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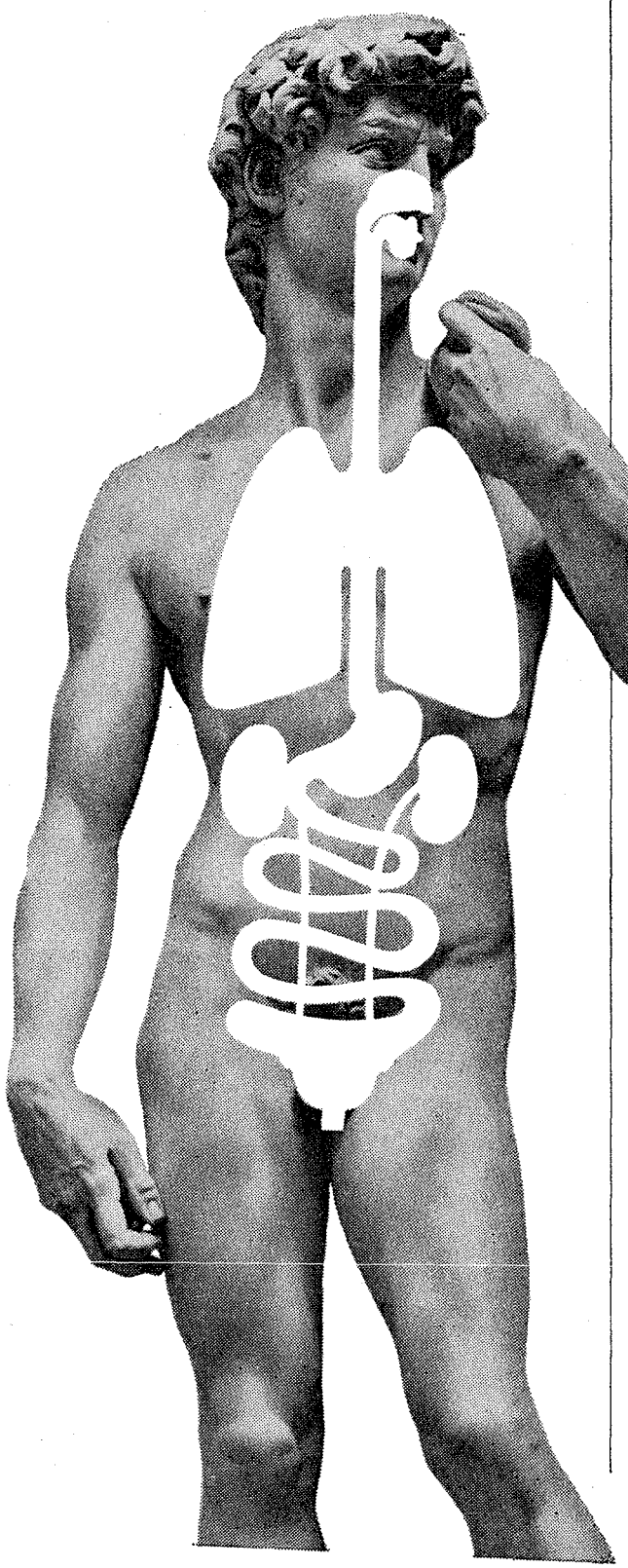

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journal of the malta medical students association

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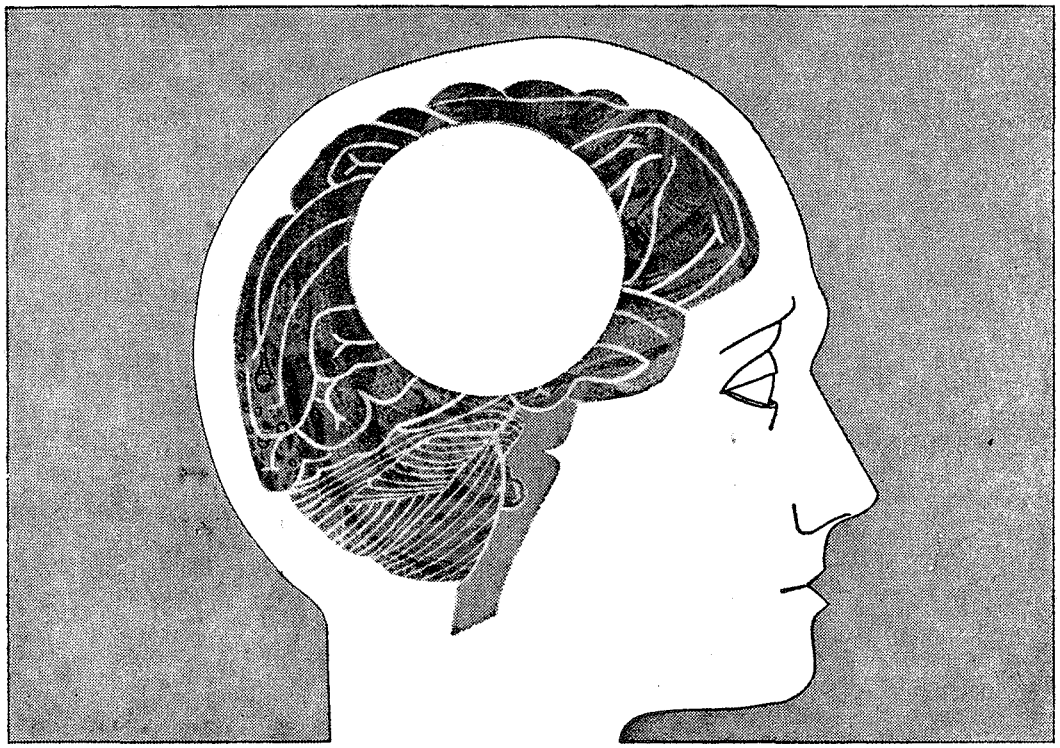

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Editorial

state of the journal

In October of 1948, six years after its foundation, the Malta Branch of the British Medical Students Association published the first issue of CHESTPIECE. In it, Charles Xuereb, the Editor, laid down the policy of the new journal, namely to maintain a balance between student and staff contributions so that both should be equally represented. This policy CHESTPIECE has always maintained. The new journal was soon a focal point for local medical thought. Soon after the first issue, a suppliment was printed in order to publicise the talk given by Dr. A. Schembri Adami, then Minister of Health, to local doctors about his proposals for a National Health Service for Malta. In December 1949, CHESTPIECE reprinted Pope Pius XII's pronouncement on Artificial Insemination. The issue of April 1950 carried among the scientific articles, one by Dr. Andreas Widemann on B.C.G. inoculation. Thus CHESTPIECE heralded the B.C.G. campaign started by Dr. Widesmann's Norwegian Team and continued to the present day by the Department of Health, which has swept tuberculosis from the Maltese Islands. In the Winter 1956 number, an article by Peter Fenech gave the news that the Association had changed its name to the Malta Medical Students Association.

Yet, in spite of all its achievements, CHESTPIECE had had some contretemps. There had been lapses in its publication, the most serious of which was that between 1959 and 1963, when CHESTPIECE was not published at all. CHESTPIECE is just emerging from one of these lapses, the last issue having been in Christmas 1972. Yet we are determined that CHESTPIECE be given a new lease of life. It is encouraging to learn that we have survived longer than any other Maltese medical journal. Thus, the first ever Maltese medical journal," L'Ape Melitense", ceased publication after only four issues. "Il Filocamo" lasted only between 1841 and 1842. "Il Barth", being founded in 1871, ceased publication in October 1877, and "La Rivista Medica" had only a spasmodic existence. To end this list, our friendly rival "The St. Luke's Hospital Gazette" is 18 years our junior.

CHESTPIECE will be with you for some time to come!!

Our founder, Dr. Charles Xuereb has recently been appointed Assistant Profesor of Anatomy at the University of Benghazi. We wish him the best of luck — our own students will miss him in the Anatomy Department.

We also wish to congratulate Dr. R. Ellul Micallef on his appointment to the Editorship of "The St. Luke's Hospital Gazzette".

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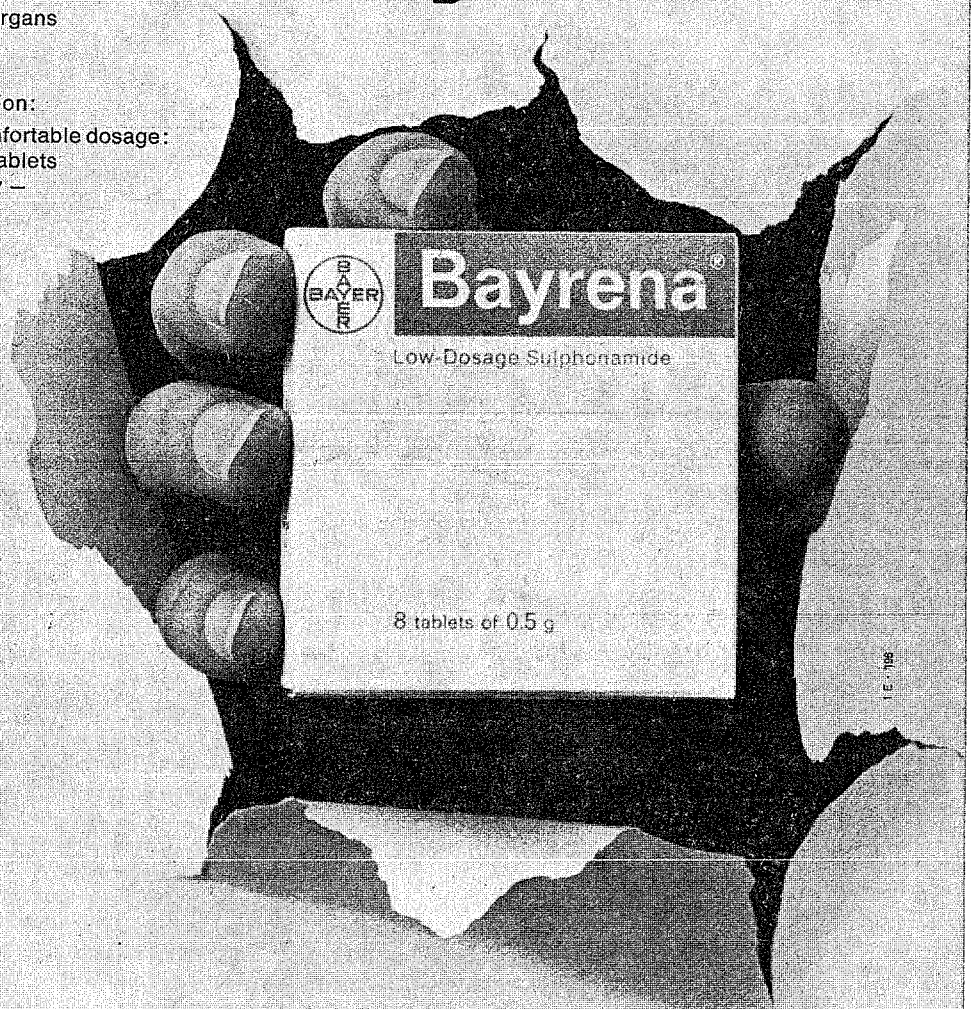

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STATEMENT OF POLICY 1975 COMMITTEE

February '75

As soon as the present committee took office, it started working hard in the interests of members of the association. Up to now, 5 committee meetings have been held, and to enable members of the association to amend statute and regulations an extraordinary General Meeting has been summoned.

Membership cards have been handed out, and in accordance with resolutions passed repeatedly at general meetings, copies of the Statute of the Association are being distributed. The policy of informing students of committee decisions, etc. by notices on the notice board will be steadily maintained.

The committee is striving to establish better relations with other organisations. In particular, efforts are being made to abide more fully with the recommendations of the International Federation of Medical Student Associations as set out in the Grey Manual (Constitution and Bye-laws.)

As regards health and Medical education, — a serious study and report on the subject is planned. We are ensuring that all international publications received by us are placed in the medical school library for all members to read.

One of the first steps taken by the committee was to appoint an Editorial Board for "Chestpiece" — the Journal of the Association. The members of the Board, both clinical and preclinical, are working hard, and in spite of the high cost of printing the journal, have succeeded in collecting a substantial quantity of adverts. "Chestpiece" will be issued soon and will establish itself as a regular voice and instrument of the student body.

For the first time, an international pharmaceutical firm (Merck Sharp & Dohme International) has held, through our association, two very rewarding meetings for clinical students. Moreover, they have kindly compiled with our request and donated a copy of the Merck Manual — an invaluable reference text to the library. Further progress in similar directions is planned. Some suggestions regarding the library are being examined, and should the need arise, more energy shall be devoted to the matter.

In spite of the problems with which the exchange officers were faced, correspondence with individuals and associations abroad was started as soon as possible. Contracts for a few places have been renewed and some funds raised. The utmost shall be done in promoting student exchange. Since several fundamental problems of exchange policy have been arising for some time, a draft of Travel Regulations is being submitted for discussion and approval at the General Meeting.

It is the policy of the committee, during its term of office, to carry out other activities such as for example in the field of sports and entertainments. At this early stage, this statement of policy is at best incomplete. A full detailed account of all work done will be submitted to the scrutiny of the Annual General Meeting towards the end of the year.

Finally, the active support, by direct help or by suggestions from all members of the association is expected. It is encouraging to note that this is already being met with.

THANK YOU.

the first approach to ward work

mr. dennis xuereb m.d., f.r.c.s.

The gap between preclinical and clinical work is wide and difficult to bridge. The student has to adapt himself from the classroom-laboratory atmosphere to the real doctor's world among patients. Some will find the metamorphosis easy whilst others will only undergo it after months of hard trying. Books hardly help you in the trial so I thought that if I put down my own experiences, still very fresh in mind, they might stand some younger colleague good stead.

To begin with I must emphasise that nothing can substitute frequent, daily, visits to the wards. Attendance must perforce be physical but mostly mental. Whilst in the ward make full use of your senses — all of them. At first you will not know exactly what you are supposed to notice, but try and make a mental note of what strikes you: a particular gait, or manner of talking or skin colour. A good memory always helps but a notebook where to jot down bits of information as they come your way is indispensable. You can then expand on your notes by looking up books at home or in the library.

Cultivate from the very start the proper attitude towards the patient. Remember all the time that he is in hospital for treatment and only secondarily for teaching purposes. Patients are diseased human beings not diseases. You will find that most of them are co-operative and understanding, but they are also anxious and sensitive. So if you are suspecting anything seriously wrong with them do not make it obvious to them. When asked direct questions about diagnoses and prognoses, be wary. The consultant himself may have thought it best not to divulge such information to them, so it would be wiser to evade such questions in a polite manner.

Before burdening yourself with the signs and symptoms of a host of diseases, for which you will have ample time, you should master the art of taking a good history and carrying out a correct examination. This is easier said than done and it takes some time before one is really good at both. Most textbooks give a good model on which to base your history taking and you are free to choose any of them. Try and master the important headings viz. History of present complaint, Past History, Social History, etc., from the very start and learn to follow sequence in your questioning. In trying to formulate your next question do not shut off your ears to the patient. Let him speak and keep your eyes and ears open all the time while he does so. Note how he describes what has happened to him. Most patients use hand movements and facial expressions which convey a lot of important information. You will learn to sift the important from the redundant information as you gain more and more experience. Certain hints you will learn to expand upon whilst others you will learn to discard. But there is no short cut to obtaining this experience — you just have to take histories. Your histories should be detailed even, perhaps, at the price of exactness. Use the patient's own words as much as possible and avoid using medical jargon until you are quite certain of its exact meaning. The ready availability of the patients' folders will often be a very tempting short-way-out to detailed history taking, but you should refrain from opening the folders before you have finished your own history. Many a time you will be thanked for pointing out something others had overlooked. Do not be afraid of making mistakes: you will learn more from one mistake *you* do than from listening to an hour's lecture from a boring speaker. The first histories may take an hour or more to take but they are nevertheless worth taking well. It is a good habit to re-write a history because the value of certain things will come out better on re-reading. During your first clinical year you will often wonder why you are asked to put all those questions — most of them do not seem to make sense. As the weeks and months go by their value will become apparent: so make an effort and follow the rules.

Examination of the patient *follows* a careful history, and this cannot be overemphasised. You will be hearing all about the newest stethoscopes and will probably soon be going round the wards with one dangling down your necks "a' la Cesario". The layman often thinks that the stethoscope makes the doctor, but this could not be further from the truth. The stethoscope, useful as it is, comes way back after more fundamental methods of examination. In books of semeiotics it comes in where they talk of auscultation, and that comes a long way behind inspection, palpation and percussion. This point needs further elaboration and I would go on by quoting the golden rule: use eyes first and most and hands last and least. Instruments come after hands.

Careful inspection is imperative and this presupposes adequate exposure of the part to be inspected. Here shyness on your part and modesty on the patients' will often be against you. Tact and respect are required to overcome this "false modesty", as a famous English gynaecologist calls it. On the first few occasions your ears will flush and your hands sweat and tremble, but this is only a temporary setback which usually fades away gradually with every subsequent examination.

Learn the proper way of examining a system or organ from the very first examination or else you will find it increasingly difficult to wear off bad habits. All the elementary things of examin-

ing the patient from his right side, closing the window when there is a draught, warming your hand before touching the patient, sitting down and using the flat of the palm when examining a patient's abdomen — all these are basic things of the utmost importance, and to make sure you understand their importance, I will tell you that examiners will be on the lookout for them.

The manner of examination of the various parts of the body you will again find in most books of medicine, surgery and obstetrics. Use yourself as a guinea pig whenever practicable, and your colleagues or brothers where these appreciate the meaning of "for the advancement of knowledge and science". Percuss anything that comes your way till you are quite sure you know what dull and resonant and their various modalities sound and *feel* like. When in doubt consult higher authority by all means, but if you are sure of something and can prove it "stick to your guns".

To conclude I will say that most of the material you are expected to know is in the wards for you to discover and learn in the right way. Most books will tell you that the smell of foetor hepaticus is "mousey" and that of uraemia "fishy", but you must smell them for yourself to know exactly what they mean. Preserve the scientific mind of your preclinical days and cultivate it further. Conserve an enthusiastic attitude towards ward work all the time, and, above all perhaps, keep your receptor organs alert. Knowledge will pile on with the years and there is no real limit to the amount any of us can pile up. The only thing is to keep an open mind, for, as Osler said: "We stop being doctors when we stop being students!"

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"drug therapy in the patient with renal impairment"

dr. tonio j. bugeja m.d.

Introduction: The kidney suffers a triple pharmacological relationship to drugs: the first is the renal damage as a direct effect of such drugs as phenacetin and heavy metals. In such cases the area of greatest damage is the papillary region of the renal medulla by reason of the highest drug concentration and lowest oxygen tension found here. The second type of damage may result from hypersensitivity to certain drugs while the third pharmacological relation is the accumulation of drugs in the blood especially those whose active form is principally excreted by the kidney in cases where the kidney is becoming insufficient. This build-up of active drug leads to varied side-effects including nephrotoxicity and further renal impairment. Cardiac glycosides, diuretics, antihypertensives, antibiotics, sedatives and analgesics and hypoglycaemic agents are a few and perhaps among the commonest of the many drugs which it may be essential to administer to the patient with renal insufficiency or overt failure.

To start with cardiac glycosides it has been shown using tritiated digoxin, that the effect of renal failure on digoxin is essentially that of changing this short acting preparation into a slightly longer acting one. The advantage of using a relatively short-acting preparation in such patients stems from the rapid shifts of potassium which occur during treatment and which may precipitate digitalis intoxication. Thus in a functionally or anatomically anephric patient on haemodialysis potassium shifts are likely to result in intoxication; this would be of shorter duration with digoxin than with digitoxin. On the other hand since hepatic detoxification is a major route of ridding the body of active digitoxin, rapid fluctuations in renal function are less liable to cause fluctuations in the blood levels as with digoxin. Smoother digitalization is thus obtained.

Diuretics are frequently used to decrease the congestion and oedema attendant on renal insufficiency. In the early stages of impairment patients can usually tolerate diuretics in standard doses provided sodium and volume depletion are carefully avoided. Once uraemia sets in though, the drug and its dose must be carefully selected. With organomercurials delayed renal excretion is liable to lead to toxic damage of the renal tubule with further impairment of renal function. Thiazide diuretics are still of major importance in mild to moderate renal insufficiency and have a low incidence of toxicity. However once the creatinine clearance falls below 30 ml/min (N =80 - 120) renal function may become further impaired and these diuretics also become much less effective. The increased renal impairment is said to be reversible on stopping the drug. Frusemide and Ethacrynic acid are highly effective in treating the oedema associated with renal insufficiency. Frusemide is not only very powerful but it has proven clinically superior to thiazides in achieving diuresis in hypoalbuminaemic states and in states of severly depressed glomerular filtration rate (e.g. creatinine clearance of 10 - 20 ml/min). Doses ranging from 80 mg/day to several hundred mg may be employed until an effective diuresis results; frusemide therapy results in little or no change in renal function unless acute volume depletion occurs. Still hyperuricaemia, hyperglycaemia and pancreatitis have been reported with thiazides and frusemide. Ototoxicity and profound electrolyte disturbances may occur with high doses of frusemide. Spironolactone usefully added to a thiazide diuretic in cases of refractory oedema, inhibits the tubular exchange of sodium for potassium and must therefore be cautiously administered in renal insufficiency since hyperkalaemia may occur.

In both benign and malignant hypertension, renal impairment can be prevented or delayed by effective antihypertensive therapy. With both debrisoquine and reserpine caution should be exercised when treating hypertensive patients with renal insufficiency since they may adjust poorly to lowered blood pressure levels. Methyldopa is largely excreted by the kidney. Therefore patients with impaired renal function may respond to smaller doses of the drug than patients with normal kidney function. In hypertensive patients with normal kidneys who are treated with hydralazine, there is evidence of increased renal blood flow; in some cases improved renal function has been noted where control values were less than normal prior to such therapy. However, as with any antihypertensive agent, hydralazine should be used with care in patients with advanced renal damage. Guanethidine may be effective in renal hypertension, including that secondary to pyelonephritis, glomerulonephritis and renal amyloidosis. Hypertension secondary to constriction of the renal artery has been treated symptomatically with guanethidine with good effect. Still cautious administration is imperative in cases of renal disease with high blood urea levels since the decreased blood pressure may further compromise renal function.

Antibiotics in relation to the kidney can be divided into those which are potentially nephrotoxic and those which become nephrotoxic in renal impairment unless the dose is adjusted: the full loading dose is administered but the

maintenance dose is curtailed to the degree of insufficiency. Considerable overlap exists between these two broad divisions.

Penicillin is rapidly inactivated, so that cumulative toxic effects occur only with doses over 10 million units per day in cases of severe renal impairment. These include neurotoxicity, muscular hyperirritability, generalized convulsions and hallucinations. As 10 million units of potassium penicillin G contain about 17 mEQ. of potassium, very high doses of penicillin should be avoided in the anuric patient. Ampicillin therapy in such patients is relatively safe and renal function deterioration and an increase in the incidence of side effects only occur with doses in excess of 500 mg 6 hourly. Similarly methicillin and cloxacillin dosages need only be adjusted in very severe cases of renal impairment. High doses of carbenicillin in patients with renal impairment may lead to bleeding disorders.

Tetracycline excretion is markedly delayed in cases where the creatinine clearance is less than 30 ml/min and then the dose must be readjusted. Besides being nephrotoxic tetracycline accumulation may interfere with protein synthesis resulting in an increase in nitrogenous load for renal excretion. It may precipitate uraemia, hyperphosphataemia and acidosis in renal insufficiency. These changes are usually reversible.

Kanamycin is liable to cause nephrotoxicity in states of renal impairment. This, unlike ototoxicity, which if it occurs is usually bilateral and irreversible is reversible a few weeks after the drug is stopped. Advanced age and previous administration of ototoxic drugs constitute a significant predisposition. With streptomycin ototoxicity is well known to occur especially with the higher doses in patients over 40 years of age. This is especially so when renal impairment occurs. Dehydration and/or hypotension in addition to high blood levels predispose to ototoxicity and in some cases uraemia. This drug can often be avoided in patients with renal malfunction. Gentamycin excretion is virtually wholly via the kidneys and the maintenance dose must be adjusted in accordance with the glomerular filtration rate. Both nephro and ototoxicity which may complicate therapy in such cases are reversible on withdrawal of the drug. The serum half-life of erythromycin is only slightly prolonged in the anuric patient so that extrarenal factors must play a role in ridding the body of the drug. It appears relatively safe to prescribe erythromycin in the usual therapeutic dosage in those patients with renal impairment.

With reference to cephalosporins, while cephalothin requires little adjustment except in the worst cases of renal impairment (due to its very low toxicity), cephaloridin has been associated with both acute renal failure and impaired renal function in patients on the recommended doses. Though these side-effects are reversible it follows that significant dosage changes are required in cases of renal malfunction. The same applies to cephalexin which can be removed by haemodialysis.

The possibility of bone marrow depression as a side-effect of Chloramphenicol and the availability of less toxic antibiotics has decreased the use of this drug in urinary tract infections considerably. Where serious infections require its use in patients with severe renal insufficiency no dosage adjustment is required (as the half-life of the active form of the drug is not increased) except in cases of concomitant liver disease or in the newborn where the rate of change of this antibiotic to its glucuronide is slower than normal.

While with nitrofurantoin potentially toxic serum levels may be reached in uraemic patients, in the case of nalidixic acid high urine concentrations can still be achieved in the presence of a creatinine clearance of less than 30 ml/min. Therefore in patients with poor kidney function higher doses should be given initially to achieve a high serum concentration early and then use a maintenance dose after 2 or 3 days.

Polymyxin B is slowly excreted into the urine; therefore if parenteral therapy is repeated more frequently than twice daily drug accumulation may occur even with normal renal function. It also follows that renal disorders would facilitate nephrotoxicity and neurotoxic symptoms consequent on high blood levels of the drug. It is recommended that patients with such trouble be given less than 1 - 2 mg/kg body wt./day. The same argument holds for colistin.

Amphotericin B is very nephrotoxic. Even in patients with normal renal function it has been reported to decrease renal plasma flow and glomerular filtration, to impair the concentrating power, produce urinary potassium loss with consequent hypokalaemia and hydrogen-ion retention; renal tubular acidosis may supervene. Not only is a reduction in dosage called for in the face of renal impairment but also frequent renal function, electrolyte and acid base evaluation is indicated during the term of therapy.

Sulphonamides should be avoided in renal insufficiency states because of the danger of crystal precipitation in the renal tubules which is more likely to occur as a result of diminished urinary output. Whenever these drugs are used a good urine output should be ensured. Sodium sulphadimidine in particular has been used in renal impairment since effective urinary and blood concentrations are obtained without much drug accumulation.

Hypnotics and sedatives are useful in combating the insomnia and restlessness that are often manifest in patients with renal failure. While chloral hydrate, the shorter acting barbiturates and diazepam can be given in the usual doses, long-acting barbiturates, chlordiazepoxide and the phenothiazines must be cautiously used, the latter mainly because of individual variation in metabolising the drug. It is necessary to distinguish the shorter from the longer acting barbiturates because while the former are

largely metabolised by the liver, the latter are mostly excreted by the kidneys.

No ideal drug is available as yet to combat the nausea and vomiting of the uraemic patients. Prochlorperazine is effective and can be used in some cases in the usual doses. Occasionally these symptoms respond well to small doses of diphenhydramine (Benadryl). This is also useful in the patient with uraemic pruritus. Oral hypoglycaemic agents are best avoided. Otherwise reduced dosage schemes are advised for patients with chronic renal insufficiency as profound hypoglycaemia may result due to an increased duration of action. Phenformin may also lead to lactic acidosis in such patients.

Salicylates are to be avoided in the uraemic patient; renal excretion is erratic and gastrointestinal irritation may worsen the bleeding directly associated with uraemia. Platelet adhesiveness is also affected. Dextropropoxyphene (Doloxene) has been used in patients with renal insufficiency. The drug is chemically close to methadone but is both less analgesic and habit forming. Its analgesic power is equivalent to that of codeine. As it is metabolized primarily by the liver it may be given in therapeutic doses to these patients without significant side effects. Other drugs which have been used in patients with renal insufficiency without untoward effects include indomethacin (but not phenylbutazone), allopurinol in primary gout or in the rarer secondary gout, diphenylhydantoin in the treatment of convulsions and amitryptylene and imipramine in depressive states.

It must in conclusion, be emphasised that side-effects of drug therapy in patients with renal impairment are both more likely and more long-lasting when they occur. The seriousness of such a possible issue demands more cautious prescribtion and administration in such cases.

urinary proteins in health

raymond agius

HISTORICAL

Proteinuria is said to have been noted for the first time by D. COTUGNO in 1770 although it was R. BRIGHT in 1827 who drew the proper conclusions from the phenomenom. Pathological proteinuria then became the subject of study by several workers. In 1878 C. VON LEUBE introduced the concept of a benign proteinuria. A few years later (in 1895) K. MÖRNER showed that normal human urine contained small quantities of protein. The figures he gave (22 to 78 mg/litre) are not far from the values most commonly accepted nowadays.

INTRODUCTION

Urinary proteins in health usually make up about one half of the macromolecules in urine. They are found in concentrations which are often too small to give a positive reaction to routine clinical tests. Owing to the extent of physiological variation and also to the variety of methods employed, it is difficult to define a range of normal values. RIGAS and HELLER[33] gave a mean value of total urinary protein output of 39.0mg/24 hrs, with a standard deviation of 5.7 mg. Several other figures often with little agreement have been quoted, such as a range of 20 to 75 mg/24 hrs[23], to a mean value of 103 mg/24hrs.[30] or even higher. About 65 proteins in normal urine have so far been described and at least half this number are thought to be plasma proteins. Most of the plasma proteins in urine originate by a process of glomerular filtration which is followed by tubular reabsorption. However it is possible that some plasma proteins may gain access to the urine in the more distal parts of the urinary tracts or in the genital secretions[4]. Some non-plasma urinary proteins are known to originate from the healthy nephron i.e. glomeruli and tubuli. Normal urine also contains proteins from the glands or shed cells of the urinary tract, and in the male seminal proteins arise from the genital tract especially from the prostate and bulbo-urethral glands[13].

FILTRATION-REABSORPTION PHYSIOLOGY

Most authorities agree that the normal glomerulus exhibits a small but significant permeability to proteins and that part of the filtered proteins are reabsorbed in the proximal convoluted tubules. The anatomical barriers, as seen under the electron microscope, which could act as filters to the macromolecules are: the endothelium, the basement membrane and the glomerular epithelium. So far there is no definite answer as to whether the basement membrane (or a component of it e.g. the lamina densa) or else the epithelial slit pore (or components of it e.g. the cell coats or the slit diaphragm) is the site for glomerular filtration of macromolecules[16]. Some workers consider the basement membrane to be the main filtration barrier[1, 18] while others favour the pore theory[19].

Calculations based on physiological data indicated that the glomerulus behaved as if it was a semi-permeable membrane containing cylindrical pores having a radius of 35 to 42 A°[19]. According to this theory, the protein molecules experienced steric hindrance at the entrance of the pore and viscous drag while moving through its lumen. More recently, experiments with artificial polymers have suggested that the glomerular membrane is heteroporous. ARTURSON et al[1] propose that the glomerular filter has a large majority of small pores of radius 20 to 28 A° and a minority of large pores of radius up to 80 A°, in the proportion, small to large, of 10,000 to 1. From this and other studies, it seems likely that the morphological structures responsible for the porous behaviour of the glomerular wall have variable pore sizes which are perhaps distributed around a mean pore size[18]. These results explain the progressive restriction of passage of macromolecules with increase in molecular size, together with the fact that some large proteins e.g. beta lipoprotein (mol. wt. 250,000) are not found in urine in health. However, mere molecular size is not the only factor involved in the selective behaviour of the glomerular membrane towards macromolecules. Thus it is known that proteins are cleared by the glomeruli at a much smaller rate than artificial polymers of approximataely the same molecular size. This has been suggested to be a purely physical phonemenom related to charge effects and a more rigid molecular structrue in the proteins[15].

The total quantity of plasma proteins filtered through the glomerular membrane in man is not known. It should be evident from the magnitude of the glomerular filtrate (170 litres/day) that a very small concentration of protein in the glomerular filtrate is more than enough to account for the normal daily urinary excretion of plasma proteins.

Reabsorption of part of the filtered plasma proteins occurs in the proximal convoluted tubules[4, 18] as has been shown by clearance, morphological and other studies. Some evidence on the subject of reabsorption is conflicting, but in health the process is thought to be selective, favouring the absorption of the smaller proteins. Pinocytosis has been suggested as a mechanism for reabsorption and it is thought that the tubular cells catabolise the protein, although return of native or partly catabolised protein to the bloodstream is not to be excluded. There is evidence that the kidney is the most important site for catabolism of many low molecular weight proteins reabosorbed by the tubules[4].

The existence of a reabsorption process for proteins implies that unless the reabsorption of

a particular protein has reached its maximum capacity (Tm) the urinary output of that protein will probably be zero. However, once this transport maximum or threshold has been exceeded the urinary output of the protein should increase linearly with the plasma concentration. Therefore, it is possible to relate the plasma concentration of a protein (P), the urinary concentration of the protein (U), the flow rate of urine per unit time (V) and the threshold for reabsorption (Tm). The glomerular clearance of the protein is given by the term:

$$\frac{U \times V}{P - Tm}$$

The ratio of the glomerular clearance of a protein to the concomitant glomerular filtration rate, i.e. G.C.P./G.F.R. is an index of glomerular permeability to the molecule. This fraction has been variously termsd "glomerular clearance ratio", "filterability", "permeability coefficient". or "sieving coefficient". The last term is the favoured one in the pore theory of protein filtration.

The clearance of proteins may be a useful index for studying renal function but several difficulties must be borne in mind[15]. Thus the existence of a tubular reabsorption mechanism about which little is known, the possibility of protein-protein interactions etc. complicate the issue. No direct relationship exists between protein clearance and molecular weight. Technical difficulties include the lack of suitable quantities of pure protein for "loading" experiments and the sophisticated nature of the quantitative immunochemical techniques. Methods employing enzyme clearances[9] offer some hope as simpler techniques.

BIOCHEMICAL TECHNIQUES

In the biochemical investigation of urinary proteins, the first step usually consists in concentrating the urine. Methods such as alcohol precipitation, evaporation, dialysis, ultrafiltration and lyophilization are used. The possibility of artifactual changes occurring during these procedures must be kept in mind when interpreting the results[25]. The concentrate is then analysed using one or more methods. Moving boundary electrophoresis was first used for this purpose by RIGAS and HELLER[33]. Electrophoresis may also be carried out on paper, cellulose acetate or starch gel. The first immunoelectrophoretic investigation of plasma proteins in normal urine was carried out by GRANT[12]. Other techniques used include gel or ion-exchange chromatography[27] and uttracentrifugation. Immunological techniques are commonly used for studying proteins originating from the urinary tract. Some qualitative and quantitative tests for urinary proteins have been recently evaluated[6].

PLASMA PROTEINS

Electrophoretic studies performed about 20 years ago suggested a resemblance between the protein patterns of normal urine and plasma[33]. The greater part of plasma proteins in the urine originate from the nephron as has been outlined above. However some plasma proteins in urine may orginate from the blood and the interstitial fluid in more distal parts of the urinary tract[4]. It is possible that some normal urinary proteins which may derive from the plasma are difficult to identify in it with the techniques currently available because of their very small concentration. The majority of urinary proteins of plasma origin have a molecular weight of less than 200,000 probably because of the molecular-sieve effect of the glomerular filtering membrane. It is difficult to classify plasma proteins in normal human urine and the problem is rendered still more complex by the fact that plasma protein fragments have also been identified. More comprehensive reviews than the following appear elsewhere[3,4].

Albumin (mol. wt. 69,000) is quantitatively the most important plasma protein in urine[28]. Results of urinary albumin excretion in health, as for many other plasma proteins, vary widely with the techniques used. Immunochemical techniques give results ranging from an average daily excretion of slightly more than 10mg.[4] to a range of concentrations from 0 to 66 mg/litre[6]. The Glomerular Clearance Ratio of albumin does not exceed 0.02% in average normal subjects[15].

Tryptophan rich serum pre-albumin (Thyroxine Binding Prealbumin) is found in very small quantities in normal urine [28]. It is a glycoprotein of low carbohydrate content and has a molecular weight of about 60,000.

Alpha-1 and alpha-2 globulins are the main plasma globulin components of urine in health. Alpha1 acid glycoprotein (orosomucoid) has a molecular weight of about 40,000 and a carbohydrate content of about 40% Its clearance is 3 times that of Albumin[4]. Alpha2HS glycoprotein is excreted in similar quantities and has a slightly higher molecular weight. Its clearance is 3.3 times that of Albumin[4] and this may be taken as evidence of the selective glomerular permeability favouring smaller molecules.

In normal urine only monomeric haptoglobin (an alpha-2 glycoprotein mol.wt. 170,000) from type 1-1 and 2-1 individuals has been observed. The fact that the polymeric haptoglobin from healty type 2-2 individauls has not been observed in urine[4] shows the size selectivity of the glomerular filter.

Caeruloplasmin, a Copper binding glycoprotein weight 150,000 and alpha-2 electrophoretic mobility is also found in very small quantities in normal urine. It demonstrates the difficulties of protein clearance as a renal function index since its clearance varies unpredictably from one individual to another[15]. This could be due to either genetically determined forms of differing molecular size (cf. haptoglobin) or else to protein-protein interactions in the plasma.

Other alpha globulins in normal human urine include antitrypsin, lipoprotein, Zn-glycoprotein and a microglobulin.

Beta globulins are generally excreted in very small quantities in normal urine. Thus, for example, only about one-third of a milligram each of transferrin and beta-2 glycoprotein I are excreted per day.

Several immunoglobulin components have been identified in normal human urine[3] and, as in the plasma, not all of them have the classical gamma globulin motility. Immunoglobulin G (mol. wt. 150,000) is found in the largest amounts, about 3 mg. being the normal daily average. In spite of its much larger molecular size, its renal clearance is about 0.8 that of albumin. This may be due to excretion in the urinary tract, relatively less tubular reabsorption or else formation of the macromolecule from easily filtrable polypeptide fragments[4]. Only about 1 mg of Immunoglobulin A is excreted per day but it is interesting to note that part of it may be secreted by epithelial cells[5]. Immunoglobulins M, D and E are either not found at all or else are excreted in extremely small quantities.

Most of the microimmunoglobulins of normal urine consist of free light chains i.e. the normal counterparts to Bence Jones protein[36]. Light chains isolated from normal urine have also been found to occur in polymeric forms[3]. Fragments of immunoglobulins in normal urine were first studied by FRANKLIN[11]. Urinary microimmunoglobulins closely related to the Fc fragment of IgG have been described[38]. Components of complement are found in very small quantities.

Immunochemical studies have shown the presence of small quantities of fibrinogen fragments in normal urine[4].

In health, urine is also known to contain small quantities of enzymes derived from the plasma, and these include lactate dehydrogenase, amylase, plasmin, trypsin, glutamate-pyruvate transaminase and others.

Protein hormones and their precursors have also been detected. These include insulin, proinsulin and hypophyseal gonadotropins.

Plasma proteins of small size, many of which are still unknown, probably form a large fraction of the proteins in normal urine. These proteins are often present in small concentrations in the plasma, but because of their size seem to be preferentially excreted in the urine[4].

NON PLASMA PROTEINS AND THEIR ORIGIN

In health, besides proteins entering the urine from the blood through the glomeruli, urine also contains (a) proteins arising from the renal cells themselves (b) proteins from the glands or shed cells of the urinary conducting and storage system (c) in the male, seminal proteins in trace quantities from the genital tract.

GRANT[13] showed the existance of numerous non plasma antigens in normal urine. A feature which seems to be common to all these proteins is that to some extent they all seem to contain carbohydrate moieties. Data concerning most of the non-plasma proteins in urine is fragmentary and many of the claims regarding their origin are speculative. BOURRILLON[7] claims that they make up to 20 to 25% of the non dialyzable constituents of normal urine and has separated them chromatographically into 17 fractions.

There is now no doubt that the healthy kidney contributes non-plasma proteins to urine. Recently it has been shown that soluble antigenic components of the glomerular basement membrane (GBM) are found in the urine of normal people[20]. There are at least two such antigens and they have low isoelectric points (between pH 1.7 and 3.8), a very high carbohydrate content and a post-albumin mobility on zone electrophoresis.

Probably the most renowned of the non-plasma urinary proteins is the glycoprotein of TAMM and HORSFALL[37]. The T and H glycoprotein is present in concentrations of up to 2.5 mg./100 ml. of normal human urine, and is an important fraction of the so called "uromucoid". Several authors[7, 14, 22] have confirmed that specific antibodies raised against the T and H glycoprotein are never precipated in blood plasma but aqueous extracts of renal parenchyma will combine with these antibodies giving a reaction of identity. Moreover, this glycoprotein can be identified in convoluted tubular cells by fluorescein labelled antiserum. The T and H glycoprotein has been extensively studied[22] and is one of the variety of soluble "mucoids" which by competing with the cellular receptors for certain viruses inhibit haemagglutination.

Other urinary proteins originate from the kidney, and these include enzymes such as carboxyl esterases, and one hormone — erythropoietin.

Some proteins could arise from the transitional epithelium of the pelves, ureters and bladder either from the surface lining or from shed cells. The origin of secretory immunoglobulin A is still speculative[5].

GRANT[13] found 4 trace components common to male urine, female urine and semen. These possibly arise from the urethra.

Components common only to male urine and identified immunologically in semen seem to be present only in small traces. Prostate and bulbourethal glands probably are the main contributors.

The female has urethral glands homologous to those of the male but no urinary proteins of non-plasma origin, peculiar to this sex have been identified so far.

Normal urine also contains several carbohydrate complexes such as blood group substances, glycopeptides etc. Glycopeptides form the major fraction of protein-related substances of normal urine[7].

PHYSIOLOGICAL VARIATIONS IN URINARY PROTEINS

At this stage it should be evident that all urine contains small quantities of protein. There-

fore, in the light of present knowledge, the term proteinuria should be taken to mean an excretion of urinary protein significantly greater than the values outlined above.

As all other physiological parameters, urinary protein excretion is subject to variation from one individual to another and also varies in the same individual from one physiological situation to another. The data given above correspond roughly to the urine from an average normal adult under basal conditions. The urinary proteins can vary with age, exercise, posture, pregnancy and possibly other factors such as sex, mental state, environment etc. In these changes from the "basal" state there is often an increase in the excretion of plasma proteins but this is not of significance in the lowering of the blood plasma protein level. However, clinically it may be difficult to distinguish on the basis of protein concentration in isolated speciments, whether a given proteinuria is pathological or else "functional" i.e. of physiological origin.

ENVIRONMENTAL FACTORS

Relatively little work has been carried out on geographical variations in urinary protein. It is known that low temperatures can produce a rise in plasma protein excretion but the mechanism of this phenomenom is uncertain.

EXERCISE

The proteinuria following mascular effort was observed for the first time by VON LEUBE in 1878. His results were subsequently confirmed by several workers.

During exercise, excretion of total urinary protein rises from a normal average of about 0.03 mg/min to as much as 2.00 mg/min. This rise is more impressive when expressed in terms of urinary protein concentration since urine flow diminishes during exercise. Thus it increases from 0.04 mg/ml. before exercise to as much as 5 mg/ml[29]. As in other functional proteinurias, the urinary proteins affected are the plasma proteins. The urinary colloids not detected in plasma do not account significantly for the rise of the urinary protein excretion which occurs during and after exercise.

Detailed studies have shown that following exercise there is particularly a significant rise in urinary levels of tryptophan rich prealbumin, albumin, alpha-1 acid glycoprotein, transferrin, immunoglobulin A and immunoglobulin G. The presence of higher molecular weight proteins in "exercise urine" might result from an increase in the glomerular permeability or else it is possible that tubular reabsorption had reached its maximum value for most of these plasma proteins. No direct relationship could be found between the molecular weight of a protein and the value of its renal clearance[28].

It is possible that in exercise release of epinephrine and norepinephrine produces a vasoconstriction of the renal glomerular arterioles slowing down renal plasma flow and glomerular filtration rate, thus allowing a better diffusion of plasma proteins through the glomerulus into Bowman's space[29]. In experimental animals renin has been known to induce proteinuria, and in rats this proteinuria seems to require the presence of certain corticosteroids and is also influenced by other hormones[26]. Whether hormonal factors are important in determining changes in urinary proteins in man during conditions of stress is unknown, but this still constitutes a possibility to be borne in mind.

POSTURE

During upright ambulation in healthy subjects the fractional daily protein excretion is high but this is usually not high enough to be detected by qualitative tests[34]. However in some healthy individuals the protein excretion on standing (orthostasis) may be quite marked. The proteinuria associated with posture has unfortunately been subjected to different diagnostic criteria and has been referred to by different names. Postural proteinuria can be broadly defined as a laboratory syndrome whose diagnosis requires the absence of qualitative proteinuria (i.e. protein excretion should be less than 0.03 mg./min.) during recumbency, and its presence during quiet upright ambulation or standing[34]. It is fairly com mon, equally found in both sexes, and commonly appears at the onset of puberty usually disappearing in the early twenties.

Some observers claim that all cases are related to lordosis, but others have found that lordosis plays no part in a majority of cases studied. It is generally held that the rise in urinary protein excretion is the result of some change in renal haemodynamics but there are two main schools of thought striving to explain the phenomenon. From the evidence gathered so far it would seem that both the postulated mechanisms do in fact play a part.

One school considers orthostatic proteinuria to be the result of the fall in venous return produced by venous pooling on assuming the upright posture. The resultant compensatory vasoconstriction affecting also the renal vessels would in some way determine an increase in plasma protein excretion. It may be of relevance to note that when experimental animals are kept upright proteinuria always follows, but division of renal nerves prevents this phenomenom from occurring[14].

According to the second school, on assuming the lordotic position the liver rotates forwards and downwards and compresses the inferior vena cava against the verterbrae. As a result there is a rise in pressure within the inferior vena cava and the renal veins, presumably producing passive venous congestion and hence a proteinuria. In some cases, the increased urinary excretion of protein comes from the left kidney only, and in this situation it is presumed that there is a rise in venous pressure in the kidney following compression of the left renal vein on the anterior convexity of the aorta.

On standing protein output was less than 1 mg./min. in 65% and more than 1 mg./min. in 35% of 350 cases of orthostatic proteinuria studied, but occasional very high excretion rates have been reported[14]. Different results of protein composition have been obtained. Some claim a strong predominance for albumin[14], while others found a rather poor selectivity of the glomerulus, with excretion of a large fraction of higher molecular weight globulins[35]. However, many of the results show the existence of concentration patterns for individual proteins that in general resemble those of normal urine.

PREGNANCY

In pregnancy[10], there is an increased excretion of those plasma proteins whose levels are increased in this physiological state. In particular, one has in mind the chorionic gonadotropin, a glycoprotein present in relatively large concentrations in the urine of pregnant women, first appearing in the second week after ovluation and persisting until about the fifteenth week of gestation.

One should note that the urine of sexually mature women during a period of about four days before ovluation contains a gonadotropic hormone, presumably of pituitary origin.

NEONATES

Normal new born infants may have higher levels of urinary protein during the first three days of life[32].

OTHER FACTORS

It has been claimed, especially in older writings, that ingestion of excessive quantities of protein may be followed by a delayed transient rise in urinary protein excretion.

Severe mental strain or emotion is also claimed to induce a transient proteinuria in some individuals.

CONCLUSION

In health, a wide variety of proteins are found in urine, ranging from the normal counterparts of Bence-Jones protein to fragments of the glomerular basement membrane. In fact, normal urine has been shown to contain most of the proteins which are present in the urine in various pathological conditions with variations only in the amounts excreted.

Many proteins experience filtration and reabsorption processes and the concept of clearance may, with caution, be applied to them also. However the behaviour of proteins is much more complex than that of small solutes and many proteins do not conform to what would be expected solely on the basis of molecular size. The site and nature of glomerular filtration of proteins are still controversial. The old "molecular-sieve" model is becoming more inadequate and it is hard to accept that the glomerular membrane behaves merely as an inert sieve. Physiological variations in functional pore size possibly associated with contractile properties in the podocyte have been postulated. Likewise, a great deal of work has yet to be done to elucidate the mechanism and selectivity of tubular reabsorption, and how far it is determined by plasma protein levels.

The importance of neural and hormonal factors in bringing about changes in urinary protein is not clear. Are the physiological changes in protein excretion secondary to haemodynamic changes or are there more subtle mechanisms acting directly on the nephron?

Relatively little is known about the nature, origin and function of the several non-plasma proteins in urine. Study of the Glomerular Basement Membrane antigenic fragments is yielding information suggesting their possible rôle as autoimmunogens involved in the causation of kidney disease. Not much is known about the functional significance of the glycoproteins produced by the urinary tract. There is insufficient explanation, for example, of the reasons for the complex chemical behaviour of the T and H glycoprotein, or of the nature and possible functions of urinary immunoglobulin A.

In future, these and other problems will probably be solved, and new ones posed. Until the normal patterns of urinary protein excretion are adequately explained, the full interpretation of the urinary protein patterns in disease will remain largely empirical.

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bacterial resistance

anthony bernard

Bacterial resistance may be of two types. In 'drug tolerance' (primary or acquired) the bacterial Strain grows in the presence of the drug either with a total indifference or in a less luxuriant manner. In 'drug destroying' resistance, bacterial products e.g. penicillinase, inactivate the drug.

Development of some degree of resistance by most species of bacteria to most chemotherapeutic agents has been demonstrated by serial transfer in the presence of the drug and although there is yet no strain resistant to all modern drugs there is no reason to believe that the development of newer drugs will keep up with the development of resistance by bacteria. This was never more painfully realised than when the penicillinase producing staphylococci emerged causing many deaths until the penicillinase resistant penicillins were introduced in 1960. (The incidence of drug tolerant staphylococci meanwhile continues increasing). Complicating this is the fact that cross resistance occurs both between related drugs e.g. sulphanomides and unrelated drugs. Sutherland showed that resistance by S. Paratyphi B to either of the drugs Pencillin G, Ampicillin, tetracycline or Chloramphenicol increased its resistance to all.

A population of bacteria resistant to a certain drug may develop as a result of therapeutic selection of naturally occuring resistant strains when that drug is used (— more so when used wrongly). The sensitive bacteria are destroyed while the resistant strains which are normally present as a very small percentage, free of the competition of sensitive strains overgrow to replace the sensitive population. In this way the incidence of sulphanomide resistant gonococci increased by 40% during the first 10 years following the introduction of sulphanomides.

Another way in which a resistant bacterial population emerges is by spontaneous mutation producing drug tolerance. These bacteria then overgrow in the presence of the drug at the expense of the sensitive strains. While this may take place in many steps taking a long time resistance to streptomycin can develop quickly in a single step.

In recent years increasing importance has been given to the production of resistance by the transfer of genetic material. The transferred genes are in the form of plasmids (non chromosomal genetic material) or episomes which alternate between being free and chromosomal. These reproduce independently of the nucleus and are responsible for characteristics not vital to the bacterium but useful in adverse conditions e.g. drug resistance and the ability to conjugate, toxin production or sugar fermentation (— this may cause confusion if S. typhi acquired the plasmid which determines lactose fermentation).

Transduction involves the transfer of plasmids or episomes by bacteriophages from a resistant organism to a previously sensitive one. This is mainly intraspecies, governed by the phage type of the bacteria involved, occuring most readily between strains of group 1 or group iii. This method of transfer of resistance, which may be single or multiple, has been shown experimentally by Jarolmen et al (1965), Novick and Morse (1967). (Lysogenic conversion does not involve transfer of a property from one strain to another, the phage's DNA confers new properties on the infected bacterium e.g. non-toxigenic C. diphtherie can be rendered toxigenic).

Soluble-DNA mediated transformation involves the direct incorporation of DNA from a resistant strain by dividing bacteria. This can occur when the donor and recipient bacteria are of the same or closely related species.

A complex of genes responsible for conjugation and gene transfer known as the sex factor gives the bacteria possessing it, the ability to produce sex pili necessary for conjugation and gene transfer. Thus the plasmid ensues its transmissibility. Without this the non-transmissible plasmids may be co-transferred with one that is.

During conjugation transfer of plasmids determining resistance to various drugs may be transferred en bloc or in part. This is known as infectious resistance. Resistance to sulphanomides, tetracyclines, chloramphenicol, streptomycin, from mixed cultures of Shigella and Salmonella has been transferred experimentally to sensitive E. coli. This resistance can then be retransfered to to sensitive pathogens. Evidence that this occurs in the human bowel has been obtained and is known to occur between organisms of all genera of the enterobacteriaceae (also with Serratia marcescens, Vibrio cholerae and Pasteurella pestis).

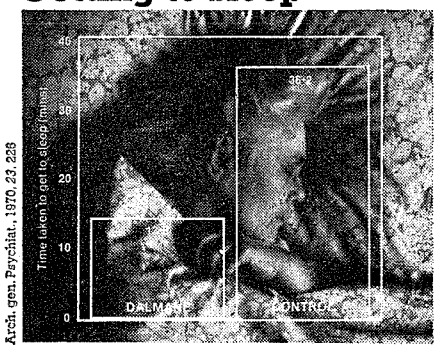
The studies of Anderson and his colleagues on the spread of infectious resistance among intestinal bacteria in farm animals and thence to man, the frequent existence of infectious resistance in E. coli and the possibility of transfer of resistance to chloramphenicol and ampicillin to S. typhi stimulated concern and renewed investigation into this potentially calamitous state of affairs. Suspision fell readily on the large-scale administration of antibiotics to farm animals in the form of feed supplements to promote faster growth and although it is known that in the absence of the drug the bacteria revert to sensitivity there is no general agreement as to the importance of this as a source of resistant bacteria,

(1) *Antibiotic and Chemotherapy* — Garrod & O'Grady.
(2) *A short textbook of Medical Microbiology — Turk &* Porter.
(3) *Bacterial Plasmids* — G.G. Meynel.

DALMANE

a new and powerful treatment for insomnia

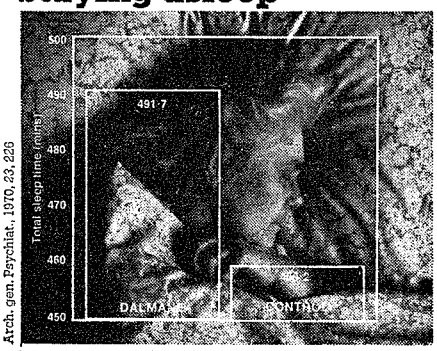
Getting to sleep



Arch. gen. Psychiat., 1970, 23, 226

Patients asleep in less than half the time
Clinical trials[1–3] have shown that Dalmane cuts sleep latency – the time taken to get to sleep – by half. In one study[3] Dalmane reduced the average sleep latency in a group of insomniacs from 36·2 minutes to 13·9 minutes.

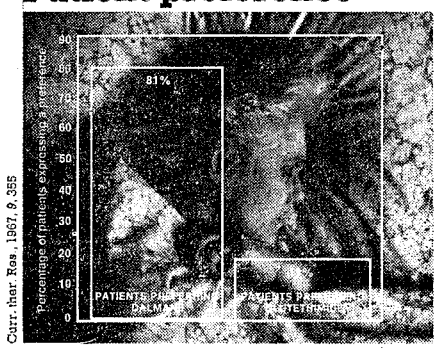
Staying asleep



Arch. gen. Psychiat., 1970, 23, 226

Average sleep of more than 8 hours
Dalmane increased the duration of sleep to – in one published study[3] – an average of 8 hours 11·7 minutes in patients who had previously suffered from insomnia. Dalmane also reduces the number of nocturnal awakenings[1,4] and the actual length of time spent awake during the night – from an average of 52·8 minutes to 24·3 minutes in one trial[4].

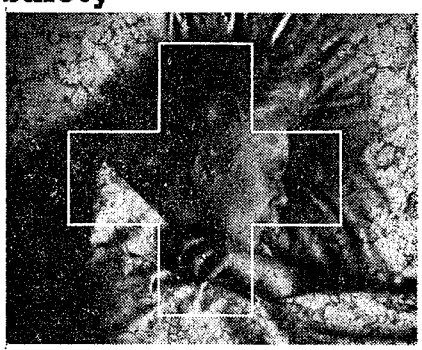
Patient preference



Curr. ther. Res., 1967, 9, 355

Preferred by a greater number of patients[5] – low incidence of side-effects
In one trial in which Dalmane was compared with glutethimide, of those patients who expressed a preference 81 per cent did so in favour of Dalmane, whilst only 19 per cent preferred glutethimide. This high level of patient preference is due to the ability of Dalmane to produce sound sleep with a low incidence of side-effects. Dalmane has been shown to produce less hangover than glutethimide in another trial[6], than a barbiturate[7], and, in one trial, even a placebo – 9 cases with Dalmane, 25 with placebo[8].

Safety



A non-barbiturate treatment for insomnia with a wide margin of safety
Dalmane has an extremely high mean lethal dose in mice and rats[9], thus suggesting that overdosage would be unlikely to present undue problems of management or threat to life. Human toxicity studies[10] in which healthy men were given large doses of Dalmane for some time confirmed that it is well tolerated

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Dalmane is a trade mark for pharmaceutical preparations containing flurazepam.

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the problem of obesity in malta and gozo

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This problem stares us in the face. Figures and statistics are quite unnecessary and I make no apology for not including them in this paper: every doctor in practice knows that the chances are that his next patient will be overweight to some extent. I propose to deal with the subject under three headings: (1) why are there so many fat people around? (2) How does obesity complicate life? and (3) What can the medical profession do to help solve this problem?

(1) Obesity is of course not limited to the Maltese Islands. It is in fact the most common nutritional disorder at present in North America and Western Europe where it gives rise to more ill-health than all the vitamin deficiencies put together. Nevertheless it has a greater incidence here than in, say Great Britain. I put forward three reasons for this. Firstly, as a people we are physically lazy. It is most exceptional for men or women over the age of 25 to take regular exercise. Cars increase and multiply and are used for ridiculously short journeys. Visits to the sea-side mean sitting down to an appetizing meal of *ħobż biż-żejt.* Tennis courts are few and far between. The average walking rate is not more than $1\frac{1}{2}$ or 2 miles per hour. Golf courses are to all intents and purposes non-existent. It is true that the amount of energy used up when walking is small (e.g. an hour at $3\frac{1}{2}$ m.p.h. = 300 calories or an ounce of fat) but this ounce of fat if added to one's meals daily would mean a weight increase of 20 lbs in a year. So, quite apart from keeping and feeling fit exercise is of some importance in weight control.

In the second place it is only recently that Malta has attained some prosperity. We have a long tradition of hard days and intermittent poverty. A fat person is a symbol of prosperity and comfort. It is possible that psychological reasons tend to push a lot of us to store fat just as we have as a race a tendency to store money.

Thirdly, until World War II pulmonary tuberculosis was a scourge here as elsewhere. The loss of weight and frailty associated with the disease made a big impression on relations and friends of patients with the result that the opposite, overweight, became linked in the subconscious mind with good health.

(2) I do not propose to go into detail regarding the various well-known complications of obesity but will merely enumerate them and discuss less obvious ones more fully. Diabetes mellitus, cholecystitis, atherosclerosis, essential hypertension, gout, umbilical and para-umbilical herniae, hiatus hernia, angina pectoris, varicose veins and chronic bronchitis are all much commoner in overweight people.

Psychological complications. Some people especially women go in for cakes and chocolates because they are unhappy. The inevitable addition to their weight makes them depressed so that obesity may at the same time create psychiatric problems and be caused at least in part by them.

Mechanical complications. By and large the human skeleton is not meant to carry heavy loads for long periods but this is precisely what we are asking it to do when we weigh 4 or 8 stones more than we should. It is therefore not surprising that low back pain due to lumbar vertebral strain or sacro-iliac disease, osteoartritis of the hips and knees and flat feet, sooner or later appear.

Accidental complications. Fat, ungainly persons are slow in avoiding traffic in the streets and machinery accidents at work. Falls are heavy and more traumatic than they should be. Burns and scalds in the kitchen are more frequent.

Surgical complications. It is well known that fat people are bad subjects for major surgery. Operations on them are less than perfect on account of difficulty of approach, depth of incision etc.

(3) To solve the problem we must first of all persuade ourselves that it exists and unfortunately this is not the case as yet. An analogy with cigarette smoking will help. Valid statistics show an undoubted link between such smoking and bronchial carcinoma. This has impressed doctors and as a result many in the U.K. have become non-smokers. The same is true in Malta. Ash trays have vanished from the BMA House in London and "No Smoking" notices are up at many medical meetings. The result is that our advice to patients regarding smoking is taken seriously. Unfortunately it is still fashionable for the young to smoke, drug dependence is strong and in spite of continuous tax increases by various Ministers of Finance we have made little impact on cigarette smoking. Turning to obesity we find that doctors are as guilty as the rest of the world. Their advice is therefore not taken seriously.

This is a pity because here fashion is on our side. The heroes of the modern age, pop singers and the like, are all slim. So before actually telling the patient how to lose weight, we should be blameless in the matter ourselves and we should persuade him or her that obesity is bad.

What about treatment? We should first of all ignore genetic factors and endocrine factors ('my doctor says it is glands' should no longer be heard) and stick to two scientific facts. (1) adipose tissue cannot come out of thin air and (2) there was not one fat person in Belsen and Buchenwald. In other words apart from exercise, dieting is the treatment and this as we know consists essentially in reducing the quantity of food and alcoholic drink taken. Meals should

consist mainly of lean meat and green vegetables. Details are out of place here.

The one question which a patient may ask which requires a careful answer is this. Why do I grow fat on the same amount of food (or less) which allows another person to stay thin? The truth is that we do now know the answer. Right now there is no evidence of any metabolic change in fat people such as a lowered basal rate, or a reduced specific dynamic action, or hypothetical failure to burn off excessive calories at night. An easily understood explanation is this. Your body is like an Austin Mini and your friend's like a Rolls-Royce. You can do many more miles to the gallon than he can and therefore you must fill you tank less often or less fully, otherwise the petrol will overflow i.e. you will put on fat.

What about the future? I am optimistic. The insertion of Gozo in the title was deliberate because there the problem is even greater than in Malta, due to a lesser impact of fashion etc. Progress is possible and the young people of today look with scorn on our corporations and feel shame on our account whenever they see pictures of the inhabitants of the Third World. As doctors, we can also advise Governments to cut subsidies on carbohydate foods, to encourage the consumption of protein and to advertise the dangers of obesity. An interesting suggestion was made recently by a junior minister in the German Democratic Republic. He said that fat people were a burden on the State in so far as they were more often in hospital so that they took more than their fair share of the Welfare cake. He suggested a tax on fat people!

pregnancy and birth in maltese tradition

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The key to the unfolding and understanding of the psychological and sociological matrix of a nation lies in its distant past. It is from this remote point in time, therefore, that we have to take our bearings in our exploratory venture for the practices and beliefs that guided our ancestors in their endeavours to keep the flame of life alive from prehistoric times to our own days.

From the evidence of the decoration of the earliest pottery to be found in Malta (Għar Dalam) it appears that the first inhabitants of the Maltese Islands came from the Stentinello area near Syracuse about the year 2500 B.C. (Trump n.d). Some of the archaeological survivals of this stone-age culture reveal the concern of these early inhabitants with the phenomena of procreation and the propagation of life.

Among these remains are the naturalistic stone carvings of the phallus (Zammit, 1930). One of these objects, now in the National Museum, Valletta, consists of three erect phalli (12 cm. in height) cut in relief and standing on a low platform; another specimen has the shape of a slab (14 cm. x 16.5 cm. x 4.5 cm.) with a rectangular depression in the centre containing in bold relief the upper extremities of two upright phalli. The fact that these objects were excavated from temples suggests that they were used in the worship of the generative forces of nature; indeed the group of three phalli has a projection at the back which may have served as a handle for carrying it about as a sacred object (Report of Museum, 1917).

Further suggestive evidence that links up with this period comes from Gozo in the form of an oral tradition according to which pregnant women from the village of Xagħra used to sit or squat on a large stone to ensure the safe delivery of their baby (Bezzina, 1968). It is probable that the stone referred to is the semi-dolmen of Sansuna at Xagħra which is also a neolithic relic.

The excavation of a statue of Priapus with head missing from a building at St. Paul's Bay recalls the Roman period in our history (218 B.C. - 395 A.D.). This Roman god was represented in the visual arts with various attributes among which was the presence of a cock's crest surmounting his head (Mizzi, 1900; Knight, 1866). The rendering of the word *crest* in the Maltese language is *għalla* which has a double meaning for besides the cockscomb it also signifies *parturition;* hence the expression, referring to a pregnant woman, of *għamlet l-għalla* i.e. she is pregnant or has given birth to offspring (Ms. 143, RML).

A native plant which bears a striking resemblance to the male generative organ was used as a fertility charm by Maltese women up to three hundred years ago. This is the *Cynomorium coccineum,* incorrectly known as the Maltese Fungus, which was worn as an amulet against barrenness by our women who suspended it between their breasts. This custom disappeared in the 17th century when it attracted the attention of a Capuchin missionary and was denounced by the church authorities (Abela & Ciantar, 1780).

Proverbs are an indication of the wisdom accumulated through the ages by a community. They reflect its attitude toward the more salient experiences of life. Since pregnancy and birth form a focal point of these experiences it is not surprising that a number of Maltese proverbs should revolve round these themes.

The scope of marriage, and therefore of sexual intercourse, in Maltese popular lore is procreation. This is the concept behind the folk song which flatters the bride:—

La tgħaddi sena minn fuqek
Lesti l-ħabel għal man-nieqa,

i.e. when you have been married one year, prepare the cord for rocking the cradle (Cassar Pullicino, 1949). Indeed a marriage without children is no harbinger of happiness *(Iż-żwieġ mingħajr tarbija ma fiehx tgawdija);* on the other hand, the birth of a baby, like a stroke of good fortune, fills the house with brightness *(Risq u magħmudija ġo kull kamra tidher dija)* and provides the parents with untold delight *(Min għandu l-ulied għandu l-hena fil-wied)* (Aquilina, 1972 a).

The great esteem with which motherhood is held by the Maltese is expressed by the saying *Il-mara tqila ġo did-dinja turi l-ħila* i.e. a pregnant woman shows her worth in this world; while the disappointment due to failure of conception is shown by the words *Mara bla żaqq bħal tieġ bla daqq* (A woman without a large belly is like a wedding without music). But a childless woman must not get discouraged for she may yet become fruitful. Indeed *Jekk fil-qamar tħuf (il-mara) issaħħaħ il-ġuf* i.e. if a woman, desirous of offspring, "walks in the moonlight, she strengthens her womb", the idea behind this proverb being the popular belief that the moon excites one's sexual urges; so much so that childless women are advised to have intercourse on a full-moon night as in this lunar phase conception is more likely to occur than at any other time. The saying *il-qamar mimli, imma le jsellimli* (Aquilina, 1972 b) alludes to such an eventuality. Literally translated, the saying stands for "the moon is full but it does not greet me", i.e. the moon is

full my menses have stopped and I have conceived.

The woman knows whether she is pregnant or not at the time when her menses are due, the absence or presence of her menstrual flow denoting her condition in accordance with the saying *Meta tasallek il-ħasla tħabbarlek il-għażla.* But even if no pregnancy occurs there is always hope of conceiving in the future as long as the woman menstruates for *Min iħammar jgħammar* i.e. she who menstruates (literally "reddens") gets impregnated (Aquilina, 1972 c).

The handicaps of pregnancy have left their impact on the popular mind. The enlarged size of the abdomen in advanced pregnancy for instance, renders awkward and cumbersome the woman's movements. Thus *mara b'tarbija ma tesagħħiex ta' Brija* i.e. for a woman with child, (the wide road) of Ta' Brija (in the village of Siġġiewi) is not wide enough for her (to pass through); in other words the pregnant woman's place is at home. Then there is the disfigurement of her body which, however, can be hidden from public view up to a certain extent, by wearing the *għonnella.* This was a form of black headgear, now hardly ever seen, which descended from the head to the back and almost down to the ankles and was so wide that it could be brought forward in front of the abdomen and wrapped round the lower part of the body. In fact the saying goes:— *Mara bl-għonnella qatt ma taf x'għamlet u x'kellha* (You can never tell what a woman did or whether she had any children if she wears this form of apparel) (Aquilina, 1972 d).

Pregnancy can interfere with the woman's routine activities. *Il-mara tqila tirbaħ l-għażż u titlef il-ħila* which, literally translated, means "the pregnant woman becomes lazy and loses her ability" that is she is incapable of coping with her chores and becomes indolent.

"Quickening", i.e. when the foetus begins to move about in the womb, is supposed to afford some relief to the mother *(Meta t-tarbija tibda tħuf isserraħ l'ommha mill-ġuf);* but the woman who gives birth to twins must be prepared to endure a prolonged labour *(Kull min itewwem fil-ħelsien idewwem)* (Aquilina, 1972 e).

A special hazard of pregnancy which must be guarded against is the emergence of longings or desires which cannot be satisfied for, according to popular belief, the newborn will bear the brunt of a birth-mark resembling in form and colour the object of her unfullfilled desire. *Mara bix-xewqa,* warns the proverb, *lewn uliedha jiġu mżewqa* (The children of a pregnant woman with an unsatisfied wish will bear on their skin the colour of the object desired) (Aquilina, 1972 f). For this reason whenever an expectant woman expresses a wish for some item of food, her family or the neighbours do their best to satisfy her craving as soon as possible lest the baby be born with a skin mark (Cassar, 1965 a) on a part of its body corresponding to that touched by the mother when expressing her wish. A pink birth-mark denotes a desire for a flower; a red tinge, for wine; and a brown one, for coffee or chocolate. According to shape birth-marks are interpreted as representing strawberries, shellfish, etc. (Repertorio, 1843). If a person neglects to satisfy the wishes of a pregnant woman, he or she will suffer from a sty by way of punishment (Arrigo, 1973 a).

More serious bodily changes can be induced in the foetus by the mother if she is not careful to avoid looking at ugly or deformed creatures; in fact no less than the birth of a deformed baby or an outright monstrosity. It is of interest to note that this idea was still upheld by some members of the medical profession in Malta up to the mid-eighteenth century so much so that a Maltese physician of this period did not hesitate to record the case of a pregnant woman who, having looked at the picture of a Moor, gave birth to a dark skinned child (Cassar 1949). To prevent such possibilities the pregnant woman, who has been exposed to unwanted sights, makes the sign of the cross with her right hand over her abdomen to ward off the harmful effects of any mental impressions she may have received (Repertorio, 1843).

The possibility that the baby might be born on Christmas Eve was a cause of some anxiety to the prospective mother for it was believed, even as late as the close of the last century, that those who were born on the 24th December were transformed once a year on that day into a supernatural being, called *gawgaw* in Maltese, during their sleep. Thus changed they roamed about the neighbourhood frightening people with their groanings. Towards dawn they resumed their human form and returned home in an exhausted state with no recollection of their nocturnal adventures. This transformation was regarded as being a punishment from God imposed upon those born on the same day as his Son for it was held that the Lord disapproved of anyone being born on the same day as Jesus Christ (Busuttil, 1922 a).

Certain bodily changes induced by pregnancy may provide a clue of the sex of the yet unborn child. Thus if the woman's complexion becomes pigmented or speckled, the chances are that she is bearing a girl; but if her abdomen is very prominent, she will give birth to a boy *(Meta l'omm tul it-tqala ikollha wiċċha qisu bil-ġlata jew nemex aktarx tkun tifla t-tarbija; meta tkun ikkupplata aktarx li jiġi tifel).* However, the phase of the moon has also to be reckoned with for babies born during the first quarter are likely to be boys while those born during the second quarter will probably be girls *(Mit-trabi li jitwieldu dawk ta' l-ewwel kwart aktarx ikunu irġiel u dawk tat-tieni kwart nisa).* To confirm the forecast, the women ties her wedding ring to a string and dangles it in front of her abdomen; if the ring sways sideways, the offspring is female; if the ring swings backwards and forwards, the baby is a boy (Arrigo, 1973 b).

It is difficult now-a-days to envisage a modern house comprising in its construction a "labour or delivery room" in which the woman

gives birth to her offspring; yet in the not too distant past several houses, even when they were of small dimensions, had such a feature incorporated in their plan. This room was known as the "alcove" *(l-alkova* or *arkova* in Maltese popular parlance). It is found in both town residencies and village dwellings. One such alcove was built in a house at Żabbar as recently as seventy years ago (Attard, 1973).

The alcove was on the ground floor or in an upper storey depending upon the size of the house. One entered it through an arched opening in one of the walls of an ante-room known in some districts as *id-dar,* literally "the house". The alcove is a diminutive room with a floor area of about five by six feet being just sufficiently large to contain a double-bed *(is-sodda tal-għamara).* In some instances seen by the writer the floor still retains the flag-stone covering that formed a distinctive feature of the traditional Maltese flooring.

The arch giving access to the alcove may be plain and undecorated (Żurrieq) or else is framed by an elegant cornice carved out of the stone. In the ornate arches, the keystone bears reliefs of the Sacred Hearts of Jesus and of Mary surmounted by an open or closed crown (Żabbar). The monogram M for Mary, the Madonna, and the initials IHS may be incorporated in the carving and placed in the space between the crown and the hearts.

In some cases (Żabbar) the archway is flanked by a narrow and low rectangular doorway which just allows a person to pass through (Fig. 1). A curtain, as large as the arch, conceals the bed from view. The ceiling is lower than that of the ante-room and is supported by one single beam. Over this ceiling is a sort of storage space or attic *(l-għorfa)* access to which is gained through a small window high up on the wall and which is reached by means of a ladder. On one specimen seen the attic is lighted by means of a small aperture (Żabbar). In another instance the low ceiling has been removed to make the alcove more spacious The original window giving access to the attic has been blocked.

The alcove itself has no window and receives air and light from the window and doors of the ante-room. Occasionally the back wall of the alcove facing the archway has a small recess or niche to one side which in the past contained a sacred image and a lighted oil-lamp.

On the whole the alcove has an atmosphere of cosiness and intimacy; so much so that when it was not needed as a labour room it was used as a bedroom by the wife and husband. When the wife became pregnant and term approached, the alcove and its bed were occupied exclusively by the mother-to-be, the husband sleeping by himself in the ante-room usually on a settee known as *il-kanapè* (Attard, 1973). Following the birth of the baby, its christening reception, for relatives and friends, was held in the ante-room (Bezzina, 1973).

It is not known when the alcove as a delivery room went into decline but an informant from Żabbar tells me that she gave birth to her last child twenty-four years ago in the alcove. Another woman from Żurrieq, now aged fifty-one years and the last of eight siblings, states that they were all born in the alcove.

Although the alcoves have now outlived their original function, some of them have been lovingly preserved forming a quaint feature of Maltese domestic architecture. Others have been mutilated or destroyed when old houses were renovated. One must stimulate interest in the alcove and encourage owners of houses containing it to preserve it, for unless it is protected it runs the risk of being lost for ever in the current spate of house-remodelling. Besides being of considerable evocative charm, the alcove constitutes a distinctive facet of our birth lore and a social and medical land-mark reflecting the life-style of a vanished epoch and the shift from domiciliary midwifery to the maternity hospital.

Not all women favoured delivery on a bed in an alcove; on the contrary some of them preferred to give birth to their baby in the sitting position making use of the parturition chair or *siġġu tal-qabla.*

This piece of furniture, differed from an ordinary chair in two ways:— (a) the seat had a horse-shoe shaped aperture, and (b) an arm rest was fixed on each side of the seat so that the woman by holding on to each arm rest during her pains was able to increase the force of the uterine contractions by bearing down.

Some of these chairs were hinged so that they could fold down flat — *siġġu li jingħalaq* — for easy conveyance by the midwife; the non-collapsable type was usually carried for the midwife by a boy or young man on his head. From this custom derives the Maltese saying *qrieh għax iġorr is-siġġu tal-qabla* i.e. he has become bald from carrying the birth-chair on his head — the implication being that he lost his hair from the constant friction of the chair on his scalp.

In some specimens the chair had a leather belt attached to its back which was brought forward and fastened over the woman's abdomen to prevent her pelvis from sliding.

As the final expulsive phase of labour approached, a large earthenware bowl — called *lembija* — filled with straw was placed on the floor beneath the chair so that if the baby was not caught in time by the receiving hands of the midwife, as it came out of the birth canal, it would slip on the soft straw inside the bowl. A variant of the *lembija* usage was the attachment of a kind of drawer underneath the opening of the seat. This drawer was made of strong cloth like a hammock and was pulled out from under the seat to receive the baby during the last pangs of delivery.

In the eighties of the last century the use of the parturition chair was condemned by the Pro-

fessor of Midwifery of our university — Dr. Salvatore Pisani — who warned midwives against its use because the sitting position was responsible for the laceration of the birth canal with unpleasant complications for the mother. His opinion carried so much weight that its use was made illegal by the Police Laws of 1883.

In spite of these legal sanctions it was not easy to persuade parturient women to do away with the chair and as midwives were prohibited from using their own chair, some families had one constructed for their own private use. In fact these chairs were still employed, although sporadically, at the beginning of the present century in some of our villages. (Cassar, 1973 a).

The mother-to-be and her family, however, did not rely solely on the midwife's assistance to ensure a smooth delivery but resorted also to other ancillary measures. Until half-a-century ago, they used to acquire part of a plant *(Anastatica hierochuntica L* or Rose of Jericho) known in Maltese as *warda tal-passjoni* (passion flower) which they placed in a vessel with water. This plant, indigenous to the Middle East, grows about six inches high and forms spikes of small white flowers. After flowering, its branches lose their leaves and become dry, hard and woody. They turn upwards and bend inwards at their free extremities but if placed in water they open up to regain their original form no matter how hard they may have become (Delia, 1970).

A woman from Attard — who possessed one of these dried plants brought to her from "Palestine" — told the writer that the association of this plant with child-birth derived from the legend which related that while the Madonna was nursing the new-born Baby Jesus in Bethlehem she used to spread his washed nappies for drying on the branches of this plant which thus acquired its wondrous powers (Fenech, 1971). In fact the belief was current in Malta that as soon as the branches of the plant opened out the expectant woman would begin to feel the labour pains and would eventually be safely delivered; the pains, however, would disappear immediately the plant was removed from the water (Cassar-Pullicino, 1947).

The story has been told of a "passion flower" that was mislaid in the confusion that ensued during the confinement of a certain woman. She eventually gave birth to three sons but the plant was nowhere to be found. At last someone remembered that it had been placed in a drawer. When this was opened, to the amazement of everyone, it was found that the stem had brought forth three branches covered with leaves (Busuttil, 1922 b).

Not all confinements however had such happy endings. There were instances where a narrow pelvis or some other abnormal condition in the mother presented an obstruction to the exit of the foetus through the birth passages. In such cases the so-called *qasma tas-sultan* or Caesarean operation had to be resorted to in an effort to save the lives of both mother and child. When the operation, for some reason or other, could not be carried out and the mother died in childbirth, both the State and the Church enforced its performance on the dead mother by a surgeon in a desperate bid to save the child; and when no surgeon was available, the parish priest himself was obliged to carry it out under the penalty, if he failed to do so, of "fulminating excommunication". In the absence of a surgeon and the parish priest, the task of opening up the abdomen of the mother and extracting the baby fell upon the midwife (Cassar, 1973 b).

Faced with the uncertainty and unreliability of human aid, women in childbirth fortified themselves by seeking the intercession of the Madonna and the saints in their hour of travail. Prayers were offered to St. Blaise, a fourth century bishop and physician, "to enlarge the width of the birth passages and shrink the size of the baby's head" to facilitate the expulsion of the foetus. The *Madonna tal-Ħlas* (Our Lady of Delivery) and the *Madonna taż-żellieqa* (literally Our Lady of Slipping) and St. Lukarda were invoked for the same purpose (Cassar, 1965 b). At Naxxar, St. Victor was venerated as a saint protector of pregnant women who used to drink water containing some powder obtained from his bones to ensure a smooth labour. This custom commenced in the late eighteenth century when his skeleton was brought from Rome and deposited in the parish church of Naxxar (Galea, 1937).

Another religious practice intended to avert an abnormal labour was the wearing by the parturient woman of a ring that had been blessed on the feast of St. Peter (29th June) during the ceremonies held in a church dedicated to this saint at Żejtun (Vella, 1927).

St. Raymond Nonnato, who flourished in the thirteenth century and who is reputed to have been born through Caesarean section, is now-a-days called upon by expectant women who offer him a lighted candle during labour (Anon 1950). Other saints are appealed to and many of our churches are the depositories of small paintings and of silver *ex-votos* in the shape of babies in swaddling clothes offered in thanksgiving for the happy birth of a normal baby.

Another form of thanks to the Almighty for a safe delivery was the tolling of a church bell — known as *il-qampiena tal-lawdi* (literally "the praise bell") at the behest of the mother, the number of strokes sounded depending upon the amount of money paid to the sexton. This custom was still extant up to three years ago at Birgu (Spiteri & Bezzina, 1973).

We began this search for the stirrings of primitive man's concern with generation in the dim days of the pagan prehistoric temples of our Island; we have reached the end in the Maltese Christian churches of our own days. The godheads have changed but man has not. Indeed, in spite of the fact that in the intervening span of thousands of years he has devised a variety of strange beliefs and quaint ways for allaying his preoccupations, there is one single

motif which underlies and unites this traditional lore and gives it meaning, i.e. the perpetual need of humanity for relief from anxiety, for supernatural support, for kindling the spark of courage and for the renewal of hope when facing the awesome and still mysterious phenomena of conception and birth.

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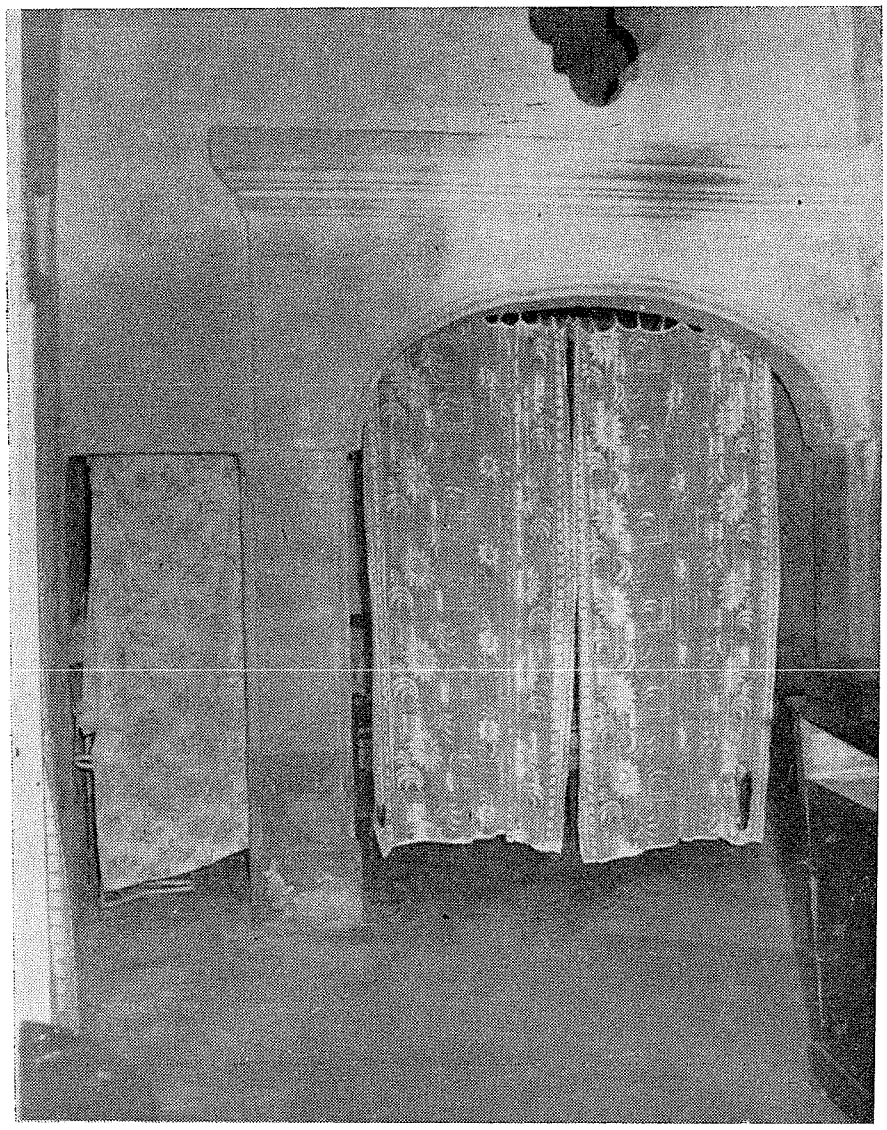

An alcove at Zabbar.

(Photo by courtesy of Dr. C. Attard)

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the aetiology and pathogenesis of emphysema

stephen gatt

The term "emphysema" was coined by Theophile Laennec in 1819 to describe what we today call "Surgical Emphysema". Surgical or Interlobular Emphysema occur when the pressure gradient between the alveolar lumen and the surrounding interstitium is exceeded. The tolerable limit to the steepness of the pressure gradient is 20 30cm. of water in neonates (1) and over 150cm. in adults. High intra alveolar pressures are generated by (a) the use of violent artificial respiration in the resuscitation of neonates or of intermittent positive pressure respiration (e.g. following electrocution or drowning) (1a) (b) severe asthma, childbirth and strenuous exercise (c) violent coughing (e.g. in whooping cough), explosions or sudden decompression (e.g. in aircraft accidents and submarine escape training) (2) (d) traumatic rupture of alveolar walls when the lung is punctured by fractured ribs, a needle exploring the chest or penetrating objects (3). This type of "emphysema" implies air suction into the tissue planes (e.g. leakages from sutures in a bronchus or from a drain-tube) or a distension of interlobular septa and perivascular sheats. Since 1819, the term "emphysema" has been corrupted to such an extent that it now relates to changes **inside** the lobule Laennec's Surgical Emphysema is not included in our definition.

In 1958 the Ciba Guest Symposium defined "emphysema" as "a condition of the lung characterized by an increase beyond the normal in the size of air spaces distal to the terminal bronchiole either from dilatation or from destruction of their walls". Since then the World Health Organization (1961) have excluded 'dilatation' from their definition and in 1962 the American Thoracic Society went even further by defining "over-inflation" as "an increase beyond the normal in the size of air spaces distal to the terminal non-respiratory bronchiole without destructive changes in the alveolar walls" thus separating emphysema from inflation.

The main difficulty in adopting these newer definitions lies in the distinction between pulmonary over-inflation and emphysema, e.g. persistent dilation of an area of lung which is intrinsically weak will lead to severe emphysematous destruction. One cannot say for sure at what point the mildest amount of destruction can be recognized e.g. lesions may be basically distensive when they are actually the result of very fine destruction which weakens the walls of air spaces so that they distend abnormally with normal pressures. For this reason, the general consensus of opinion is that we should include 'over-inflation' as a Mild or Grade Itype of emphysema. Indeed, though 'over-inflation' is primarily reversible, prolonged dilatation may lead to irreversible destruction. For the purpose of this paper I have adopted the 1958 Ciba definition of emphysema because though more recent definitions are more precise they have the shortcoming of being impracticable.

The classification of emphysema is based on the structural changes in the Secondary Lobule of Miller. The lobule, which is 1-2cm. in diameter, is the fundamental anatomical lung unit. It is roughly pyramidal and demarcated by a thin, fibrous membrane more highly developed in the upper lung fields. At the centre of the lobule are 5-10 terminal bronchioles, 1mm. in diameter, with no cartilage or submucosal glands and no air sacs or alveoli. The terminal non-respiratory bronchioles divide into 3 orders of respiratory bronchiole. The 3rd. order respiratory bronchioles open into alveolar ducts whose walls are virtually non-existent except for some smooth muscle strands. The wall of the alveolar duct is covered with outpouching alveoli which are in contiguity with the pulmonary capillaries so that they form a gas-exchanging unit. The alveoli are situated peripherally in the lobule. The alveolar duct musculature constricts in response to a depression in airway pCO_2 so that inspired air is deflected from poorly perfused alveoli to lung areas with a more adequate blood flow. The respiratory bronchioles are situated at the centre of the lobule while the alveolar ducts and sacs are aranged in the peripheral zone.

On the basis of the arrangement of structures within the lobule pulmonary emphysema can be classified into:

PARTIAL LOBULAR
- CENTRILOBULAR (including focal dust emphysema)
- PARASEPTAL

PANLOBULAR

IRREGULAR (related to scars).

Panlobular and Centrilobular emphysema can be divided further into (a) Mild, when there is pulmonary over-inflation (and, probably, the early stages of destruction). (b) Severe (4), when there is a resognisable pathological change in the structure of air spaces distal to the terminal bronchiole.

In Panlobular emphysema the entire lobule is affected whereas in Partial Lobular emphysema changes are localized either to the centre of the lobule (Centrilobular emphysema) or to emphysematous near scars (Irregular emphysema).

Bullae are dilatations of air spaces over 1cm. diameter associated with very severe panlobular emphysema (5).

Blebs are collections of air or gas in the sub-pleural connection tissue of the lung resulting from rupture of the pulmonary alveoli immediately beneath the pleura (6).

Severity of the emphysematous process is classified as follows:

	REID	W.H.O.	
	Normal	Normal	Air spaces are so small that they cannot be distinguished clearly without magnification. There is no retraction.
Grade	I	Mild	Air spaces are abnormally large, up to 1mm. diameter. Retraction is slight.
	II	Moderate	Air spaces are a little bigger than 1mm. but architecture is still intact. Retraction is striking.
	III	Severe	Air spaces are up to 5mm. diameter. Retraction is such that blood vessels and bronchi are elevated above the surface.
	IV	„	Air spaces are 'holes' larger than 5mm. diameter which may be confluent and extend through the whole thickness of a 1cm. lung slice.

Emphysema is more common in men than in women and the Centrilobular form is 20 times more common than the Panlobular type (7). Emphysema causes disability or death in about 3% of all patients at post-mortem (8).

Pathogenesis

The internal surface of an emphysematous lung is reduced although the total volume may be unchanged, increased or reduced. Since inspiration is a more powerful force than expiration, in emphysema air-trapping (9) occurs from obstruction to the emptying of intra-alveolar air. Inspiration is accompanied by dilation and shortening of the large and small air passages as far distally as the bronchioles and alveolar ducts. Emptying of the lung is brought about by the elastic recoil of alveolar walls and the contraction of muscle fibres in the alveolar ducts, the surface tension having been reduced by alveolar surfactant (10). If small bronchi are obstructed air reaches the lung tissue distal to the obstruction through pores of Kohn from adjacent portions of lung whose air supply is unimpeded (11). Young children possess a few, ill-developed pores of Kohn but with increasing age the pores become larger and more numerous and collateral ventilation assumes a greater importance.

The current hypotheses of the pathogenesis of emphysema are:

i. Chronic bronchiolitis causes temporary or permanent obliteration and destruction of respiratory bronchioles so that air passes by collateral ventilation into air passages distal to the obstruction and, as a consequence of prolonged 'air trapping' in the acinus, air passages beyond the mucous or mucopus obstruction are disrupted producing an 'air pool'. The pressure distal to a bronchial obstruction in the collaterally ventilated lung is raised during expiration especially in forced expiratory efforts, e.g. coughing, which may be sufficient either to drive out the obstructing mucous plug or, if bronchiolar obstruction is permanent, to disrupt the walls of the 'pool' and establish a free airway with neighbouring acini producing a 'common pool' (12). Chronic inflammatory damage to respiratory bronchiole walls leads to weakening of the second and third order respiratory bronchioles which subsequently dilate and break down so that the emphysema is primarily centrilobular (or sometimes, panlobular) in type (13). Contiguous alveolar tissue is also involved in the inflammatory process

ii. Acute attacks of bronchiolitis cause:
   a. narowing of the terminal and respiratory bronchioles which impedes normal expiration,
   b. collapse of air pasages due to a loss of the extra-mural attachments supporting alveolar walls (15),
   c. extensive atrophy of the walls of medium-sized bronchi due to a loss of bronchial cartilage and muscle and peribronchial conective tissue.

Damage to lung parenchyma occurs. If, for example, the peribronchial connective tissue is lost the bronchioles will collapse in expiration (16).

iii. Ischaemic changes in the bronchi and peripheral parts of the lung, e.g. alveolar walls, can occur because of:
   a. occlusion of bronchial arteries (17),
   b. ischaemic obliteration of alveolar capillaries,
   c. bronchopulmonary anastomoses which develop when ischaemia occurs and which can lead to secondary haemodynamic changes in the pulmonary circulation and produce a decrease in the blood supply to the lung parenchyma (8).

iv. Peribronchial coal-dust deposits weaken the muscle fibres in the walls of respiratory bronchioles and destroy the peribronchiolar alveoli.

v. Traction exerted by respiratory movements causes damage to the distal respiratory bronchioles (19). Actually, traction by itself will only cause over-inflation but if it is associated with, say, bronchiolitis the change can become irreversible.

Emphysema is the result of an interplay between mechanical forces, destructive inflammatory changes, degenerative changes with advancing age, ischaemic atrophy, a variety of dusts and fumes (including cigarette smoking) and, possibly, genetic factors.

PANLOBULAR EMPHYSEMA

"A lobular emphysema which involves all air spaces beyond the terminal bronchiole more or less evenly".

It is a common form of emphysema and is of the destructive type in 78% of cases (20). It may occur in any part of the lung, but there is a tendency for it to occur more frequently anteriorly, i.e. in the lingula, middle lobe and anterior basal segment of the lower lobe (21). The normal alveolar diameter of 0.1mm. increases with age to 0.2mm. at 30 years but remains the same in later years. The average diameter of respiratory bronchioles and alveolar ducts increases from 0.2mm. at 20 years to a maximum of 0.7mm.

In mild panlobular emphysema the spaces are abnormally large holes of 1.0mm. or more in diameter scattered throughout the lobule. The respiratory bronchioles and alveolar ducts enlarge by stretching, and the cup-shaped alveoli become shallower (i.e. saucer-shaped). In moderate panlobular emphysema there is partial destruction or atrophy of fine respiratory tissue and the number of intact alveolar walls is reduced. The small (5-10 micron diameter) pores of Kohn become large, perforated, cribriform fenestrae (22). In several panlobular emphysema there is complete destruction of respiratory tissue. Since pulmonary arteries and arteioles are more resistant than other structures, some branches of the pulmonary arterial tree will remain patent (23).

Environmental and racial factors must be taken into consideration in reviewing the regional distribution of panlobular emphysema. It is more common in the tropics than in temperate climates and more severe in the U.K. than in other countries especially S. America and Africa. Though age may not be important in aetiology the lesions increase in severity through the years possibly because there is more time for harmful agents to act on the lung (24). Mild panlobular emphysema in old people is as common in men as it is in women but when it is coexistent with centrilobular emphysema it may be associated with cigarette smoking and chonric bronchitis and is therefore more common in males.

Aetiology:

i. Congenital :
   a. Congenital defects in a bronchus lead to air-trapping during expiration and consequent overdistension in the zone supplied by that bronchus (25).
   b. Congenitially maldeveloped alveolar walls may undergo premature degeneration or may fail to develop properly (26).
   c. Familial emphysema may be associated with
      i. homozygous autosomal recessive serum 2, — antitrypsin deficiency (27),
      ii. ? familial mucoviscidosis. Fibrocystic disease may be significant in the production of emphysema but usually results in bronchiectasis and diffuse interstitial fibrosis (28).
   d. Abnormalities of smooth muscle, elastin and collagen associated with emphysema are being investigated.

ii. Experimentally, emphysema can be simulated by producing an acute bronchiolo-alveolitis (using nitric acid or papain) but rarely occurred folowing bronchiolar scarring from acute bronchiolitis or fibrogenic dust foci (using silica, asbestos and road dust) and was never associated with non-fibrogenic dust foci (produced by using perpex, fibreglass, wood or carbon dust) (29).

iii. Inhaled chemical substances, e.g. cadium fumes in anticorrosion coatings (30).

iv. Distensive forces (e.g. severe astha and blowing wind instruments) combined with chronic inflammation (31).

v. Ischaemia due to pulmonary and bronchial artery obstruction (32).

CENTRILOBULAR EMPHYSEMA

"Emphysema of the centre of the lobule from involvement of respiratory bronchioles".

It can be (a) mild, when the air spaces appear enlarged but there is little destruction of the alveolar wall,
or (b) severe, when the pulmonary vessel remnants are all that is left to indicate alveolar wall destruction.

Gough prefers to reserve the term 'centrilobular emphysema' for a condition associated with histological evidence of bronchiolitis (32a). Mild centrilobular emphysema is common especially in people exposed to coal-dust-, haematite-, graphite-, laden atmospheres. In these cases, however, there is no evidence of bronchiolitis and some prefer to call it 'dust reticulation' and include it with the pneumoconioses. Pneumoconiosis is a comprehensive term covering a group of dust-diseases defined in the N.I. (Industrial Injuries) Act of U.K. as 'fibrosis of the lungs due to silica dust, asbestos dust or other dust and includes the condition known as dust reticulation'. The lesions in this mild type of emphysema are darkly pigmented clusters of dilated respiratory bronchioles surrounded by dust cells (33) which may become incorporated within the wall and entombed by the alveolar lining cells (34). Though centrilobular emphysema does occur in some coal workers, destructive centrilobular emphysema is not characteristic of coal-dust exposure. In severe destructive centrilobular emphysema the lesions are more than 1mm. diameter and remnants of the arteries and arterioles cross the emphysematous spaces. Small, rounded, calcified nodules (? healed tuberculous lesions) are sometimes found attached to these strands especially at the apex of the lung. Lesions are usually large at the apex and small at the base. This is attributed to either the differences in pressure, or poor circulation in the upper lobe (35 & 36). The emphysematous spaces are modified proximal respiratory bronchioles and terminal non-respiratory bronchioles.

Aetiology:

Common all over the world possibly due to a universally distributed agent, e.g. cigarette smoke or a virus. It is more common in males and only rarely occurs in non-smokers.

i. Coal-dust, graphite and haematite cause distensive 'focal' emphysema but together they account for a very small percentage of cases and there is never an associated bronchiolitis. The dust is carried to the lobule centre where it accumulates and weakens the respirator bronchiole walls. The dilation is maintained by:
   a. traction of pulmonary elastic tissues on the airways (37),
   b. inspiratory force required to expand pigment-laden macrophages (38).
   c. shrinkage of masses of pigment-laden macrophages (38).

ii. Irritant gases absorbed by carbon particles may cause mild emphysema.

iii. Disruption of bronchiolar clearance mechanisms at the lobule centre (39) by:
   a. inflammation due to H. influenzae, Str. pneumoniae and viral infections.
   b. chemical inflammation especially cigarette smoke, smoking habits and centrilobular emphysema being closely related.

iv. Mechanical overinflation associated with other causes will produce permanent destruction of airways and is responsible for the balloon-like appearance of the lesions and the relationship between the size and vertical position of the punched-out spaces at the centre of the lobule.

v. Gaseous irritants commonly encountered in industrial regions, e.g. sulphur dioxide, ozone, oxides of nitrogen, phosgene, nitric acid and papain, damage the lobule centres possibly due to the pneumonia finding a 'locus minoris resistentiae'). Cigarette smoke, ozone, aluminium oxide particles and sulphur dioxide reduce the surface tension of elastic recoil permitting over-inflation and tissue disruption.

PARASEPTAL EMPHYSEMA

"Emphysema adjacent to the septa from involvement of the alvealar ducts and alveolar sacs".

The lesions are often pigmented and remnants of the pulmonary venules pass out radially towards the septa. There are no intact alveolar ducts or sacs and spaces communicate with small air pasages at the lobule centre.

Aetiology:

Not certain, but probably due to a combination of injurious agents, mechanical factors (e.g. spontaneous pneumothorax,
diaphragm's forceful action or the respiratory expanding force trying to overcome airways obstruction and, in the process, pulling degenerate lung parenchyma from its framework (4),
and inflammation.

IRREGULAR EMPHYSEMA

"Irregular emphysematous involvement of the acinus adjacent to scars". It is also known as scar or paracicatricial emphysema.

Aetiology:

This type of emphysema is seen in relation to scarring, e.g. old, healed tuberculous lesions. The bullae can rupture (especially in the young) producing spontaneous pneumothorax.

> "Since the days of Laennec and Baillie work on emphysema has come a long way. Today, we have solved most of the problems regarding its nature but we are left with a mass of conflicting evidence from which we have to sort out the important from the irrelevant."

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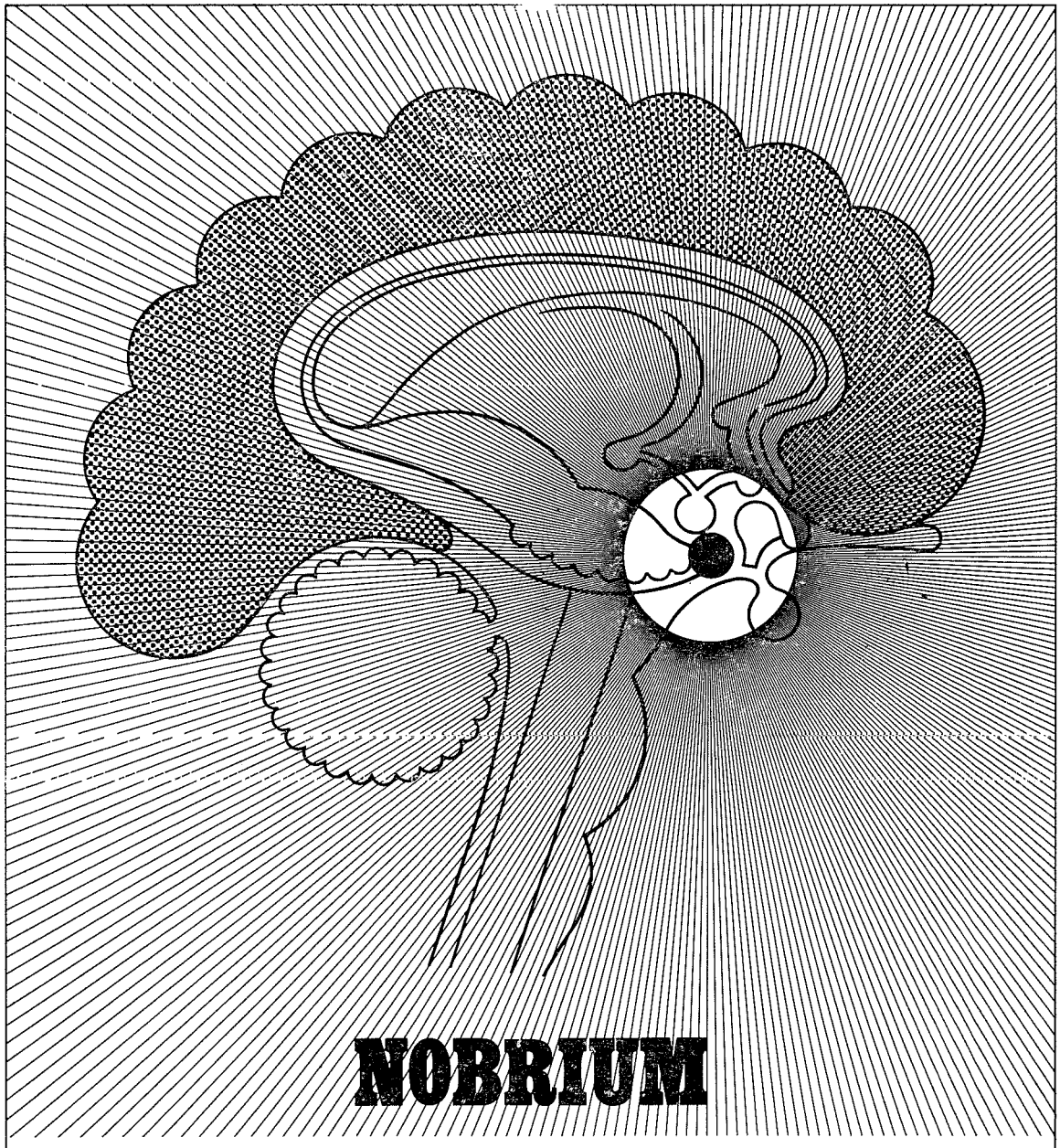

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