiological data include (1) case-history reports of the relative prevalence of "P.malariae" in nephrotics and controls (2), comparisons of the incidence of the nephrotic syndrome in the tropics with that in temperate countries, and (3) time-trend studies of the effects of malaria control on the incidence of nephrosis.

Case-history studies:

Watson (1905) reviewing the clinical features of "P.malariae" infections, remarked on the presence of oedema and albuminuria in several of his patients.

Clarke (1912) wrote 'I believe that the occurrence of oedema in the tropics of such nature as to make one think of parenchymatous nephritis is a reason for making a search for quartan malaria para sites imperative'. Out of 62 cases of 'nephritis', 29 of them (48%) had "P.malariae".

McFie et Ingram (1917) reported nine cases of the nephrotic syndrome from the Gold Coast, all the patients were under 10 years of age and all had "P.malariae" in the peripheral blood.

Giglioli (1930) made a survey of kidney disease and its relation to malaria in British Guiana during 1923-29 and noted the close relationship between 'P.malariae" and the nephrotic syndrome. Subsequent reports from Sumatra, Surinam, Kenya, New Guinea and Senegal (Surbek, 1931; Lambers, 1932; Carrothers, 1934; James, 1939; and Senecal et al., 1960) supported Giglioli's hypothesis.

In Nigeria, Gilles and Hendrickse (1963) studied 113 nephrotic children, 920 ill non-nephrotic children, and 430 'healthy' village children. The vast majority of the patients were seen at or referred from the General Practice Clinic at University College Hospital and were mainly Yorubas resident in and around Ibadan, though some patients came from further afield. All the ill children (nephrotics and non-nephrotics) were collected over the same period of time, they were of similar age (2-10 years) and had a similar sex distribution. The 'healthy' children were all Yorubas living in a village 11 miles from Ibadan (Akufo), of similar age and, sex, and also examined over the same span of time. Only one thick and thin

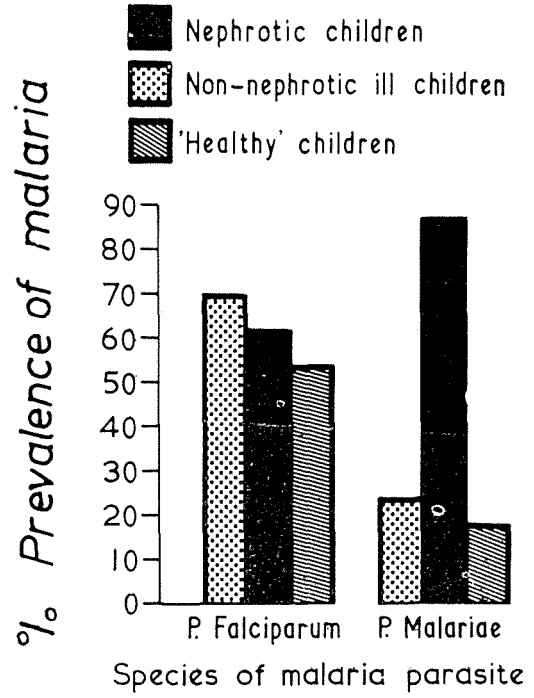

FIG. 1. Prevalence of P.falciparum and P.malariae in nephrotic children (113); non-nephrotic ill children (920) and healthy' village children (320), in the Western State, Nigeria (Gilles and Hendrickse 1963).

blood film was taken from each individual in all three groups of children. The results of this study are summarized in Table I and are shown graphically in a histogram (Fig. 1.). They show a highly significant greater prevalence of "P. malariae" parasitaemia in the nephrotic children ($p < 0.001$ for both sets of controls). Thus as many as 88% of the 113 nephrotic children examined were infected with "P.malariae" either alone or in combination with "P.falciparum," whereas, the overall "P.malariae" rate was 24% in the 920 non-nephretic ill children and 18% in the 340 'healthy' village children.

Kibukamuscke and al. (1967) have also reported a higher prevalence of "P. malariae" parasitaemia in 16 children with the nephrotic syndrome seen in Uganda.

Thuriaux (1971) working at a children's hospital in the Yemen Arab Republic reported that 10 out of 16 nephrotic children aged 2-10 years showed "P.malariae" in their blood (62.5%) while the overall prevalence of "P.malariae" in the same age group among outpatients at the same hospital over the same period (April 1967 — March 1968) was about 3%.

It is clear, therefore, that despite some shortcomings, prevalence data from parts of the globe as wide apart as New Guinea in the East and Guyana in the West, provide convincing evidence of an association between childhood nephrosis and "P.malariae" infection (Fig. 2).

The natural history of "P.malariae" infection in the Western state of Nigeria was studied by Bruce-Chwatt et al., 1953, and Gilles, 1967. It will be noted that the peak age distribution of the nephrotic syndrome in Ibadan corresponds closely to the peak age specific prevalence of "P.malariae" This complementary epidemiological evidence is interesting even though it is not conclusive.

The peak age at onset of childhood nephrosis in the Nigerian studies occurred at between five and seven years (Gilles and Hendrickse, 1963). In contrast the peak age at onset in temperate countries has been between one and three years, (Barnett et al., 1952; Lawson et al., 1960; Arneil, 1961; and White et al., 1970). It is highly unlikely that ,at University College Hospital, Ibadan, where admissions of ill children under two years of age are very numerous, nephrotics are selectively being missed.

Incidence studies:

Incidence studies based on hospital data are notorious for their bias and cannot be directly applied to the community. Thus,

TABLE I

Prevalence (%) of malaria parasitaemia in nephrotic and non-nephrotic nigerian children (aged 2-10 years).

Group	Number examined	Prevalence of parasitaemia (%)					No. parasites seen
		P.falciparum	P.malariae	P.falciparum & P.malariae	Overall P.falciparum	Overall P.malariae	
Nephrotic children	113	2	28	60	62	88	10
Non nephrotic ill children	920	52	6	18	70	24	24
"Healthy" village children	340	44	6	12	56	18	38

Overall Infection Rate :	*P. malariae*	*P. falciparum*
Nephrotic/Non-nephrotic ill children	$x^2 = 183.3$ n = 1 P = < 0.001	$x^2 = 2.3$ n = 1 P = < 0.1
Nephrotic/Healthy children	$x^2 = 177.1$ n = 1 P = < 0.001	$x^2 = 1.03$ n = 1 P = < 0.3

the incidence and prevalence of the nephrotic syndrome in tropical populations is unknown and comparisons with temperate countries cannot legitimately be made. In contrast, comparisons between data derived from hospital series in Europe and elsewhere and hospitals in the tropics, despite certain snags, may not be as unrepresentative as might appear at first. Thus, in Ibadan, 50 cases of childhood nephrosis were encountered yearly in one of the two hospitals in the city (Gilles, 1967). In Durban, where "P.malariae" does not exist, fewer than 12 cases were observed over an eighteen month period among all children attending the three largest general hospitals, one of which has a turnover of African children three times that of University College Hospital Ibadan, (Klenerman 1960; Walt, 1960). Similarly, in a series from Glasgow, where there were about 500,000 children at risk, the average yearly number of admissions with nephrosis was only ten (Arneil, 1961). Kibukamusoke (1966) has also stressed the high incidence of the nephrotic syndrome in Kampala and Lagos. It is true that hospitals such as the University College Hospital Ibadan and Mulago Hospital, Kampala, enjoy a rather special position in their local environment and may attract patients from far and wide. A similar situation however can exist to some extent in temperate countries, in relation to a renowned renal unit at a children's hospital in a big city such as London or Glasgow.

Time-trend studies:

Giglioli (1950) predicted that when malaria in Guyana was eradicated the nephrotic syndrome would become less frequent. Thirty years later, following the eradication of malaria from that country, Giglioli (1962b) reported a decline in the prevalence of albuminuria, and the virtual disappearance of nephrosis in children. Thus, in one area of the country where malaria had been hyperendemic, 108 cases of 'chronic or subchronic nephritis were recorded, mainly in children' by Giglioli between 1923 and -1929 (pre-eradication years). In contrast, in the same area between 1958 and 1960 (about 10 years after successful eradication of malaria) only 12 cases of acute, sub-acute and chronic nephritis were recorded out of a total of 6,408 admissions. There was no case of 'nephrosis'. Even allowing for the

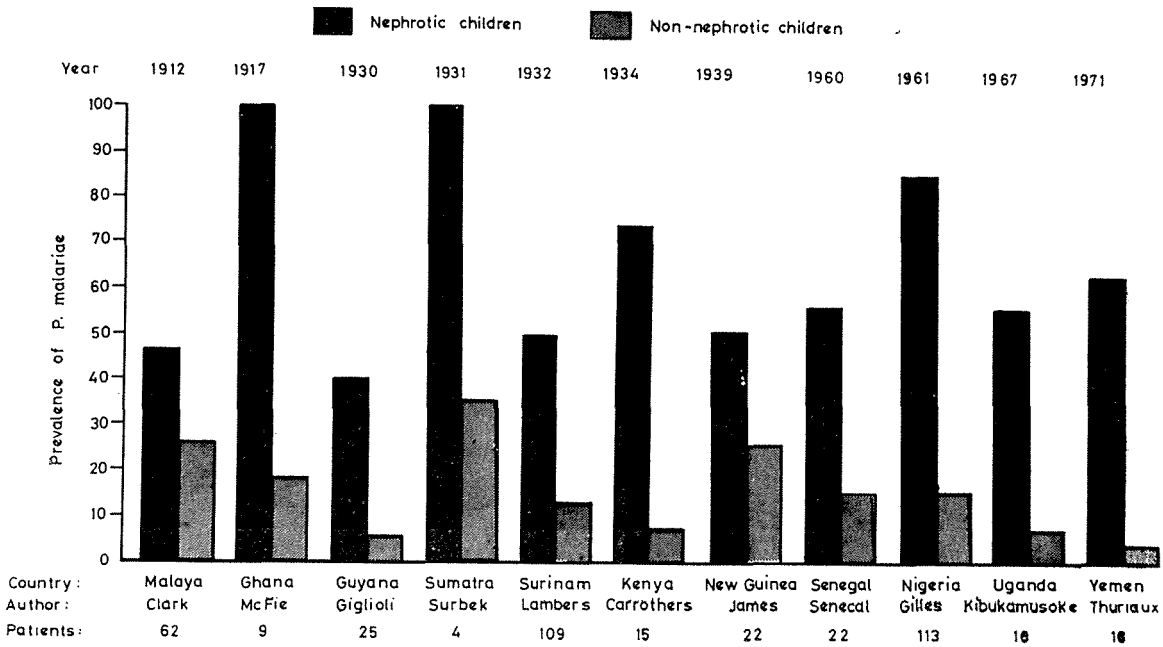

FIG. 2. Worldwide reports on the associ ation between P.malariae and the nephrotic syndrome.

relative imprecision of the renal terminology used and the lack of accurate renal morbidity data for the period between 1929 and 1958, these results can hardly be shrugged off. The possibility that 'other factors', e.g. the introduction of antibiotics and improvement in basic health services, might have been responsible for the decline, rather than the eradication of malaria, could be relevant to renal diseases such as acute nephritis or pyelonephritis, but hardly to 'nephrosis', since no evidence is forthcoming that such 'other factors' have significantly affected the incidence of childhood nephrosis in Europe and America during the past century .

In this context the observations of Carter (1961) from Freetown, Sierra Leone are interesting. He observed that in the city where malaria had been brought under control, the nephrotic syndrome was rare, although in other respects the paediatric problems resembled those in Ibadan. Unfortunately, unlike Giglioli's observations, the prevalence of the syndrome in the years before malaria control is not known.

In Ceylon, James and Gunesekara (1913) reported a high proportion of cases of kidney disease in the colony; it would be interesting to know what effect if any malaria eradication has had on the incidence of nephrosis especially among children.

Mandle (1970) has recently reported that in the thirty-year period preceeding malaria eradication in Guyana, there was a decline in deaths from all causes including renal disease and malaria, but that following malaria eradication there was a notable acceleration in the decline in deaths from renal disease and tuberculosis. The evaluation of morbidity and mortality of such time-trends of disease in the tropics are notoriously difficult to assess.

McGregor et al. (1956) followed up 52 Gambian children from birth, half of whom were protected from malaria with weekly doses of chloroquine while the other half were left unprotected. Three years later these workers were able to examine 16 protected and 13 unprotected children in detail. 61,5% of the unprotected children had "P.malariae" parasitaemia, but only one unprotected child (who had "P.malariae) had heavy proteinuria. This child had no oedema or other evidence of renal dysfunction.

If this low 'attack rate' is applicable in other areas of the tropics, community based cohorts to determine the incidence and prevalence of albuminura and of the nephrotic syndrome in persons with "P.malariae infection and controls, will be extremely difficult to construct because of the large number of children needed and the length of observation that will be required. In this context, it is of interest that over a period of 10 years Giglioli (1962a) has been able 'on more than one accasion, to follow through the different evolutionary stages of the disease from an uncomplicated and mild quartan malaria with simple intermittent albuminuria, to quartan malaria with persistent albuminuria and hyaline and granular casts in the sediment, to established nephrosis with extreme generalized oedema and ascites'.

MORPHOLOGY

The morphological changes in renal biopsies in Nigeria differ in the frequency with which the different types of lesion are encountered, from those described in non-malarious areas (Chung et al., 1970; While et al., 1970).

Thus, in Nigeria, the most common renal lesion is 'segmental capillary wall thickening of the tuft associated with a mesangial increase of PAS positive material leading to sclerosis of peripheral capillary loops." These lesions appear to progress to total glomerular sclerosis. "Minimal change' kidney, (seen in the majority of European childhood nephrosis cases), proliferative and membranous nephritis are not common.

Electron microscopy studies reveal "segmental fusion of foot processes of the epithelial cells with thickening and irregularity of the lamina densa of the basement membrane of the capillaries". Small lacunae are noted in the basement membrane. Deposits of basement membrane like material are seen in the mesangium and luminal surface of the basement membrane. The

detailed pathological appearances have recently been published and correlated with the clinical and immunological findings (Hendrickse et al., 1972).

PATHOGENESIS

Four possibilities come readily to mind. Firstly, the notion of a fortuitous association between quartan malaria and the nephrotic syndrome is highly unlikely in view of the universitality, consistency and degree of the correlation. Secondly, there is no evidence to suggest that "P.malariae" damages the kidney by direct action.

The third, and perhaps the most difficult argument to refute, is that nephrotic children merely exhibit a greater susceptibility to infection with "P.malariae". On general logistic grounds, one could argue that since "P.falciparum" and "P.vivax" are the two malaria parasites most widely distributed throughout the tropical world, it would seem reasonable to suppose that if a nephrotic were to exhibit a propensity for a malaria parasite, it would be to the more predominant rather than to the less common protozoal agent. Furthermore, no increase in the overall incidence of nephrosis in the tropics (despite the loopholes in the available data) would be expected. Finally, the results previously mentioned of malaria eradication in Guyana (despite certain flaws), together with the observations from Sierra Leone cannot easily be shrugged off as meaningless. The magnitude and exactitude of the community cohort studies that would be needed to dispose of this third hypothesis, is a daunting thought.

Fourthly, Hendrickse and Gilles (1963) advanced the suggestion that the nephrotic syndrome might be due to glomerular damage caused by the deposition of immune complexes.

IMMUNOLOGY

Preliminary evidence in support of the view that immunoglobulins and complement deposits occur in the glomeruli of nephrotic Nigerian children was presented by Dixon (1966). Soothill and Hendrickse (1967) showed that part of the complement component (beta-1-C) was found in the macro-molecular fraction of serum in affected children suggesting that it might be bound to soluble antigen-antibody complexes.

In renal biopsies from 93 Nigerian patients (50 children and 43 adults) immunofluorescence showed that immunoglobulins G and M were present in 96%, the third component of complement in 66%, and "P. malariae" antigen in 25% of cases (Houba et al. 1970). Examination of eluates from nephrotic kidney specimens confirmed that specific antibodies against "P.malariae" were present in most of them (Houba et al. 1971). The immunoglobulin deposits varied from a coarse to a fine granular pattern (Fig. 3) and the distribution of IgG sub-classes in glomerular deposits was related to the pattern (Houba and Lambert, 1974). Both morphological and electron microscope changes showed considerable variation (Allison et al. 1969; Hendrickse et al. 1972).

TREATMENT

The results of treatment of this quartan malaria nephrosis are unsatisfactory. There

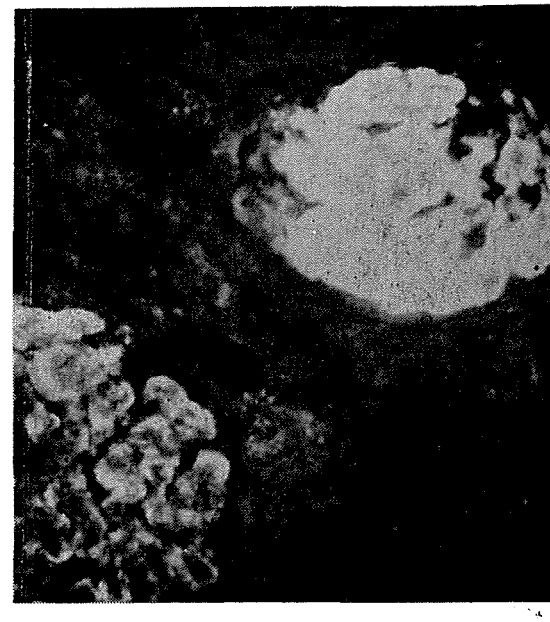

FIG. 3. Note fine granular pattern on left and coarse on right.

is no response to radical treatment with antimalarials and a poor response to corticosteroids (Adenyi et al. 1970). Good responses to azathioprine and cyclophosphamide have been reported in patients with coarse or mixed granular patterns of immunofluorescence but not in patients with a fine, granular pattern (Houba et al., 1974; Hendrickse et al. 1972).

Several important questions remain unanswered. Why do only some individuals develop the nephrotic syndrome when at some time or another in endemic areas all the children are infected with "P.malariae?" How does the lesion start? What factors are responsible for the chronicity of the syndrome? Many unsolved problems still remain over this nephropathy associated with "P.malariae" infection.

SUMMARY

There now exists overwhelming evidence of an association between quartan malaria and the nephrotic syndrome in childhood, and all the clinical, laboratory, morphological, immunological and epidemiological data available strongly support the concept of 'malarial nephrosis' as an immune-complex disease. This syndrome responds poorly to all forms of treatment which have been tried so far and usually progresses to renal failure and early death.

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THE ATTRIBUTES OF A MASTER SURGEON

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Eponymous and commemorative orations and lectures feature prominently in the activities of many academic bodies. Among those that will be familiar to my audience tonight I need only mention the Hunterian, the Harveian, the Goulstonian, the Bradshaw, the Vicary, of the old-established, and the GordonTaylor and the Watson-Jones among the newer ones. These constitute notable landsmarks in the calendars of events of the various institutions sponsoring them. The honour of being chosen to give one of these lectures is much sought after. "Si licet parvis componere magna", within the modest ambit of our Maltese academic world, I consider myself highly honoured in having been chosen to give this, the fourth P.P. Debono Memorial Lecture of the Association of Surgeons and Physicians.

In these circumstances, the difficulty of the choice of a subject induces the lecturer to seek help in studying how his predecessors have tackled the task, and in considering what the eponymy itself calls for. Thus, some of these lectures are largely and appropriately biographical in content, and others outright historical in treatment: some evoke a philosophical meditation on the more abstract aspects of a subject, while others are technical expositions of the lecturer's own special experience and interests in the field. Then there are some which, echoing Polonius's assessment of the versatile actor's gamut of the "tragical-comical-historical-pastoral", offer a happy melange. In choosing to speak of the ATTRIBUTES OF A MASTER SURGEON I have elected for the combined Philosophical-biographical approach.

Let me start by stating the obvious: I consider P.P. Debono to have been a Master Surgeon, and therefore in ruminat-

* Lecture delivered under the auspices of the Association of Surgeons & Physicians.

ing over my concept of the Master Surgeon I could, and indeed I shall, hold up to you the portrait of the man saying ECCE HOMO, and let it speak for me. But as P.P. died in 1958, and as this biennial lecture was started in 1969, the members of the audience who were privileged to know him personally must sadly and inevitably be in the minority and a dwindling band. So I shall try to tell you something of P.P. the man and P.P. the surgeon who was a Master Surgeon.

Some sardonic wit, an American no doubt, has altered the tag "De mortuis" to read "de mortuis nil nisi BUNKUM", and Samuel Johnson more elegantly says that "In lapidary inscriptions no man is upon oath." This nothwithstanding. I am confident you will absolve me from any charge of insincerity, or of fulsome flattery, as I now proceed to read to you the two obituary notices that I was painfully, yet pleasantly, privileged to write for P.P.

The first is from the Times of Malta of the 5th. June 1958, two days after he died; "The death of the Hon. Professor P.P. Debono, O.B.E., M.D., D.P.H., F.R.C.S., removes from the Maltese medical scene a Master Surgeon, and one whose name as "Pietru Pawl" has been a household word to the highest in the land as to the humblest country folk for the last thirty-five years. No man in his lifetime can ever have packed so much hard and exacting work as P.P., with his superhuman energy; and no man can ever have had more reason to be well satisfied with the results of that work, the bringing of health and the alleviation of suffering to countless thousands.

Yet he had in full measure the fine humility of the great Physician and could be far more easily drawn to speak of what he was pleased to call his "mistakes and failures" than of his innumerable and brilliant successes.

Professor P.P. Debono established Modern Surgery in Malta and his successors and pupils owe him an immeasurable debt. In his time he contended with and overcame difficulties which recent advances in medicine have greately reduced; and to the end no one was more progressive than he.

He was no mere surgical craftsman, but possessed an immense academic stature, and in his work one admired his depth and range of knowledge as much as his superb judgement and his marvellous dexterity.

His approach to surgery was lion-hearted. Hs mettle was never more in evidence than during the War when he coped with the great majority of thousands of seriously wounded persons round the clock, day after day, for month after month, while never abandoning a burden of routine surgical work and teaching that would have broken any lesser man.

The fruits of his achievement live on in the generations of doctors who were privileged to sit at his feet, for it is difficult to say whether he was greater as a surgeon or as a teacher.

As a lecturer and as a clinical demonstrator he was immensely popular and so felicitously did he combine intelligence with versatility that one learned from him much more than surgery. Though so richly endowed himself with ability he was patiently tolerant of even the weakest among his students, and he never hesitated in taking on his own broad shoulders responsibilities which were too much for his assistants. He was far from effusive by nature, but no doctor has ever been more respected, or even more truly loved by his colleagues.

If ever man died in harness, it was he, and although we shall sadly miss his ability, his wisdom, his experience and his kindliness, his host of patients and friends are happy that he went with his great talents and faculties unimpaired."

The second is from the British Medical Journal of the 9th. August 1958: "Professor P.P. Debono established modern surgery in Malta. He combined in the highest degree intellectual abilities and skilled craftsmanship, and coming to surgery by way of physiology and pathology, he proved an ideal teacher whose precept and example founded a sound surgical school in the island. His versatility was remarkable, and he had more than made his mark in bacteriology and pathology

before his superabundant energies were providentially turned towards surgery. Even in his most hectic surgical period, however, his interest in natural history never flagged, and his students habitually regarded him as their mentor in practically every subject of the medical curriculum.

During the first world war, when Malta was 'the Nurse of the Mediterranean', he was inspired by contact with Sir Charles Ballance and men of similar calibre who were treating the wounded from Gallipoli. His training in England made of him a teacher of the British school, and he was very well known to the leaders of British surgery of his time. The second world war, in which Malta occupied a most honourable front-line position, brought him the burden and the glory of treating almost single-handed the thousands of serious civilian casualties of enemy bombing; it is safe to say that no surgeon in the Commonwealth had a task of equal magnitude in operating for months and months of continuous bombardment in makeshift hospitals with the slenderest resources. Yet throughout that period he also coped successfully with routine surgery and with his teaching.

P.P. Debono was a true general surgeon of such high quality that the results of his incursion into any part of the human body could bear comparison with those of most specialist surgeons. His approach to surgery was lion-hearted, and his courage was matched by superb judgement and marvellous dexterity. He reached the peak of his achievement when he was yet denied those ancillary advances of anaesthesia and chemotherapy that we now almost take for granted. Surgery was not made easy for him, but he did seem to make it easy for others. He was magnificent in times of stress, when his own broad shoulders seemed made for the burdens of all around him; very seldom was he known to lose patience with his assistants, and never to stoop to blaming them when things were awry. He has created in Malta an example and a tradition which his pupils and successors are honoured in attempting to preserve".

I stand here before you tonight to aver that what I wrote then was true, and is still true today, and I call upon many of you here as my witnesses. At the risk of some repetition, I would like to add further touches to this personal portrait and I would even wish where necessary to paint him for you 'warts and all.'

Quite simply, my mission tonight is an exercise in Hero Worship, sincerely and unashamedly such. As we go through life, surely most of us fix (or 'fixate' if you want pseudo-psychological jargon), must pick on some outstanding contemporaries as our models and patterns. (I here deliberately omit the real Heroes of the past and the imagined Heroes of the realm of fantasy). In my surgical formation my Hero was and still is P.P. Debono. He holds pride of place even above other great surgeons at whose feet I have sat, like Grey Turner; and in praising P.P. I have always tried to pay him the tribute of that which is the sincerest form of flattery. One indulgence, however, I would crave of you — do not for an instant think that in drawing for you the picture of the great attributes of P.P. I have ever been tempted to look into a mirror!

The Master Surgeon is no Master unless he is an inspiration to all about him. He must be a shining example, he must light the vital spark in others. He must be a Father of surgeons, a creator of a school of surgeons, of a dynasty of surgeons. I have seen somewhere a table showing the unbroken chain of master-pupil succession among the great surgeons of Central Europe from the late years of the last century well into the second half of this, from the Czernys and the Bilroths to our own contemporaries. Nearer to us in time and place and personal contact, Sir Charles Illingworth has produced to date some 12 or 15 eminent surgeons holding professorial chairs. The greatest of the Master Surgeons will do this consciously and deliberately by training their aptest pupils; but any master surgeon will do it unconsciously by mere contact and insipiration. P.P. Debono belongs to this second category. There are many motives or reasons some worthier than others, which induce one to take up surgery as a

career; the best and highest of these is the intrinsic merit of the discipline as one of the most soul-satisfying forms of medical practice. In Surgery the man with the right attributes should find his fulfillment, his justification for living and working. This conviction can be gained only by seeing surgery practised by a Master. But no one who is a dull clod can be a Master Surgeon. His belief in and his dedication to surgery must be of the highest order. Sir James Paterson Ross has written: "Although the pupil can benefit greatly from his master's technical skill, he will learn even more from his behaviour, the manner in which he conducts his daily duties. The pupil absorbs from his master the habits of thought, technique and of personality. Often enough we know the Master of the past generation by the pupils of the present." The surgeon who leaves behind him no tradition, no self-confessed pupils to carry on that tradition, is no Master.

You will have gathered that I do not place as the most eminent attribute that excellence in craftsmanship which we expect of any great surgeon. It is the best attributes of Soul, Spirit, Character, call it what you will, that raise the greatest above the merely great. Special character facets distinguish the surgeon from other doctors: much has been written on this topic, notably Ian Aird's slim volume "The making of a surgeon". Let it suffice to say that you should take all that, raise it to the superlative degree, and you have what makes the Master Surgeon.

After Inspiration I shall choose to dwell on the Dedication of the Master Surgeon, by which I mean his willingness to give himself to his patients entirely and wholeheartedly.

Surgery is not the easiest, it is not even the most lucrative way of making a living — but it is the most demanding in the best sense of the word. to the dedicated surgeon, it is his way of life. It demands sacrifice of time and leisure, and peace of mind and sleep, and family and friends, and of much else that sweetens and savours life. Its demands on the Master Surgeon can be exorbitant, being commensurate with his own great responsibilities before God and men. Fame is NOT the only 'spur that the clear spirit doth raise to scorn delights and live laborious days.' For most Master Surgeons their calling means a life-time sentence of hard labour, with little hope of remission even for good conduct. The amount of work that P.P. Debono managed to get through consistently for years and years was so prodigious as to verge on the incredible.

Throughout practically all his career, he had to cover the surgical needs of the whole population of Malta and Gozo, sharing the burden most unequally with three other surgeons, none of whom engaged in the major surgery that he excelled in. It was only in the last 5 or 6 years of his hospital practice that he shed Orthopaedics into the willing and able hands of Alfred Craig, and that I began to take a fair share of other major general surgery off his broad shoulders. You must remember that this work-load included all emergency surgery — there simply were no resistrars between the consultant and his raw housemen in those days! To be sure, the range of major surgery was somewhat more restricted than it is now, but it was not very narrow and the essential surgery got done. Also even in waiting-list surgery like that for hernias, P.P.'s was the lion's share. Of course, part of this intolerable burden was of his own making, since he could not or would not delegate work even to his staff colleagues, let alone to the smaller fry. On one occasion, Dr. Charlie Podesta as P.P.'s right-hand man, general factotum, anaesthetist and resuscitator, and myself as favoured houseman, were so overcome with the windfall of being given a circumcision to do, that we had to share the actual excision and suturing. And it was not unknown for certain notorious tough characters among the male nurses, like 'it-Tobby' and Manwel Zerafa to make a surreptitious gash into a superficial abscess and then report 'Infetahlu, sur Professur!! Once PP tried to fend off the complaints of a patient awaiting a much-postponed prostatectomy with the excuse that, the man being grossly obese, P.P.'s finger was too short for the job;

whereupon the patient burst out "Good God, am I waiting till your finger grows longer?!" I do believe that if the one and only E.N..T. Surgeon in Malta had not been his own brother, P.P. would have removed all the tonsils on the island as well !!

This formidable workload was only half the story — P.P.'s private practice burden was enough for six ordinary mortals. Not only was much of the operating conducted on the kitchen table in the private homes, even in the farmhouse, sometimes (not always) with general practitioner assistance, sometimes (not invariably) plus a so-called nurse, but he was at the beck and call of every doctor in Malta and Gozo for domiciliary consultations, at a time when it was unthinkable for anyone to hazard coming to hospital without such prior consultation. Then at the Blue Sisters' Hospital on several afternoons a week, and late into the evenings, as I well remember from the period when I was his personal assistant, he would take into his stride 3 or 4 major abdominal cases, with 6 or 7 hernias thrown in for good measure.

I have called this Dedication, ladies and gentlemen. You can also call it Stamina, not just physical but above all psychological toughness, the durability and the resilience of steel.

I firmly believe that the Occasion calls forth the Man, and that of all occasions War is the greatest selector of Supermen. The first World War launched Debono into Pathology, and possibly turned his thoughts to Surgery; its aftermath, the Influenza pandemic, removed from his path a possible rival, and he seized his chance with both hands. In the second World War, on the civilian medical war front, Malta was supremely fortunate in having two first-class men at their peak — Professor A.V. Bernard for preparation and administration, and P.P. Debono to deal with the surgical casualties. I leave for another occasion an account of War Surgery as we learned it and experienced it in Malta from 1940 to 1943, but I must repeat that even for sheer volume of work, and high-class work at that, P.P. must have been unmatched in most parts of the world ravaged by the conflagration. This was his finest hour — and what an interminably long hour it was. In my judgement, Debono of Malta during the War was not just a Master, but a GRAND MASTER, as great as La Valette!!

As I would have you see the whole man, by way of contrast I shall say what little I know of P.P.'s leisure pursuits, for even he did not perpetually breathe the air laden with ether fumes or pungent with the reek of BIPP. I suspect that most of his leisure time was taken up by looking after his not inconsiderable property estate! Some of this was farmland at Manikata, and he delighted in the company of farmers. He was a good judge of agrarian produce. He kept parrots and other livestock, not all edible. His knowledge of Natural History was wide and deep, and he was a collector in a rather desultory way. He snatched time for the occasional game of bezique or bridge. I do not think he found enough time for much general reading; I can remember him making only one literary reference, and that to Flaubert's 'Salammbo', a puerile pseudo-historical exercise in technicoloured violence quite unworthy of the author of 'Madame Bovary'. In 1947 P.P. made an unexpected diversion into the murky atmosphere of politics, an aberration which I did not regret as it helped me to take over most of his major surgery! It s said that at a public meeting in Rabat he ended his peroration with the appeal "O Sinjur, tihom id-dawl, biex jivvutaw ghal Pietru Pawl". In his brief spell as Minister of Health he introduced some worthwhile reforms, and then he was one of our better Speakers.

The Master Surgeon is obviously marked by destiny to become a Leader, a Captain. His intrinsic merits bring him to the top and keep him there. He may be "primus inter pares", but there is never any doubt of his primacy. Being human, he may sometimes develop into a despot and a tryrant, as Sauerbruch did — but far more often he exercises his authority justly and fairly. The stress of critical decision and hazardous action in major surgery calls for a Man of Iron. As he stands over the body of his patient fighting off

Death with his own two hands, the surgeon can be excused if he shows not only a certain greatness of gesture but even a degree of grandiosty, provided that this comes naturally and is not an affectation put on for an audience. No true surgeon stoops to displays of temperament or to prima donna "attitudes — but the Master Surgeon often finds himself cast in the rôle of the gifted actor responding to the high drama of surgery. Panache is what many master surgeons exhibit — but that does not mean that they are all flamboyant extroverts. It means that they are obviously in command of the situation, and just as obviously the right men to be so placed. The surgeon under stress must, above all other attributes, show Equanimity, which is not quite the same as Osler's 'aequanimitas' but a moral quality just as beautiful even when translated into the modern slang of Unflappability!! When life is at stake, it is this quality in the surgeon that usually tilts the balance in the patient's favour. Everyone here who worked with P.P. knows that he was ALWAYS in command of the situation, that he was NEVER dismayed or distraught.

A man is great only in proportion to his awareness and acknowledgement of his own weaknesses and limitations. The Master Surgeon is greatest when he recognises and admits his mistakes and failures — indeed he would be no master at all if he failed this crucial test of character. He who by his superb gifts is so well placed to see the deficiencies of others, must first and foremost and above all see his own. In this, as in so many other things P.P. set us a fine example.

The Master Surgein must almost invariably be a great Teacher. It is through his teaching that he spreads his influence and perpetuates his talents, surely a legitimate ambition, even an obligation, of the gifted Superman. The method of this teaching may vary, but it is always of the highest quality. P.P. Debono was a superb teacher. In the lecture room he used the briefest of headline notes to guide him for continuity and comprehensiveness in delivering lectures characterised by fluent language, striking emphasis, clarity, memorable phrasing and particularly by practicality and common sense. He concentrated on what the undergraduate needs to know of the common and important conditions. He had a gift for communicating the principles and the spirit of the subject, rather than the mere details which can be found in any textbook. Indeed, the notes I made from his lectures were superior to any textbook then available and I still find valuable use for them today. As a bedside teacher, whether at formal clinical lectures or on ward rounds, he was yet more fascinating. The great teacher transmits the fruits of his own experience and of the wisdom of others. P.P.'s endowment from both these sources was rich, wide, deep and up-to-date. In 1940 he was teaching us and applying to his patients with war injuries, the principles deriving from Trueta's experience in the Spanish Civil War. His teaching and practice on fractures was inspired by the most recent writing of Bohler and Watson Jones. Crohn wrote on regional ileitis in 1932, and P.P. was telling us all that was known about it in 1941. The credit goes to P.P. that his pupils needed to add little to the rich store he had given them so as to cope successfully with the hazards of the Fellowship examination. When I look back at topics like hiatus hernia which did not feature prominently in his teaching, I realise that he was handicapped in diagnostic aids; and of other problems like cancer of the lung and diverticular disease of the colon, I am certain that these were not as prevalent in Malta then as they are now. But P.P. gave his students all he had, and that was superabundance. He was original and 'avant garde' in some of his concents — he suspected the existence of the diabetic autonomic neuropathy that is such a 'new' topic these days, and I found in England in 1945 that his ideas on gangrene in diabetics were regarded as novel and valuable. His versatility knew no bounds — he knew more about leprosy than anyone in Malta, and possibly more about amoebiasis than anyone in Europe. To us he was our "universal Doctor", the very compendium of all medical teaching, a polymath. He taught us 'rag and-bottle' anaesthesia with

Professor P.P. Debono

both ether and chloroform where his experience and mastery ensured safety, while with spinal anaesthesia in thousands of cases he very seldom failed. In communicating with patients or students he would put things in a nutshell, with terse and vivid expressions sometimes aphoristic in quality, but more often earthy and homely. To a man with peripheral arterial obstruction he would say "You can choose — either you cut your smoking, or I cut off your leg." When tapping a hydrocele for a farmer, he would say "that fluid makes a good fertiliser for your plants',, and we students would ever remember it must have some nitrogen content. Speaking of excision of lymph nodes from the neck, he would warn "This is not an operation to tackle in the back room of a dispensary." He may not have invented the term "abdominal policeman" for the omentum, but I feel sure it was he who said that unlike some constables it never moved AWAY from a trouble spot. Likewise, I am not sure that he originated the expression "The principle of Mohammed" for collapsing the rigid chest wall onto an inexpandible lung, but he certainly impressed us deeply with the concept. On cancer he said that it "went berserk" if interfered with by partial removal — not so the tuberculous lesion, where the 'vis medicatrix naturae' could be trusted to deal with residual disease. And what could be more vividly memorable, though gastronomically deterring, than his description of the faeces smeared with blood in cancer of the rectum as "Iz-zalza fuq il-bragoli".

It is a great pity that his wealth of knowledge and experience can find perpetuation only through the transient medium of his pupils, since he left all too little in writing. However, my own students will vouch for me that I enever tire of preaching 'the gospel according to P.P.' — and I can modestly claim that I have now preached it to several generations since P.P. chose me as his Demonstrator in 1944, a year and a half after I had 'chosen' him as my first Chief immediately on qualifying. He taught us to keep good case histories, and particularly with his war casualty records he started the rudiments of a central filing system — we have not progressed much at St. Luke's since his day. He was a good organiser, and would have been a better one if he did not have so much to do with scanty assistance: even he, a formidable bulldozer in action, was not immune from the frustrating shackles of bureaucracy. Like every great Captain, he was a good judge of the worth of every member of his team; as brash and cocksure tyros we learned from P.P. proper respect for the diagnoses of certain general practitioners whom he himself rated highly. He picked Dr. Natu Zammit for training in Radiology, to become the confident, competent colleague we owe so much to; and he pushed Dr. Pep Darmanin Demajo into self-taught anaesthesia on discerning his technical aptitude, resourcefulness and composure under stress which is as vital to an anaesthetist as to a surgeon.

When due acknowledgement has been made to the superlative intellectual attri-

butes of the Master Surgeon in the Science of Medicine, it must be admitted that he has to pass brilliantly in the crucial test of the Art or craft of his calling. The use of the Healing "Hand" is of the very essence of Surgery, even etymologically, guided though that hand must be by head and heart. The Master Surgeon to fulfill his high mission, must be an outstandingly good operator producing consistently good results. There are many widely different manners of operating, and each of them is appropriate to the surgeon concerned and to the operation itself. The Master Surgeon is usually versatile in technique, and always adaptable to the circumstances of the particular case in hand. At most times the meticulous control of bleeding is essential — but there are moments when the surgeon has to be 'bloody, bold and resolute'. It is fashonable nowadays, particularly among those who cannot achieve it, to decry speed in operating, or at least to pretend that there is no need for it. But judicious speed every day saves as many lives as are sacrificed by indecisive dawdling, and the really good surgeon who knows his anatomy and knows his own mind can smoothly and effortlessly attain the ideal combination of delicacy, neatness, accuracy, safety — and speed! I think that you will now need no telling that P.P. Debono was brave and was fast! Patients or their doctors often can, and I think they should, choose their surgeon according to the type of operation they need — I shall only say that if I were bleeding furiously or if I harboured a formidable tumour, I would want a P.P. Debono to operate upon me. Obviously the Master Surgeon will master difficulties that deter or defeat the lesser man.

P.P. was of the true bread of general surgeons in all-round confident competence. I would now like to illustrate this facet of his work in two very different fields — first, with the humble but very necessary operations for Hernia. I doubt if any surgeon in any part of the world had a vaster experience or better results than P.P. had. He did not choose his cases: the majority were labouring men, well advanced in years, with hernias of some age too. Of huge irreducible hernias he would say that the contents had been exiled so long from the abdomen that they had 'lost the rights of citizenship.' I attribute his good results to the stress he laid on a correct anatomical assessment of the structural defect and on the adaptation of the method of repair accordingly. He graphically illustrated this by saying "If you have a small hole in your sock you stitch it; if it's a larger hole you darn it; if it's a very large hole you patch it." Long before Lytle's anatomical writings on the internal inguinal ring, P.P. evolved his repair of that site with a method that I always demonstrate to my assistants as Debono's U stitch. P.P. used for repair a pedicled strip from the edge of the external oblique aponeurosis, and he invented a special instrument for it on the Reverdin principle which was much superior to Gallie's needle. This technique and his method for direct hernias deserve immortalisation as 'Debono's operation' rather more than several eponymous operations I could name.

P.P. was nothing if not boldly progressive and ambitious, so it was natural for him in his later years to take up the challenge of Thoracic Surgery. At first this meant solely operations for pulmonary tuberculosis, and when I was a student in the war years he was already doing many successful thoracoplasties. In the aftermath of war there were so many cases, and the general standard of treatment at the old Connaught Hospital was so poor, that the Colonial Office and the Nuffield Trust gave high priority to providing staff and equipment to tackle the scourge. I was sent in 1946 to train under Holmes Sellors and Vernon Thompson at Harefield Hospital , and there P.P. came too on a brief visit to see the modern thoracoplasties as modified by Semb and by Price Thomas and by my two masters. When I returned to Malta I joined P.P. as his junior partner and we set up the nucleus of a team operating at both the Connaught and the Central Hospital. Somewhat to my disappointment, until his retirement in 1950, he still went on doing all the thoracoplasties, much better and much more safely,

— but he did delegate to me all the other types of operation of those days, including the delicate and tedious Jacobeus pleural adhesion sections. I suspect that this was not from any feeling that he was too old a dog to learn new tricks, but because he relished more the large and spectacular operations. As he often told me, he "felt happier and safer handling a knife than a syringe." He left too early to undertake lung resections for tuberculosis, and indeed when I myself took these up after my long stint at thoracoplasty, I was soon happily 'put out of busness' by the advance of chemotherapy. However, in 1947 at the Bugeja emergency Hospital, P.P. had achieved his ambition and made Maltese medical history with the first pulmonary lobectomy by dissection. This was for a chronic abscess in a young woman from St. Paul's Bay, and was a complete suc cess. I was privileged to assist him, and "Dede" not only puzzled out the complexities of controlled respiration but had to fashion his own endotracheal tubes out of ordinary rubber tubing! Resection for cancer of the bronchus was naturally P.P.'s next target, but success eluded him, and it was not until 1953 that I did our first successful pneumonectomy at St. Luke's, with the traditional beginner's luck and survival of the patient for eight years! Spurred on by my accounts of what I had seen Grey Turner achieve at Hammersmith, P.P. could not rest without tackling the cancerous oesophagus, and he made the attempt, with me assisting and Dr. Richie Casolani anaesthetising in 1948 at the Blue Sisters' hospital, unfortunately without success; I was more lucky with my first case in 1951 at the Central Hospital. Finally, many of you will remember from Dr. Paul Cassar's fine account in the last Memorial Lecture, P.P.'s spectacular crowning glory with the successful ligation of a patent ductus arteriosus.

Ladies and gentlemen, when today we look at what P.P. Debono and his like achieved in their time, lacking all facilities we now enjoy, we must whole-heartedly proclaim: "There were GIANTS in the land, in those days"!!

As I look upon, and look up to, the **MASTER SURGEON,** he who stands in the vanguard of the eternal battle against the Captains of the Men of Death, I ask with Wordsworth:—

"Who is the Happy Warrior? Who is he
That every man in arms should wish to be?
— It is the generous Spirit ———
Whose high endeavours are an inward light
That makes the path before him always bright:
Who, with a natural instinct to discern
What Knowledge can perform, is diligent to learn:
Who, doomed to go in company with Pain,
And Fear and Bloodshed, miserable train!
Turns his necessity to glorious gain!
In face of these doth exercise a power
Which is our human nature's highest dower:
Controls them and subdues, transmutes, bereaves
Of their bad influence, and their good receives:
By objects which might force the soul to abate
Her feeling, rendered more compassionate
———————————"

Ladies and gentlemen, **PETER PAUL DEBONO,** the **MASTER SURGEON** was the HAPPY WARRIOR.

SKIN CANCER (EXCLUDING MELANOMA)

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SUMMARY:

A brief review is given of the incidence, aetiology, and the pathological presentation of the commoner forms of skin cancer with particular reference to its occurrance in the Maltese slands. Methods of treatment are discussed.

EPIDEMIOLOGY and AETIOLOGY:

Skin cancer accounts for a large percentage of malignant disease in general. Most published figures about incidence are bound to be inaccurate and incomplete because many skin cancers are treated in private clinics without histological verification and without being notified. However, if the data available in Cancer Incidence in Five Continents, Volume 2, are re-arranged (Gordon & Silverstone), it is possible to show that when persons of Celtic and Anglo-Saxon ancestry are exposed to sunlght in different zones of lattitude from high to low, the incidences of skin cancer range from 5 per 100,000 in Sweden to well over 100 per 100,000 in Queensland, Australia. On the other hand, members of the black races, who as a general rule live in the lower lattitudes, have a skin cancer incdence of less than 5 per 100,000 of the general population. This also applies to the Japanese whether they are domiciled in Japan or in Hawai.

Examination of the Malta Cancer Registry records show that during the five year period 1969 to 1973 a total of 448 primary skin cancers (excluding melanomas) were registered. his gives an annual incidence of 27 per 100,000 of the general population. Table 1 compares our own incidence with that obtained in some areas of the world which are warm and sunny and to which people from the British Isles and Northern Europe migrated (Doll, Muir & Waterhouse, 1970).

There are obviously certain factors, partly genetic and partly environmental, which influence the development of skin cancer. Silverstone and Searle (1970) showed very clearly that reaching a ripe old age and having a history of keratosis are the factors most likely to be associated with a positive history of skin cancer. Other factors are a susceptibility to sunburn and residence in the tropics as against the subtopics. Outdoor occupation and a Celtic ancestry exercise less influence than is usually believed. No such scientific influence than is usually believed. No such scientific aetiological studies have been carried out in Malta. Examination of the

TABLE 1

Skn Cancer-Annual incidence per 100,000 by sex.

Country	Male	Female
South West England	28	15
Malta	40	16
South Africa, Cape Whites	133	72
Texas, U.S.A., Non-Latins	168	106
Queensland, Australia, Whites	265	156

Malta Cancer Registry records however does confirm that 89% of all the skin cancer patients were above the age of 50 when diagnosed and that there was an associated keratosis in over 60% of them.

Multiple skin cancers are common. Bray (1939) noted that out of every 100 patients with skin cancer at the Sidney Hospital Radium Clinic, 30, after a period of time, had to be treated for new lesions. Up to date, of all the patients with skin cancer treated at our Radiotherapy Department between 1969 and 1971, 12% have already required treatment for other new skin cancers. These percentages do not, of course, refer to patients originally persenting with multiple lesions.

PATHOLOGY:

The vast majority of skin cancer are basal cell or squamous cell carcinomas. The basal-squamous cell carcinomas should, to all intents and purposes, be considered as squamous cell cancers as they are of equal potential danger. Adenocarcinomas arising from the skin appendages are extremely rare. The exact relative proportion of the various histological types is uncertain due to the fact that in very few large series have all the lesions been histologically examined. Lighthouse, Korpf & Garfinkel (1965), have shown that a clinical diagnosis, even in experienced hands, of basal cell carcinoma is found on histological examination to be squamous cell carcinoma in up to 25% of cases. In our own series, out of a total of 448 consecutive skin cancers, the ratio of Basal cell to Squamous cell cancers was as 2.56 is to one. Table 2 gives a breakdown of the various histological types. It must be appreciated that these figures are partly based on a clinical diagnosis as histological confirmation was only obtained in 64% of cases.

Metastasis from squamous cell skin cancer to regional lymph nodes is not uncommon. Distant metastasis is much rarer; in our own series it was only recorded in one individual. Basal cell cancers can very rarely metastasize. Burman (1969) surveyed the world literature and found a record of about 50 patients in whom there was histological confirmation of this. In our own small series none of the Basal cell cancers metastasized either to glands or distantly.

Deaths from skin cancer are now rare. The case mortalty rate is said to be less than 1%. In our series there were only two fatalities. One was in an old lady with an advanced B.C.C. which had eroded most of the nose and facial bones who died of a massive haemorrhage; the other death occured in a man with S.C.C. who after three years of treatment for his primary lesion developed metastasis in the cervical and supraclavicular nodes and later generalized distant metastasis.

TREATMENT:

1. **Prevention:**

Prevention must be based on two premises:

a) Ultraviolet radiation is the major aetiological factor in the development of skin cancer (Urbach, 1969).

b) Normal persons show a wide varia-

TABLLE 2.

Skin Cancer Pathological types by sex.

	Male	Female	Both Sexes
Squamous Cell	96	28	124
Basal Cell	196	105	301
Basal-Squamous Cell	16	5	21
Other	0	2	2
Total	308	140	448

tion in their degree of susceptibility to developing skin cancers. Fitzpatrick, Pathak & Lane Brand (1972) mention the following characteristics which predispose to susceptibility:

In Children: Light skin that sunburns easily and does not tan.

Freckles.

Red Hair.

In Adults: Light skin that sunburns easily but does not tan.

Freckles.

Red hair.

Signs of solar degeneration such as solar keratosis, talengectasis, connective tissue degeneration and solar or 'senile' lentigo.

Many skin lotons or creams which screen off the ultraviolet radiation from the sun are available. Most of them contain para-aminobenzoic acid in ethanol. Physicians should learn to recognize those persons who are most at risk of developing skin cancer and advise them to use one of these preparations from early youth. Patients who already have solar keratosis should have this treated with a 5-Fluorauracil skin preparation once their keratosis is cured, they should be encouraged to apply an ultraviolet barrier cream prophylactically.

2. **Surgery and Radiotherapy:**

There is no doubt that both surgery and radiotherapy can effectively cure the vast majority of skin cancers. Whether surgery is superior to radiotherapy or vice-versa is not a valid subject for debate. Both modalities have their indications and contraindications the choicie of one or the other or of a combination of both depending on a large number of factors such as age of patient, size and site of the lesion, its dept of infiltration and the quality of the skin around it. Perhaps the most important factor is the skill of the surgeon or the radiotherapist and the amount of time, care and individual attention which they are prepared to devote in order to achieve the final aim which is the cure of the patient of his disease wtih as little discomfort as possible and with the likelihood of producing the best possible cosmetic result. Both surgeons and radiotherapists should be aware of their limitations and they should discuss new patients jointly if this aim is to be achieved.

The old idea that one should in all cases "first try radiotherapy as surgery could always be used later if this fails" was exploded by Rank who showed that out of 226 lesions treated primarily by surgery the recurrence rate was only 1.3% whereas in 197 recurrent lesions (mostly radio— therapy failures) the recurrence rate was 15%. The opposite also holds good in the sense that radiotherapy is less successful when dealing with surgical failures due to the diminished vascular supply.

Small, discreet, superficial basal or squamous cell carcinomas can be destroyed equally well by excision or by radiotherapy. On the whole surgery is to be preferred because it is cheaper, quicker and also because the surgical scar will withstand further exposure to the atmosphere better than a radiation scar. This is a most important factor in the younger patients. Old patients may find it difficult to remain still during radiotherapy and they may also find it difficult to attend for repeated daily treatments.

Larger lesions and especially those lesions which occur in sites such as the eyelids, the periorbital area and the medial triangle of the cheek are usually dealt with by radiotherapy. Here surgical excision would almost invariably require plastic repair. This also applies to the external nose if the lesion is larger than a few millimetres. Surgery is usually to be preferred in areas such as the perineum, the vulva, the scrotum and the hands and feet as these tolerate irradiation badly.

Where good plastic surgical facilities are available, the large deeply penetrating tumours should be dealt with surgically as the long term results, both curative and cosmetic, are likely to be better. Where no such service is available, radiotherapy using deep X-rays or in some instances telecobolt, can give very gratifying results.

CYTOTOXIC DRUGS:

Falkson and Sculz in 1962 observed that solar keratosis disappeared in patients

receiving 5-Fluorouracil systemically for advanced carcinomatosis. This lead to the development of a 5-F..U. cream for topical application. We have now been using this cream selectively for 5 years and like Chiaffitelli and many others have found it to be most effective in the treatment of solar keratosis especially when there are multiple lesions; we have also found it useful for dealing with multiple superficial basal and squamous cell carcinomas, curing at least 50% of them.

Bolisario claims a 92% overall cure rate for basal cell carcinomas using a mixture of Colcemid, triodolciran and methotraxate in ointment form. He also claims to obtain excellent cosmetic results. We still prefer to use conventional methods (surgery or radiotherapy) for the solitary infiltrating lesions and only use 5-Fluorouracil cream for superficial but extensive ulcers and for the superficial multiple ones. The method of application of the cream is most important. The patient must be instructed to apply it over and around the lesion twice daily; he must wipe of the surface ointment and the debris from the lesion with a clean piece of gauze prior to each application. Any crust which is present must be removed from the surface of the ulcer at frequent intervals so as to allow the cytotoxic cream to come into close contact with the malignant cells. Unless these instructions are followed religiously it is unlikely that healing will occur. The average time needed for complete destruction of the carcinoma is three to four weeks. A dry, or occasionally a moist erythema, similar to that obtained during radiothery, occurs; if severe, this is easily controlled by the application of a steroid ointment.

CONCLUSION:

Although skin cancer notifications are bound to be erratic and incomplete, it can be stated that its incidence amongst the white races increases as the geographical location moves to a lower lattitude. In Malta skin cancer is commonly found in the fairer skinned, mostly outdoor labourers such as farmers, fishermen and stone miners. Basal cell carcinomas in Malta, as in most other countries, are much commoner than squamous cell cancers; this is more evident in females. Treatment methods include prevention, surgery, radiotherapy and in selected cases, cytoto xic topical application.

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THE OPERATION OF A VENEREOLOGY CLINIC IN THE WEST END OF LONDON

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As a result of the Venereal Disease Regulations of 1916, facilities were established in Great Britain for the free and confidential treatment of venereal diseases, divorced from Dermatology Clinics. These Venereology Clinics became the responsibility of Regional Hospital Boards after the National Health Act of 1946. James Pringle House is one such outpatient clinic of the Middlesex Hospital, situated in the heart of London. The tendency nowadays is to refer to such clinics as 'Clinics for Genito-Urinary Medicine'. This helps to remove the stigma from the diseases, and encourages patients to come forward. Whether this name describes more aptly the kind of work undertaken there is debatable however. Out of approximately 10,000 new patients seen every year, about one quarter suffer from Gonorrhoea or Syphilis. The bulk of the remainder is made up of people suffering from Non-specific Genital Infection, Candidiasis, and Trichomoniasis, in that order of frequency. Despite a sizable Maltese community in the adjoining area of Soho, the number of fellow countrymen presenting at the clinic is minute.

Reception

The doors of the clinic are open to the public from 9.00 a.m. to 6.00 p.m. Patients are referred by general practitioners, by consultants from outside hospitals, and by family planning clinics. Many come of their own accord, and some arrive wth a contact slip given to them by a sexual partner who is infected and is being seen at a Venereology Clinic.

Most patients are seen by appointment. As a rule new patients are alloted 20 minutes, and followup cases 10 minutes. However a number of patients without an appointment attend each day demanding urgent attention. These are slotted into gaps created by patients with an appointment who do not turn up, on a first come first served basis. As the number of patients who attend without an appointment roughly equals the number of defaulters, the clinic manages to run smoothly.

New patients are interviewed by the receptionist. Details of their name, sex, age, address, nationality, occupation, and method of referral are typed in a case sheet. This is given a progressive reference number, and is available to the doctor when he is ready to see the patient.

The Clinics

At all times three doctors are available in the male clinic and two in the female. In addition to the relevant medical history, details are taken of recent and past sexual intercourse, going back three months. This must be taken further back if the patient is suspected of having harboured secondary or infectious latent Syphilis, because all contacts must be chased up and examined. As explained later this is mainly the responsibility of the Contact Tracer, but the doctor is interested in the nature of the intercourse and precautions taken, because this influences the examination and samples taken. The sheath is said to decrease the risk of contagion if used properly (Richards R.N., 1974). Early Syphilis in London nowadays is predominantly a disease of promiscuous homosexual men (British Cooperative Clinical Group, 1973). Passive homosexuals should undergo proctoscopy and have rectal swabs taken. A throat swab is indicated if orogenital sex has occurred wtih an infected partner. And so on.

In the short time available the general physical examination must obviously be orientated towards the manifestations of sexually transmitted diseases. The responce of the pupils to light and accomoda-

tion is noted, the reflexes are elicited, the appreciation of vibration sense tested for, and the presence of skin rashes, enlarged glands, and ectoparasites looked for. Special attention is paid to the external genitalia, and to the oral and anal orifices, being on the lookout for discharges, erosions, ulcers, and warts. The respiratory and cardiovascular systems are assessed.

Female patients are examined with a bivalve speculum. The condition of the vagina and cervix are noted. The following specimens are obtained with a sterile platinum loop:

i. Specimen from the posterior fornix. This is smeared with a drop of saline on a slide for the dark ground microscopy of Trichomonas Vaginalis, and is also inoculated into liquid Feinberg-Whittington medium for culture of the same organism.

ii. Specimen from the lateral fornix. This is smeared on a slide and Gram stained for the direct microscopy of Candida, and is also plated onto Sabauraud's medium for culture of the same organism.

iii. Specimen of mucus from the cervical os. This is smeared on a slide and Gram stained for the direct microscopy of the Gram negative intracellular displococci of Gonorrhoea, and is also plated onto Columbia Agar medium for culture of the same organism.

iv. Specimen from the urethra. This is processed like the cervical specimen.

Suspicious ulcers are squeezed at the base, and three smears made from the serum which exudes with a drop of saline on a slide for the dark ground microscopy of Treponema Palldum. Cervical smears for the early cytological changes of cervical cancer may be performed with an Ayre spatula, especially in high risk groups. A bimanual pelvic examination is done at the end to look for signs of pelvic disease. Disposable polythene gloves are worn throughout the external genital and pelvic examinations.

The slides are processed, examined, and reported on the spot by nurses who become proficient at spotting the causative organisms by dint of doing it all the time. They also report on the presence of polymorphonuclear leucocytes, epithelial cells, and other organisms in the stained smears.

In the male clinic the nurses oblige by taking the specimens also. Specimens from the urethra are plated onto Sabauraud's medium, inoculated into liquid Feinberg-Whittington medium, plated onto Columbia Agar medium, and smeared on slides for staining and dark ground microscopy. A two glass urine test is performed for threads or flakes in the first glass when urethral discharge is scanty, and cloudy urine in both glasses is posterior urethritis. The urine is also examined for protein and glucose.

The doctor performs proctoscopy on passive homosexuals. Specimens from rectal discharge are taken and processed as for urethral discharge, except that culture of the Gonococcus is done on the more selective Thayer-Martin medium. If indicated, the throat is swabbed with cotton wool on a stick and the specimen plated onto the same medium.

Blood samples for serological tests for Syphilis are taken from all patients on the first visit. Disposable plastic syringes are used throughout, and disposable polythene gloves are worn when drawing blood from patients who have had serum hepatitis. If requested, the result of the Venereal Disease Research Laboratory test is available within minutes using a Manual Slide Test.

Within minutes of the first examination, therefore, laboratory findings are available to add support to a diagnosis of Candidiasis, Trichomoniasis, Gonorrhoea, early Syphilis if treponemes are present in the lesions, and, by exclusion, Non-specific Genital Infection. The patient can be treated and followed up accordingly without delay.

The Laboratory

The rourine serological tests for Syphilis undertaken in the laboratory are the Venereal Disease Research Laboratory (VDRL) test, and the Treponema Pallidum Haemagglutination (TPHA) test.

The VDRL test, which is a flocculation test using a cardiolipinlecithin-cholesterol-carbon antigen (Searle Diagnostic), is performed on an Auto-Analyser on neat

serum, and in titre if positive. Quantitative tests are important because they provide a standard against which further change or lack of change may be compared. The VDRL test measures a reagin in the serum, and is prone to give both acute and chronic Biological False Positive results. It takes one technician one morning to supervise the test on about 100 sera obtained the day before and stored in a refridgerator. The same technician does other laboratory chores concurrently.

The TPHA test is technically easy to do, and quite cheap to run if only microlitres of reagent are used. It involves the reaction between the patient's serum and a component of T. Pallidum (Nichols Strain) which has been adsorbed onto previousiy fixed sheep red blood cells. Haemagglutination occurs when serum containing antibody to T. Pallidum is mixed at a suitable dilution with the sensitized red blood cells suspended in distilled water. The test is performed manually, and again it takes one technician one morning to do the tests on the same 100 sera. The test is available commercially in kit form (Fujizoki Pharm. Co. Ltd). A special absorption diluent is included in the kit to eliminate Biological False Positive reactions, which then causes the test to have almost the same sensitivity, specificity, and life-long positivity of the Treponema Pallidum Immobilisation (TPI) test (Johnston N.A., 1972) which is technically more difficult to perform.

The Fluorescent Treponemal Antibody Absorption (FTA Abs) test is performed on sera which are positive on routine tests as a double check. A variety of non specific antibodies are first absorbed away from the patient's serum. This is then incubated with T. Pallidum fixed to a microscope slide, to which the antibodies adhere. Anti-human globulin tagged with fluorescein is then added, and this binds with the patient's antibody coating the treponema. flouresce a faint green on a dark background. The test is specific, sensitive, and easy to carry out if the equipment is available (Mackey D.M., Price E.V., Knox J.M., 1969).

Despite the TPHA test and the FTA (Abs) test there always remain a certain number of sera in which the final diagnosis of Syphilis will depend on the TPI test. Facilities are not available at James Pringle House for this test, and these sera are sent to the Venereal Diseases Reference Laboratories at the London Hospital.

The culture plates are examined after 48 hours incubation. Candida produces a characteristic white colony on Sabauraud's medium. Trichomonads are pipetted from the bottom of the Feinberg-Whittington liquid medium and looked for under the dark ground microscope. In this same medium the yeast cells of candida form characteristic germ tubes. The Gonococcus produces typical pinhead sized semitransparent colonies on Columbia Agar medium which contains 5% horse blood, if care is taken to provide it with an atmosphere of CO_2 in a candle jar. A few drops of a 1% solution of tetramethyl-p-phenylenediamine are dropped on the colony, which goes purple if it is N. Gonorrhoeae (the oxidase reactione).

Because of the presence of other members of the Neisseria group in the throat, a positive culture from this site presents diagnostic problems. In this case the colony is subcultered onto C.T. Agar medium, and filter paper soaked in Dextrose, Maltose, Lactose, and Sucrose added on top. The different members of the Neisseria group ferment these sugars to varying extents with the production of acid (Cruickshank, 1965). C.T. Agar which has a pink colour, contains an indicator which causes the agar to turn yellow when acid diffuses into the medium. A true N. Gonorrhoeae may be identified by the pattern of sugars it ferments. All positive Gonococcal colonies are subcultured for quantified antibiotic sensitivity tests. There is a correlation between failures and the lessened sensitivity of Gonococci to antibiotics. When cultures do not verify a diagnosis of Gonorrhoea entertained on direct microscopy, the original slide is retrieved from storage and examined by the experienced pathologist. The organism may fail to grow despite being present in the discharge. In the case of women, the smears are frequently negative for gonococci, whilst the cultures

are positive.

Other facilities available to the doctor is the detection of anti-bodies in sera to the Herpes Virus, and the detection of the cytopathic effect of Herpes Virus on foetal lung tissue culture, but these are performed in a virus laboratory in the main hospital.

Treatment

Rapid diagnosis facilitates prompt and rational treatment. A supply of oxytetracycline tablets, metronidazole tablets, nystatin pessaries, and a variety of antifungal and steroid ointments are available in the doctor's desk to be handed over to the patient free of charge. Gammabenzene hexachloride powder, benzyl benzoate emulsion, podophyllin solution, and trichloracetic acid crystals are at hand and applied by the nurses.

Uncomplicated cases of Gonorrhoea receive one intramuscular injection of 5 mega units of benzyl penicillin made up in 5 ml. of a 0.5% solution of xylocaine, thirty minutes after 1 Gram of probenecid by mouth. If this fails or the patient is allergic to penicillin, a single intramuscular injection of 2 Grams kanamycin, or three sulphametoxazole trimethoprim tablets twice a day for three days are administered. The patient is discharged as cured after three negative cultures at weekly intervals, but is instructed to return after three months for a repeat of the serological tests for Syphilis.

Early Syphilis is treated with 600,000 units of procaine penicillin intramuscularly daily for ten days. Patients allergic to penicillin receive erythromycin 500 mg tablets four times a day for 15 adys. Serological tests for Syphilis are repeated at monthly intervals for three months, then at three monthly intervals until one year after treatment. The cerebrospinal fluid is examined at the end of the first year after treatment. If the VDRL test becomes negative in the first year it is repeated at six monthly intervals during the second year, and if still negative at the end of the second year the patient is discharged as cured. If it remains positive it is repeated at three monthly intervals until it is persistently negative.

Non-specific Urethritis is the commonest condition seen in men. Its treatment is most unsatisfactory. For a first attack a five day course of oxytetracycline 500mg tablets twice daily is prescribed, and the patient told to abstain from sex and alcohol. Recurrences are common however, and at this stage a further course of ten days is prescribed. The further treatment of those patients who relapse more than once is not standardised, and depends on the personal experience of the doctor in charge.

Since the advent of modern therapy the vast majority of patients with sexually transmitted diseases are treated sucessfully as outpatients. The occasional person who needs inpatient treatment is admitted in a general medical ward, and care is taken not to distinguish him in any way from the other patients in the ward.

The Contact Tracer

Control of sexually transmitted diseases depends on the tracing of infecting contacts (Scottish Health Services Council, 1974). It is desirable to see the regular sexual partners of patients who have relapsing Non-specific Genital Infection, Candidiasis, Trichomoniasis, and Scabies. The onus of explaining this to the patient rests with the doctor at the time of examination. On the other hand, tracing the contacts of patients with infectious Syphilis and Gonorrhoea, being of vital importance from a public health point of view, is undertaken by professional Contact Tracers, two of whom are employed full time at James Pringle House.

Contact Tracers are otherwise known as Health Visitors. However this is a misnomer, because they try to achieve their aim without moving from the office, and regard an outside visit as an admission of failure causing loss of time and money (The Health Education Council, 1976).

The Contact Tracer interviews all newly diagnosed cases of Gonorrhoea and infectious Syphilis. A rapport of trust is set up, care is taken not to moralise, but in the meantime a detailed sexual history is taken. The patient is given a slip of paper

to deliver to the person who has presumably infected him, and one for each sexual partner since, including the wife or husband. The slip of paper contains the name of the clinic from where it is being issued, the patient's reference number, and the diagnosis in the official code of the Department of Health and Social Security, e.g. B — Gonorrhoea. The contract will hopefully realize or be convinced by the patient that it is in his interest to present at a V.D. Clinic with this contact slip in order to be examined and treated. After the contact is examined, the findings are entered in the same code at the back of the contact slip which is sent back to the clinic it was issued from. By this method a check is kept on the efficacy of contact tracing.

Very often the use of the contact slip may be obviated by the patient volunteering to phone his contact directly. Habitual promiscuous male homosexuals in particular are becoming so aware of their increased risk of contracting and spreading Syphilis, that some members of that community keep a name and telephone number book of all contacts for the preceeding three months, knowing that this is the longest incubation period of the disease!

At the end of the clinic the doctors review the case sheets of those patients who had an appointment but defaulted. If these constitute a public health hazard because they may still be infective, a note to this effect is entered in their case sheets against the date. Before filing away the day's case sheets into potential oblivion, clerks examine all the notes. A list of the dangerous defaulters is made and handed to the Contact Tracer. At this stage a telephone call, letter, or in the last resort a house visit is mandatory.

As appointments cannot be fixed more than three weeks in advance, patients being followed up for Syphilis every so many months have their name entered in a dairy against the date near whichth ey are expected to attend. It is the Contact Tracers duty to check the diary every morning and see that the patients scheduled to attend do so, and chase them up if they default. This method is also applied in the short term to patients whom the doctor suspects may default despite a firm appointment a few days hence.

The Medical Social Worker

A Medical Social Worker works part time in the department. There are many patients wth personal, financial, emotional, domestic, and other problems who can benefit by talking to her.

The Psychiatrist

Some patients attend the clinic with genuine sexual problems such as impotence. Others suffer from mental disease expressed as a persistent, unjustified fear of venereal infection. The services of an experienced psychiatrist are available in the clinic once a week to deal with these problems.

Discussion

There is much to be said in favour of one department being responsible for the care of the patient and all his contacts, male or female. Training in dermatology is not particularly relevant to the examination of patients, especially females. A good knowledge of Gynaecology is essential in the examination of the latter. While it is all right to practise Venereology with Dermatology, British experience indicates that it is more advisable to have independent V.D. clinics.

There is no doubt that James Pringle House is well equipped to deal with the problem of Sexually Transmitted Diseases, and may be looked up to as a model on which to organize an efficient clinic should the need arise. James Pringle Honse caters for a restless cosmopolitan community whose sexual attitudes and behaviour differs from that of the Maltese. The behaviour of the infective agents, once present, is similar in both countries however, and there is a lot to be derived by observing the latest diagnostic and therapeutic techniques adopted in more advanced centres. Besides, in this age of rapid communication the behaviour of our youth will be conditioned more by that of their counterparts abroad. The growth of tourism inevitably brings with it an increased risk

of exposure to the diseases.

In the clinic I was impressed by the frequency with which Gonorrhoea in particular was discovered in patients who were asymptomatic, especially females who came forward for a check up after taking a risk. This raises the disturbing question of whether the extent of the problem in Malta is being grossly underestimated. Only a change in attitude towards these diseases will allow potentially infected asymptomatic persons to come forward for examination. This, combined with efficient contact tracing will supply the answer. Antibiotics in themselves are not the ultimate solution to the problem. Should the rising tide of Sexually Transmitted Diseases which is affecting Europe reach the shores of Malta, then a clinic operating partly on the lines sketched above would be a very desireable thing to have.

Summary

A period of employment at James Pringle House provided the opportunity of observing how the growing problem of sexually transmitted diseases is being dealt with in London. Paramedical staff plays a vital role in the efficient running of the clinic. Diagnostic procedures which could be adopted to advantage in Malta are discussed. It is regretted that the services of professional contact tracers are not available in Malta. Failure to chase up asymptomatic carriers leads to underestimation of the problem, and constitutes a public health hazard. While it is all right to practise Venereology with Dermatology, British experience indicates that it is more advisable to have independent V.D. clinics, especially if the incidence of Sexually transmitted diseases reaches the epidemic proportions it has done in most countries.

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ABDOMINAL INJURIES IN ROAD TRAFFIC ACCIDENTS

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Incidence

The incidence of closed abdominal injuries in patients admitted to St. Luke's Hospital after being involved in road traffic accidents, though not alarmingly high, is certainly not negligible. Of course, in cases coming to post-mortem, abdominal injuries are found in a higher proportion, usually associated with other lethal injuries to head and chest. This comparatively low incidence is probably due to the fact that most traffic accidents take place at low speeds, partly because our roads do not encourage high speed driving (Camilleri, 1968). It is possible that with improvement in our roads the incidence of these injuries will rise though never to such proportions as in countries with long stretches of first class roads and motorways.

Abdominal injuries can be sustained by pedestrains knocked down by moving vehicles, drivers thrown forward against the steering wheel, passengers knocking themselves against the interior of vehicles and cyclists who hit their abdomens against the handle-bars. In contrast to head injuries, which are commoner in those sitting in the front seat, the position of passengers inside a car seems to have no bearing on the incidence of abdominal injuries. Although horse-drawn vehicles are still fairly common on our roads their drivers do not appear to sustain abdominal injuries to any great extent. A number of different mechanisms may be responsible for producting these injuries including compression, avulsioin, shearing tsresses, direct laceration by bony structures and excessive rise in intra-luminal pressure in the case of hollow viscera. Fixed organs are more liable to injury than mobile ones with the exception of the pancreas which is injured in only 1-2% of cases. In trauma to the upper abdomen, the spleen is most often involved (Wilson, 1963), followed by the liver and kidney. Hollow viscera are less commonly damaged. Injuries to the bile duct, gall bladder and ureters are rare and damage to the adrenals is even rarer.

Diagnosis

The diagnosis of blunt intra-abdominal injury is always difficult and often obscured by shock, unconsciousness and the presence of other injuries to the head, chest and limbs. Not infrequently more than one abdominal viscus is involved. Parietal damage, haemoperitoneum, peritonitis and retroperitoneal haemorrhage may occur separately or together. Intraperitoneal injury may not be apparent for hours or days, for example small intestinal perforation, retroperitoneal damage to the duodenum or colon, gangrene of small bowel following injury to the mesentery and delayed rupture of the spleen. The value of repeated observations, preferably by the same experienced observer, cannot be too strongly emphasised.

History of the accident from the patient if he is conscious or from reliable witnesses, if he is unconscious, is often helpful. One should try to assess the velocity of impact from the state of the vehicles, whether the patient was thrown out and his position in the car at the time of the accident. No matter what other injuries exist one must always think of the possibility of abdominal injuries especially in the unconscious patient. If a conscious patient complains of pain in the abdomen, loin or back the matter must be given serious consideration. Where possible, inquire about the site and radiation of the pain, the passage of urine and whether it contained obvious blood. A desire to pass urine with inability to do so is very suggestive of bladder and/or urethral injury. The presence of shoulder pain may signify

diaphragmatic irritation from blood or intestinal contents.

On examination, the presence of pallor, cold clammy extremities and a rapid weak pulse are as important an indication of internal bleeding as a low blood pressure. Signs of continued bleeding when all visible bleeding has been stopped and the blood volume restored point to the abdomen as the source, provided thoracic injuries and major pelvic fractures have been excluded. The imprint of clothing on a yielding part of the abdominal wall means severe compression against the spin or back part of the pelvis, often with damage to mesentery or bowel wall (London, 1969). Local tenderness and guarding may or may not indicate damage to underlying structures. A rectal examination should be done in all cases as it may reveal rectal injury or a displaced prostate in complete rupture of the posterior urethra. In general, isolated abdominal physical signs can often be misleading (Proctor, 1967) and a general consideration of the clinical picture including the patient's response to resuscitation is often more helpful. Distension, increasing or spreading tenderness and rigidity and a rising pulse rate, however, are all significant.

There are three diagnostic ancillary methods which aid in the general if not in the specific diagnosis. These are radiology, diagnostic peritoneal tap and, to a lesser extent, laboratory investigations. Plain X-Rays of the abdomen may show fractures of the lower ribs or pelvis or the presence of free gas in the erect or lateral films. In retroperitoneal rupture of the duodenum, retroperitoneal gas bubbles with an exceptionally clear Psoas shadow may be found. Similarly, obliterated left renal and Psoas shadows, possibly with elevated left diaphragm, increased density in the left upper quadrant and shifting of the gastric air bubble suggest injury to the spleen. Of the specialised radiological procedures, using contrast media, I.V.P. is mandatory to exclude serious renal injury, when suspected, as well as to confirm the presence of a functioning contralateral kidney. Gastrografin studies and cysto-urethrography are occasionally useful for demonstrating gastrointestinal and bladder/urethral injuries. Arteriography of the liver, spleen and kidneys remains of limited scope, particularly for technical reasons (Shepherd, 1971). Scanning with radioactive gold has been advocated to detect liver injuries (Walt, 1969). Four quadrant diagnostic peritoneal tap using a number 18 lumbar puncture needle or fine polythene tubing introduced through a thoracocentesis needle, can be of great assistance, if positive. The withdrawn fluid can be haemorrhagic, bile-stained or contaminated with faeces. A high amylase content in this fluid is very suggestive of pancreatic injury. A negative peritoneal tap, however, is of no significance (Morton et al., 1957). Of the laboratory investigations, serial haematocrit readings are of more value than a single haemoglobin estimation on admission. A very high serum amylase, when present, suggests damage to the pancreas, although it is not specific. Microscopic haematuria directs one's attention to the urinary tract.

In practice, the most important decision is whether to explore or not rather than to determine which particular organ has been damaged. If in doubt, it is better to look and see than to wait and see.

Management

As in many cases abdominal injuries are found in association with other severe injuries to the head and chest, it is essential to perform a rapid initial assessment of the patient's condition, establish and maintain a patent airway and ensure effective respiratory exchange as a first step. The restoration of a depleted blood volume is of little or no avail unless respiratory function is quickly restored and adequately maintained (Gissane, 1967). Following this, severe bleeding must have high priority in treatment (Ward McQuaid, 1971). The requirements are rapid resuscitation using a wide bore intravenous cannula and adequate amounts of blood. Plasma or high molecular weight dextran may be used until blood becomes available. The insertion of a central venous pressure catheter is a useful guide to the adequacy of replacement and prevents overtransfu-

sion. It must be remembered that the surgical control of bleeding is often an integral part of resuscitation.

At laparotomy, wide exposure, is essential to allow proper inspection of all organs. Splenic rupture is easily and rewardingly dealt with by splenectomy. In liver injuries the objects are to stop the bleeding, to excise devitalised tissue by segmental resection or even lobectomy (Little and Williams, 1969), if necessary after extending the incision into the chest, and to provide drainage. Routine decompression of the biliary system by a T-tube is not universally accepted (Faris, 1972). Hilar injuries and those at the junction of the hepatic veins and the inferior vena cava remain a problem. Kidney damage is usually handled conservatively (Opit et al., 1960) and nephrectomy at emergency laparotomy for blunt injury should be rare, unless the kidney is diseased. Simple colonic perforations may be sutured; more severely damaged right colon may be dealt with by resection and anastomosis (Roberts and Lavelle, 1966); badly injured left colon is preferably exteriorised. Retroperitoneal haematomas near the bowel, especially duodenum and colon, must be explored (Ward McQuaid, 1971). Pancreatic injuries may require simple drainage (Thompson and McFarland, 1969), repair (Roberts and Lavelle, 1966), distal pancreatectomy or a Whipple type procedure depending on the extent and site of the injury. Ruptured diaphragm should be looked for and repaired. If left, it can lead to strangulation later (Miller and Howie, 1968) (Ward McQuaid, 1969). Bladder and or posterior urethral injuries are not uncommonly associated with severe fractures of the pelvis. Although it is usual to attempt catheterisation when these injuries are suspected, this is by no means the universally accepted management (Miller, 1961). Mitchell (1948, 1963) considers that catheterisation often converts an incomplete into a complete urethral rupture with the inevitable risk of stricture later. He advocates suprapubic cystostomy in all cases followed by endoscopic assessment of the damage after two to three weeks.

One must remain alert to the posibility of delayed and late complications developing days or weeks after the original injury (Petty, 1973). These include delayed rupture of the spleen (Kamal, 1967) and bowel, haemobilia and abscess after liver injuries and late pseudocyst formation in the pancreas. Late ileus usually means peritonitis, and may be due to gangrene from missed mesenteric injury.

Conclusion

In conclusion, abdominal injuries from road traffic accidents are likely to become more common with increase in traffic density and improvement in the roads, encouraging, if not permitting, faster speeds. I am convinced, and statistics support my contention, that a properly fitted and worn seat belt can decrease considerably the incidence and severity of abdominal injuries to car occupants. When, however, these injuries occur we should endeavour to diagnose and treat them early and energetically because as Gissane pointed out in 1962, the Bimingham experience leaves us "in no doubt that any decrease in mortality and morbidity rates following severe intra-abdominal injuries is dependent more upon early and adequate resuscitation and surgery than upon technical virtuosity at a later stage" (Gissane, 1962).

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DEPRESSION IN GENERAL PRACTICE

V. S. ZAMMIT

General Practitioner

Attempts to classify depressive illness have become increasingly more complex and controversial. Perhaps from the General Practitioner's point of view it is wise to adopt this simple but clear classification.

1. A naturally motivated mood or normal non-patholigical reaction
2. Reactive or neurotic depression and
3. The depressive Psychosis.

Experience in our field shows that only about 5% of all depressions that we encounter daily belong to group (3). In my opinion any case belonging to this group should be immediately referred to the psychiatrist or to a mental hospital — preferably the former as admission as an in-patient is costly, regressive, diminishes the patient's self esteem and leaves him with a stigma which causes both embarassment and difficulties later on in life. General Practitioners should never treat such cases at home without the consultant's help and under no circumstances should they prescribe any of the monoamino-oxidase inhibitors. It is rather a pity and also a tragedy that General Practitioners are not always aware that their patients have been prescribed these preparations. General Practitioners must be aware that they must not prescribe any of the tricvolic antidepressive drugs, reserpine, pethidine, sympathomimetic amines, methyldopa, tyramine containing food such as cheese, yoghurt and bread beans and alcohol in view of the serious and sometimes false effects.

It is no exaggeration to state that at least 15% of all adult cases that come to surgery are suffering from "depression" — the bulk being reactive which is an exaggerated response to adverse external circumstances — viz — family conflict including marital discord, excessive use of alcohol, unemployment, financial worries, bereavement or grief reaction, problems of adolescence, and of old age, school problems, medical illness, the unmarried mother, postpatum depression and postoperative reactions. A small proportion of this percentage belongs to the endogenous type of depression which, as we all know, belongs to the realm of psychosis. Very often as is the custom in Malta the patient is frequently brought in by a relative who gives the initial presenting features. Without being impolite I usually ask the relative to leave the room as I believe that this is the first step to break down the barrier of the patient's initial reaction of "You cannot possibly help me". Furthermore this helps in gaining the confidence of the patient and to establish the most important and fundamental criteria of family practice — the patient-doctor relationship. A word of warning regarding female patients — stress in front of the relative that there will be no "initial" physical examination — this I feel puts the patient's mind at rest and diminishes some the worries that she may be harboring some serious physical illness. During the first session I usually listen to the patient's complaints hardly giv-

ing any advice but encouraging him in dishing out his problems, fears and worries. After having gained the patient's confidence I then proceed to a thorough physical examination. I never do this just to please the patient, but to avoid falling into one of the most dangerous diagnostic pitfalls, I always ask myself this question "Does this depression result from or does it mask a physical ailment — the cure of which will return the mental state to normal." Look out for tuberculosis and chronic sepsis particularly when associated with influenza, watch out for the young woman whose depression results from too rapid weight reduction by dieting. Vascular disorders especially atherosclerosis and Parkinsonian degeneration can also give rise to an intense depression; do not forget that hypothyroidism may present as a depressive illness. Watch out for personality changes as these are often associated wiih brain tumours. After the complete examination I ask the patient to come again in a few days time and this has proved of immense value as it is during these calls that his real problems come out. It is disastrous in my opinion as a General Practitioner to bring out pad and pen and to prescribe the first tranquillizer or antidepressant that comes to mind and to ask the patient to see you in one month's time. Many patients may not need any medicines. These patients need help, understanding, sympathy, and advice — drugs will tidy over some of the symptoms but will never solve their problems. Let us limit ourselves to a few drugs so that we can acquaint ourselves with their mode of action, their benefits and side effects. I have spent many an hour including Sunday evenings discussing their problems with our local priests, their employers and teachers ,the social and insurance officers and relatives — at times I have also gone to their neighhours to get down to the bottom of their problem — in some cases I have met with success but in others unfortunately I have failed — maybe because I could not find enough time and the necessary qualified help to devote to such cases. I believe the time has come, if such cases are to be treated properly and urgently, to have in each district trained non-professional helpers. The kind and understanding priest, teacher or policeman are not good enough — they must know what they are dealing with. Perhaps in the not too distant future with community care pushing us along we will have "District Psychiatric care" with the psychiatrist/General Practioner, mental health officers and other helpers discussing four or five cases per session every month or so.

As you are aware, modern research has tended to make the difference between the anxiety states and depression fairly clear but the clinical manifestations overlap considerably and it is obvious that most patients diagnosed as suffering from anxiety state show some depressive symptoms and that a large proportion of depressives show a greater or lesser amount of anxiety. In order to help me in reaching a diagnosis of depression I have been using for a number of years charts based upon and adapted from the Hamilton Rating Scale for depression — from these I have concluded that depression can be diagnosed if these five symptoms are present viz disturbed sleep pattern, loss of interest, loss of apetite, loss of libido and diurnal variation of symptoms. Remember that the initial attack of depression often comes later on in life whereas neurosis comes earlier on.

Having established the cause of the patient's depression and having excluded any physical cause including the taking of reserpine and contraceptive pills I usually plan what line of action is best for the patient. I usually "but not" invariably prescribe an anxiolytic or a tranquilizer or an anti-depressant.

During the various psychotherapeutic measures the dialogue with the family doctor probably plays the most important role as this enables the patient, to purge himself of his problems. I always give these patients "weekly appointments" on days during which I know that the work load is not too heavy so that I can devote at least 20 — 30 mins. per sitting until the case is under control. These weekly appointments help me in seeing that patients are taking tablets regularly and that their moods are better. Furthermore such sessions often

help me to spot the early signs of the greatest hazard of any depressive illness viz "suicide". This must never be taken lightly even if the patient makes only a passing remark about it. In such cases I always call one of the members of the family and advise re preventive measures — if the patient lives alone I ask him to stay with his relatives until he improves: If I notice that the depressed patient, is not responding well to treatment within the expected time of 4 weeks I have always sought psychiatrict help and where suicide is a real threat have sought hospitalization.

I have noticed in my practice that a high proportion of depression is encountered in female patients and yet the five cases of successful suicide that I have been were all males, — three of them aged between 30 — 36 years, one aged 45 years, the other 80 years. Incidentally three took an overdose of barbiturates, one died by hanging and the other threw himself under a bus the next day after I advised him that he needed a Prostatectomy for his obstruction.

In my view, in certain respects the family doctor has an advantage over the psychiatrist because he has probably known the patient, his family and his environment for a long time. He knows what type of personality he is dealing with — emotional or mentally strong, stable or misleading attitudes. He knows whether the patient tends to exaggerate his symptoms or makes light of them.

He may know that the patient is very sensitive in his reactions to the words and actions of others. He may know the patient's personal events such as lack of success in his employment, quarrels with friends or family members. The General Practitioner being part and parcel of the family is fully acquainted with its problems: moral, social or financial. This acquaintance will contribute sometimes decisively in constructing the real picture of the disturbance. In case it is necessary he will find it much easier than the consultant to contact the family without the patient's awareness.

We are all aware that in psychiatry the evidence provided by the family, in comparison with that offered by the patient is more commonly useful than in other branches of medicine (excluding Paediatrics). However in some cases conditions and reciprocal relations with the family may have helped or indeed determined the development of the patient's depression. From the family's evidence one can assess the majority of the patient's illness, how much it is effecting his human relations. Through it also the General Practitioner can more accurately find out the time and mode of onset and the eventual course and later the effect of treatment.

The General Practitioner has the advantage that he is in constant contact with other helpers — the priest, the teacher, the policeman. These he can readily and easily talk to, obtain information and advice as to management of a case. A recent example is a young girl who gets severe hysterical attacks at Zabbar Secondary School. The headteacher referred this girl to me asking for advice. The girl told me that everytime she goes out into the yard she gets vivid recollections of last year's air-disaster. I wrote back to the teacher advising her to move the girl to another school which she promptly did. The girl is now much better and happier — incidentally **no** drugs were prescribed to this young girl. Of course not all cases can be scived as easily and quickly as this. We are all aware that treatment of the mentally sick patients especially those suffering from depression is one of the most time consuming and exacting demands on the General Practitioner but with all the sources available at his disposal the General Practitioner can and will succeed in most cases.

There is no quick way round this help — some will take months to recover but the hours of exhausting listening and advice and the minimal use of the prescribing pad usually repay dividends in the end.

SUBJECT INDEX

AUTHOR INDEX

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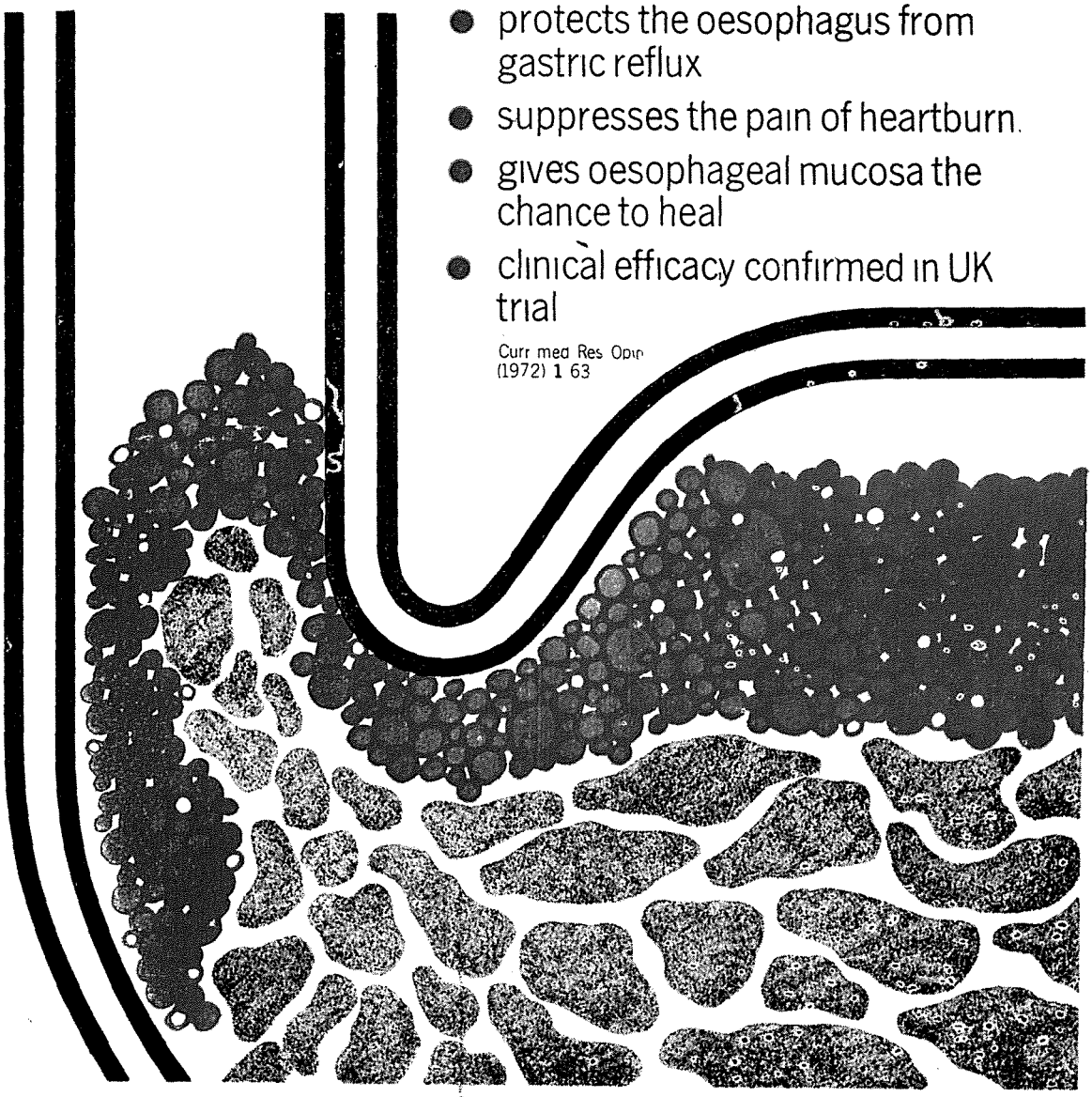

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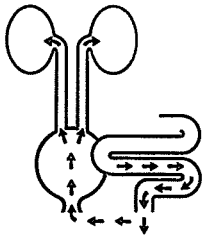

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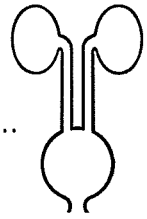

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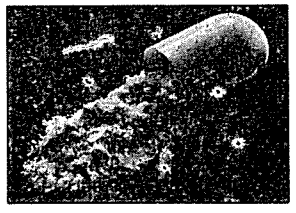

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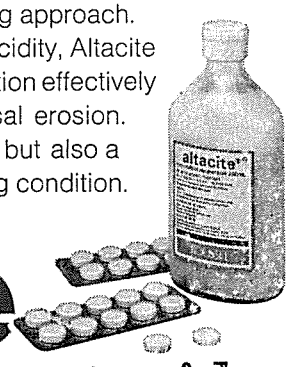

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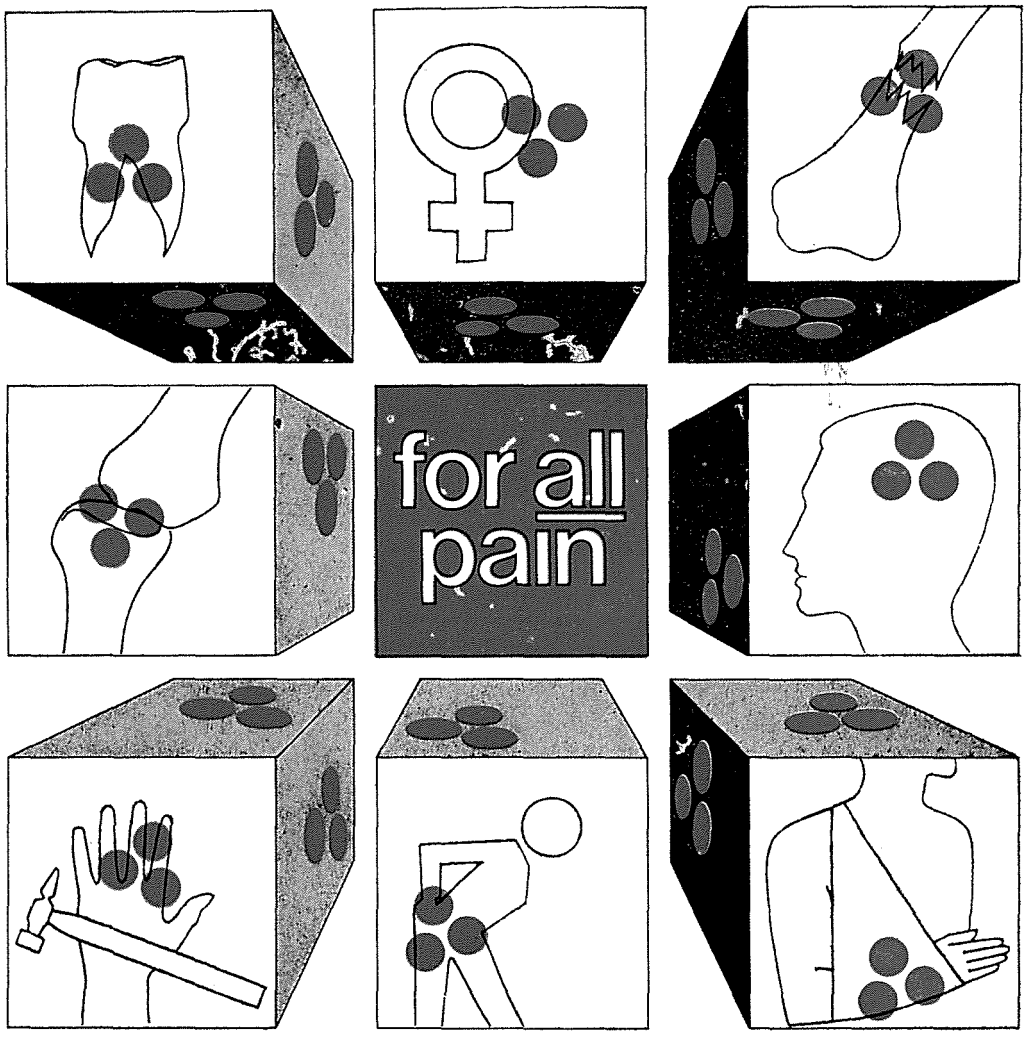

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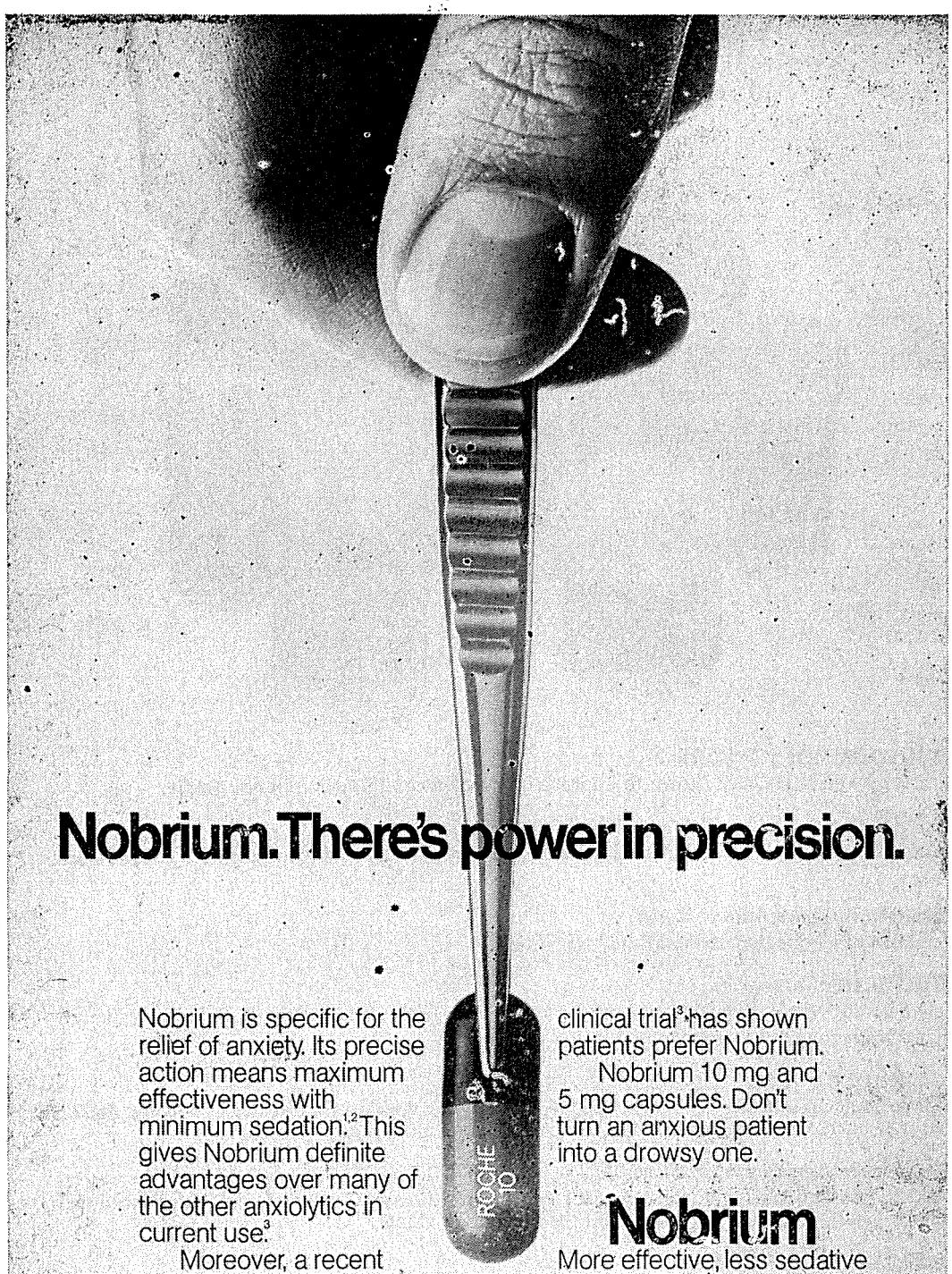

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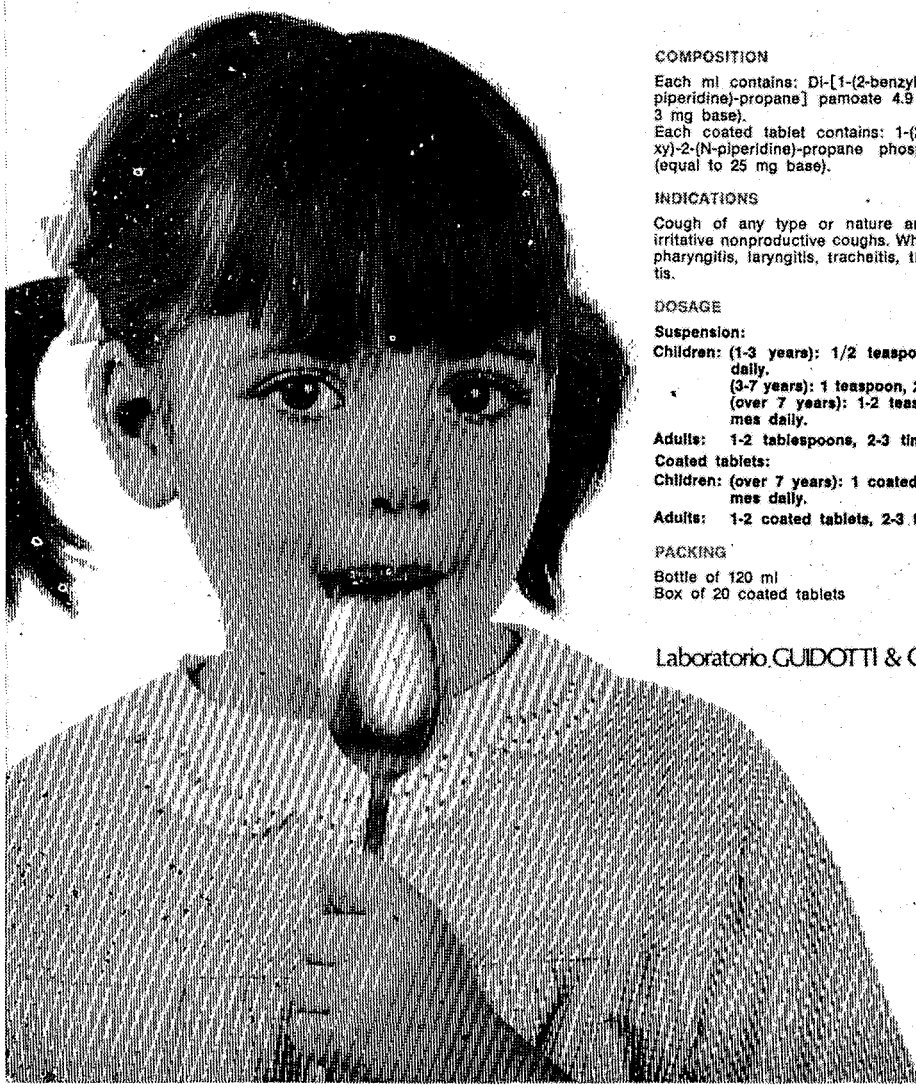

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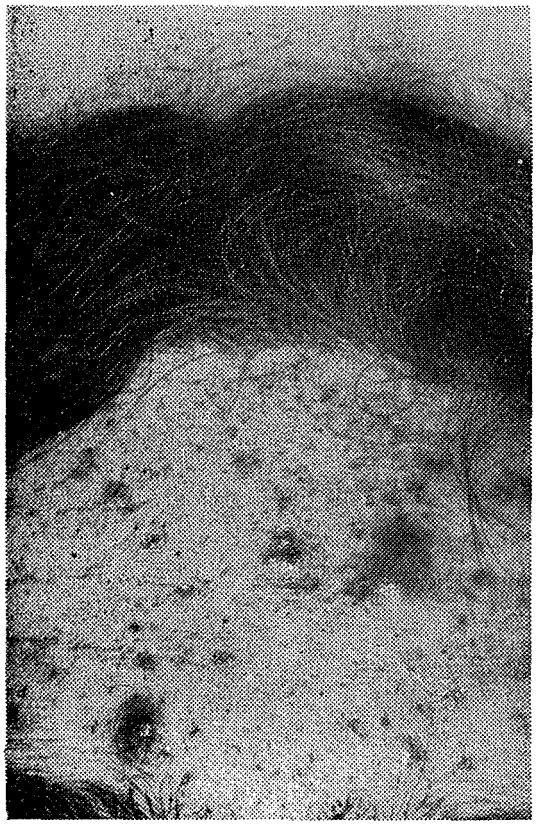

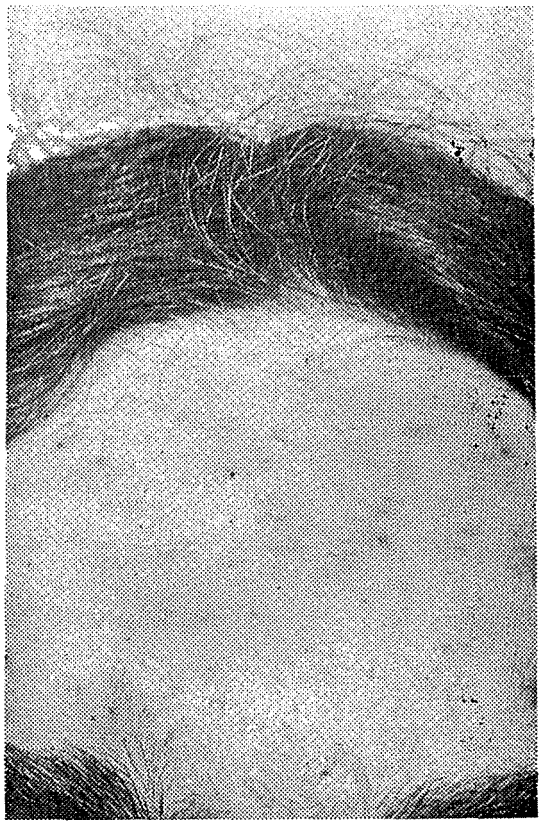

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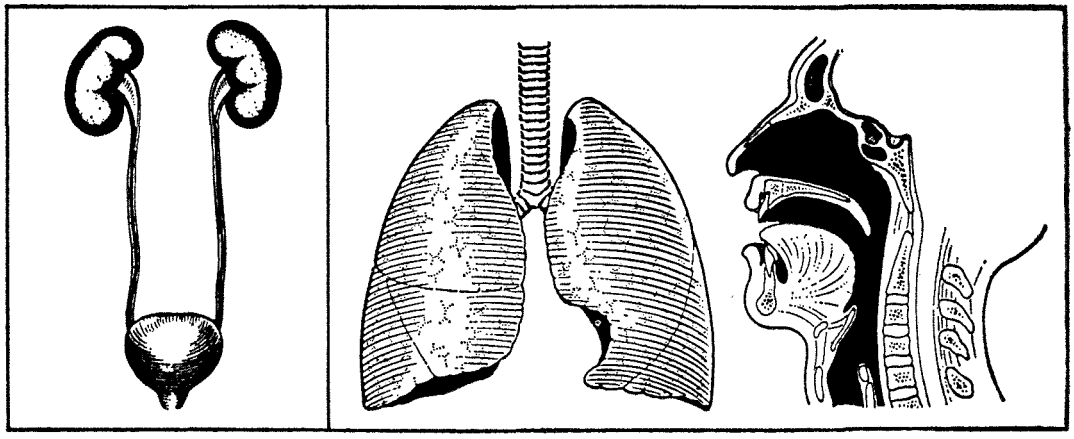

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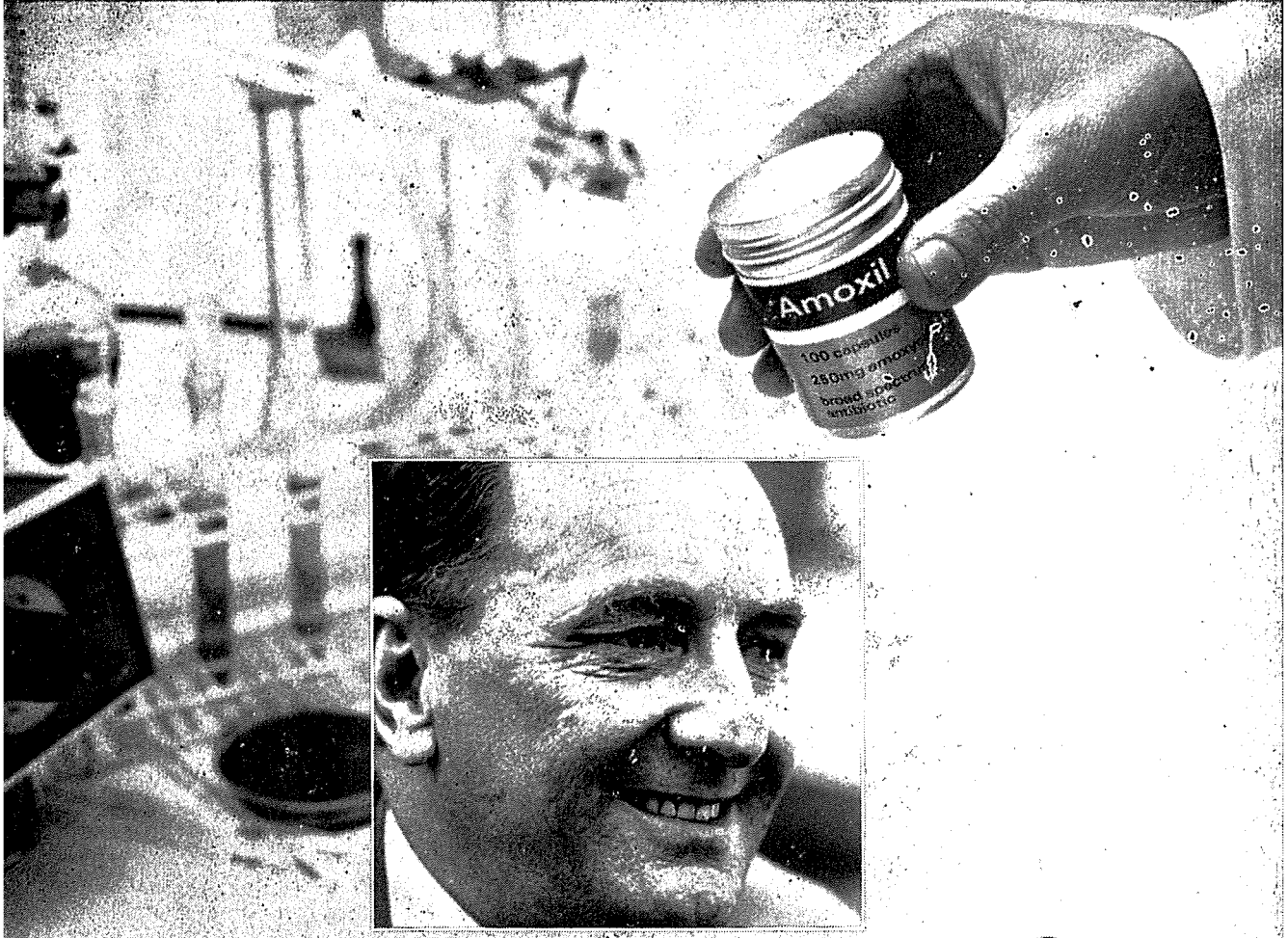

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URINARY TRACT INFECTIONS AND GONORRHOEA

The very high levels of active antibiotic achieved in kidney tissues and urine are of decisive importance in the treatment of urinary tract infections and gonorrhoea.

E. N. T. INFECTIONS AND BRONCHITIS

The clinical superiority of PONDOCILLIN in acute and chronic bronchitis is due to the exceptionally high concentrations obtained in lung tissues during treatment with this antibiotic.

ORIGINAL LEO RESEARCH

Capsules of 350 mg and 175 mg of pivampicillin hydrochloride in bottles of 12 and 100. Capsules of 350 mg also in strip-foils of 4.

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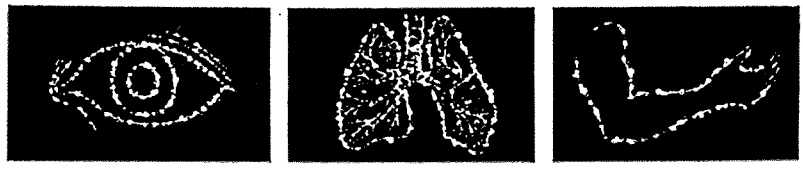
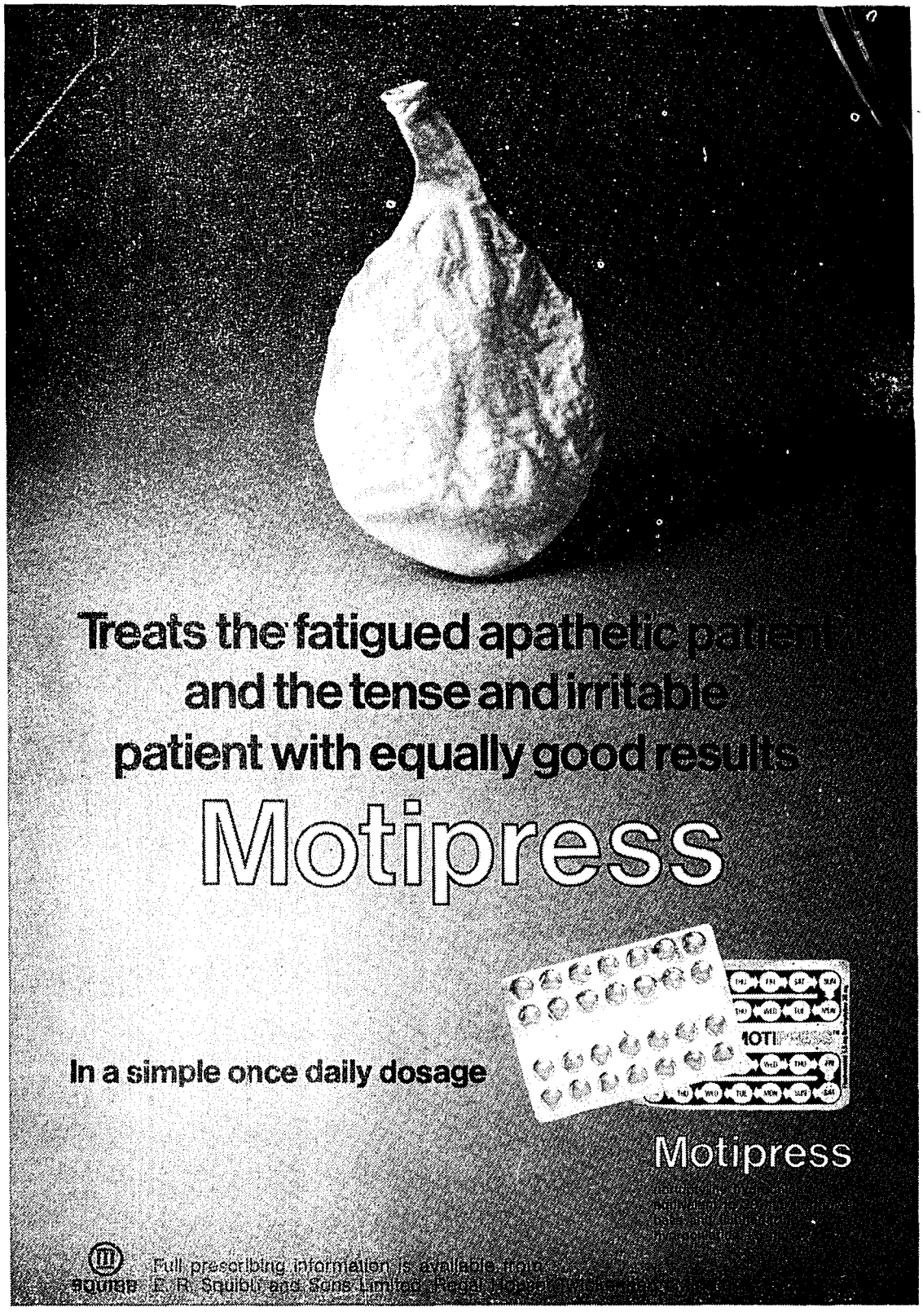


Local Agents: K. & M. Ltd., Valletta Malta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