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The sick patient is a frightened, desperate and helpless human being. How often do medical and paramedical staff members consider patients as such? In my little experience as a medical student and as a house physician-surgeon, I have observed that there is a gross lack of awareness of this obvious fact; indeed, how many times have we witnessed arrogance in our wards and how often do patients complain that they are not told results of investigations after so many uncomfortable venepunctures, for instance, or that the consultant fails to have a modest word with them?

It is true that the workload in our hospital is rather heavy and much is expected from all; we are fallible humans ourselves with personal problems of our own; we do encounter situations which drive us to our wit’s end: our facial expression, tone of voice and general demeanour frequently leave much to be desired. A vicious circle is set up as the already morose surroundings are further influenced by our ill-temper.

The patient, very young, adult and old alike, finds himself, often quite unexpectedly, in a new and rather hideous environment: the impressive sharp instruments, steel equipment and machinery; the sounds that pollute the air: the moans and groans of patients in pain, sputum being propelled from the depths of respiratory tracts of chronic bronchitis, the clutter of metallic instruments, the voices of stern professors; the cocktail of odours of urine, faeces, drugs and disinfectants.

As though to add insult to injury, many patients are subjected to frequent blood sampling, starvation, uncomfortable tubes through every existant orifice, IV infusions, radiological procedures, not to mention the embarrassing clinical examination particularly in front of a batch of students! Procedures that are routine to us often are very new to the patient.

Our attitude towards the sick and the choice of words we use to express ourselves must be improved considerably if we are to succeed in instilling a sense of security into these unfortunate beings. We must perform our daily tasks with dedication. We have to manage each patient individualistically. We must try to look upon and treat each case as a whole human being not as an isolated illness. We must all endeavour to provide as pleasant an environment as possible, be prepared to offer our valuable time and energy to be able to win the patients’ confidence. Attempts in this direction are ultimately highly rewarding to all. Tackling the sick individuals’ problems becomes a challenge and results of our treatment more gratifying.

THE EDITOR

Editor’s Letter

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Diaphragmatic Hernia

A Five Year Period Presentation of Cases at St. Luke’s Hospital

Definition
A diaphragmatic hernia is the term used to define the herniation of abdominal organs through a congenital defect in the diaphragm. This term is thus not used to indicate a hiatus hernia or traumatic hernias.

Statistics
In the United Kingdom the incidence of diaphragmatic hernias is one in every 2000 live births. In Malta the incidence calculated over a five year period is one in every 1500 to 2000 live births. It has been estimated to be the cause of 8% of perinatal deaths and this figure demonstrates the high risk of the infant with such a hernia.

Embryology and Pathology
The separation of the pleural and peritoneal sacs of the embryo is completed between the eighth and the ninth week. The middle part of the forming diaphragm is composed of a mesodermal plate known as the Septum Transversum, while the lateral spaces known as the Pericardio-peritoneal canals are closed by the pleuro-peritoneal membranes.

If the diaphragm fuses late and the mid-gut returns early into the abdomen, then it would be possible for the elongated mid-gut to slip through the persistent gap in the diaphragm into the pleural cavity. This event will prevent the closure of the diaphragm and the gut will develop in length and calibre within the pleural space. The development of the lungs is thus effected.

The normal lung continues to develop new bronchial branches up to the 14th to the 16th week of intrauterine life. Pressure on the lung by the herniated mid-gut from the 8th to the 14th week may then have a considerable effect on the lung development. This happens both on the side of the hernia as well as on the contralateral side because of the mediastinal shift and the pressure on the contralateral lung bud. This provides an explanation for the frequent occurrence of bilateral pulmonary hypoplasia, which carries such a bad prognosis when it occurs to a severe degree.

Anatomy
The commonest hernia in the newborn occurs in the posterolateral part of the diaphragm, on the left side more often than on the right. (Bochdalek 1848). There are no sacs in the Bochdalek hernia, the pleural and peritoneal cavities being in direct communication. This type of hernia must be distinguished from congenital eventration of the diaphragm in which a sac of mesothelial tissue actually separates the abdominal from the thoracic viscera.

Finally, the anterior retrosternal hernia of Morgagni presents at birth very infrequently.

Cases
There were seven cases of diaphragmatic hernias over the five year period 1980-1985 at St. Luke’s Hospital. Six of the hernias were of the Bochdalek type, all affecting the left diaphragmatic dome, while the seventh hernia was of the Morgagni type and this presented at the age of two years. Five of the Bochdalek hernias were operated at birth while the sixth died before surgical intervention was possible.

The calculated incidence over the five years was of 1 in 1500 - 2000 live births. The average mortality of the six cases including the case which was not operated was around 65%. The following table compares the sex, birth weight, gestation, one minute Apgar score, presentation and associated anomalies in the seven cases.
Discussion

The calculated incidence was of 1 per 1500-2000 live births. The male to female ratio was approximately 1:1 and all of the cases involved the left side of the diaphragm. In all the Bochdalek hernias there were no relevant findings in the family history nor in the antenatal examination. Two mothers had rheumatic fever in childhood but this was incidental. On the other hand in the Morgagni hernia there was a family history of Marfan's syndrome, which is known to be associated with defects of connective tissue including diaphragmatic hernia (McKusick V.A., Pyeritz R.E. 1979). Up to now there has been no established cause of this congenital anomaly but evidently diaphragmatic hernias of both types are very commonly associated with other congenital anomalies.

Presentation

Diaphragmatic hernias usually present immediately after birth. The presenting features result from the mechanical effects which the herniated abdominal organs have on the already hypoplastic lungs. Increase in the amount of intra-thoracic contents also causes shifting of the mediastinum to the opposite side. The commonest presenting problem is therefore cardio-respiratory embarrassment. The infants present with a low Apgar score, tachypnoea, cyanosis and shifting of the heart to the opposite side which may give the impression of a dextrocardia. The diagnosis is confirmed by a plain X-Ray of the chest which shows the presence of air-containing abdominal viscera in the chest, together with mediastinal shift. In cases where the amount of herniated viscera is large, the abdomen has a scaphoid appearance. In two of the described cases, which had a relatively elevated Apgar score, the diagnosis was suspected by slight tachypnoea and the presence of bowel sound within the thorax. The diagnosis was confirmed by chest X-Ray.

Management of Diaphragmatic Hernia

Diaphragmatic hernias must be considered as emergencies of the first order. Although the treatment is ultimately surgical there are a number of resuscitation procedures which should be performed in order that the infant reaches the operating theatre in the best possible condition.

Oxygen must never be given by face mask or bag as the swallowing of air into the intestine will cause further distension and deterioration in respiratory function. The infant should be intubated as soon as possible and oxygen then given by IPPV. An infant nasogastric tube should be inserted and frequent aspiration performed to prevent fluid accumulation and to decrease the risk of aspiration pneumonia. In cases where a pneumothorax develops before surgery the chest should be drained via a tube drain in the second intercostal space.

Indications for Operation

The exact degree of lung hypoplasia cannot be assessed pre-operatively and one is practically duty bound to repair any such hernia, well knowing that a proportion of these children will not have the respiratory potential to survive. This can only be found by clinical testing during convalescence and subsequent post-mortem in those that die.

Operative Treatment

The choice of incision depends on the surgeon but a sub-costal incision (usually on the left) gives good exposure, provides an opportunity to inspect the abdominal viscera and perform a gastrostomy for gastric decompression.

The abdominal viscera are gently pulled out of the chest, a Malecot catheter passed through the ninth intercostal space and connected to an underwater seal. The defect in the diaphragm is then closed.

Continued Overleaf
The Role of H-Y Antigen in Gonadal Differentiation and Anomalous Sexual Development

Gonadal differentiation involves the organization of indifferent gonads containing primordial germ cells into either seminiferous tubules or primary follicles. This process, which in the human becomes evident in the 7th week of gestation, appears to be determined by the presence or absence of a Y chromosome. The indifferent gonad differentiates into a testis in the presence of a Y chromosome and into an ovary if a Y chromosome is lacking. The number of X-chromosomes is irrelevant to testicular or ovarian differentiation, although it does affect the later maturation and function of the gonads. The genes on the Y chromosome exert their influence on gonadal differentiation through the intermediary of a male determining factor which has now been identified as the H-Y antigen. The correlation between gonadal development and the presence of a Y chromosome has exceptions, examples of which are 46 XX males and 46 XY females. Testicular differentiation appears to correlate better with the presence of H-Y antigen. This paper reviews the H-Y antigen in various anomalies of sexual development and the light it has shed on the mechanism of gonadal differentiation.

Discovery of the H-Y Antigen

The H-Y antigen was first recognised as a transplantation antigen in mice. Highly inbred strains of mice are genetically identical so that skin grafts transplanted between members of the same inbred strain should be accepted. It was noted, however, that in such animals slow graft rejection occurred in male to female grafts but not in grafts between males or between females or from females to males. This implied the existence of male-specific transplantation complications may arise from the variety of associated anomalies affecting the heart and large vessels. In general infants who require prolonged ventilation are those who have marked hypoplasia of the lungs, having therefore a smaller chance for survival. The overall mortality is in the region of 65%. The long term morbidity results from other congenital anomalies frequently associated.

References
antigen which was presumed to be determined by a Y-linked gene. Since the histocompatibility antigens in mice had already been labelled H-1, H-2, H-3, etc., the new antigen was named H-Y.

At the time of its discovery the role of the H-Y antigen in sex determination had not been recognized. However, it was noted that an identical or closely similar antigen was also detectable in all the other mammalian and non-mammalian species which had been studied. The strict phylogenetic conservatism of a sex-specific antigen throughout vertebrates from frog to man suggested that the H-Y antigen could have a fundamental sex-associated role and might even be the male determining factor by which the Y chromosome controlled gonadal development. Solid support for this hypothesis was soon forthcoming from studies of the H-Y antigen in a wide variety of anomalies of sexual development in man and animals.

Detection of H-Y Action

The H-Y antigen is found in all male tissues associated with the plasma membrane of cells. It is most readily demonstrable on spermatozoa which are quickly immobilized and killed when exposed to specific antiserum containing H-Y antibodies. This forms the basis of the sperm cytotoxicity test which can be used for the detection of H-Y antigen on any other cells including leucocytes, liver, spleen, kidney, brain and gonadal cells. The cells to be tested are exposed to H-Y antiserum in appropriate dilution before reacting it with sperm. If the cells have H-Y antigen, they will absorb H-Y antibody which will no longer be available for reaction with the sperm and consequently a smaller proportion of sperms will be killed. Dead spermatozoa can easily be visualised and counted microscopically.

The H-Y antigen can also be detected using fluorescent-labelled antibodies and other immunological techniques.

Location of the H-Y Gene

There is plenty of evidence that the structural gene for the H-Y antigen is located on the Y chromosome. The H-Y antigen is always present in 46 XY males. Increased amounts are detectable in males with two Y chromosomes (e.g. XYY and XXXY) indicating a gene dosage effect. Normal levels of H-Y antigen are found in males with a non-fluorescent Y chromosome, in whom the brilliantly fluorescent distal segment of the Y chromosome is missing but male sexual development and function are completely normal. Moreover, studies of H-Y antigen in individuals with various structural abnormalities, including deletions or isochromosomes of the short or long arms of the Y chromosome, indicated that the H-Y locus was situated in the pericentric region of the Y chromosomes and probably on its short arm. Anomalous situations including the presence of H-Y antigen in XX males or XX true hermaphrodites and its absence in some cases of 46 XY females with ovarian dysgenesis have been very difficult to explain, but have nevertheless provided important insights into the mechanisms of action of H-Y antigen.

H-Y Antigen in XX Males - Inducer for Testicular Development

The clinical condition in 46 XX males resembles that in the Klinefelter Syndrome (47 XXXY); in both conditions the testes are small, spermatogenesis is impaired and the genitalia are normal male. The proposed theories attempting to explain the testicular development and consequent male phenotypes in XX males have postulated the presence of occult Y chromosome material. In fact, with refined cytogenetic techniques, Y chromosome material has been detected either translocated on to an X chromosome or an autosomal or as occult mosaicism in some tissues or in a small proportion of cells.

Although some cases of XX males still defy cytological detection of some form of Y chromosome material, H-Y antigen has so far been detected in every case, although it may be reduced in amount in some individuals. In certain animals, particularly rodents, XX sex reversal is fairly common and in some cases appears to be transmitted as an autosomal dominant condition: XX or XO males carrying the autosomal dominant gene, Sxr (sex-reversed) are sterile males and express H-Y antigen; XX animals transmit the gene without being adversely affected by its presence. This autosomal gene could represent translocation of a minute, cytologically undetectable fragment of the Y-chromosome.

Much more intriguing, however, is the situation in polled (or hornless) goats of Saanan breed which produced XX phenotypic males manifesting H-Y antigen as a condition following an autosomal recessive mode of inheritance. It is manifested in XX animals, homozygous for the abnormal gene and transmitted by the parents both of which are heterozygous carriers of the abnormal gene without affecting their fertility. A remarkably similar situation has also been reported in humans in a family with three XX-males and a pedigree strongly suggestive of autosomal recessive inheritance. Such a mode of inheritance is not convincingly explainable as the basis of translocated Y chromosome material and it is likely that H-Y antigen expression and testicular differentiation can be invoked by autosomal recessive genes.

The H-Y Antigen in XY Females

There are two broad categories of 46 XY phenotypic females - the testicular feminization syndrome and XY gonadal dysgenesis. In the testicular feminization syndrome, testes, XY chromosomes and H-Y antigen are invariably present but the external genitalia are undoubtedly female. This condition, which is also found in rodents, is caused by an X-linked mutant gene conferring tissue insensitivity
to androgens\textsuperscript{13}. Early testicular differentiation is not affected.

In XY gonadal dysgenesis, the affected individuals lack testes and are phenotypically female with dysgenetic or streak gonads. There are two distinct types of this condition with different aetiologies depending on whether the subject is H-Y negative or positive.

**XY Gonadal Dysgenesis without H-Y Expression - Evidence for an X-linked Reppressor Gene**

The easiest way to explain absence of H-Y antigen expression in the presence of a Y chromosome would be deletion or suppression of the H-Y locus. Although the condition is rare in humans much valuable information has been derived from the curious situation in the Scandinavian wood lemming in which females outnumber males and about one half of the females have XY chromosomes but are phenotypically normal and fertile females\textsuperscript{10}. Genetic studies have shown that in these animals there is an X-linked gene which blocks synthesis of H-Y antigen and testicular differentiation by repressing the H-Y locus\textsuperscript{11,24}.

A similar X-linked repressor gene may also account for the reported cases of XY gonadal dysgenesis without H-Y expression in humans. In fact, several cases of familial XY gonadal dysgenesis compatible with X-linked inheritance have been documented\textsuperscript{7,12-19}. Although XY females in the wood lemming are fertile, the condition is still basically similar to that in humans. In the wood lemming with, in effect, only one X-chromosome, as in other rodents with XO sex chromosomes, the gonads develop into normal ovaries containing follicles, but their fertile life span is reduced. Similarly, in human females with XY gonadal dysgenesis, or XO Turner Syndrome, ovarian and follicular development are normal in foetal life but rapidly degenerate thereafter\textsuperscript{19}. Streak gonads lacking ovarian follicles are the only remains by the time of puberty.

**XY Gonadal Dysgenesis with H-Y Antigen Expression - Evidence for Specific H-Y Receptors.**

This condition is highly paradoxical because testicular failure occurs in spite of a normal Y chromosome and H-Y antigen expression. It could be explained if one postulates the existence of specific gonadal H-Y receptors, which, in this case fail to bind with the H-Y antigen. Nevertheless, H-Y antigen is found on all male tissue cells bound to the plasma membrane. This introduces a new concept in H-Y antigen expression: the H-Y locus directs the synthesis of H-Y antigen which then binds to the plasma membrane of cells. There are two H-Y antigen binding sites:

a) the non-specific membrane anchorage site which is present on all tissues, and,

b) the specific gonadal receptor.

It is the binding of H-Y antigen to the specific receptor on the gonad which is responsible for inducing testicular differentiation\textsuperscript{16} and it is precisely this process which fails in H-Y positive ovarian dysgenesis. Specific gonadal receptors for H-Y are found in the gonads of either sex and will bind with H-Y antigen to induce testicular differentiation whether this is produced endogenously by the cells themselves or is available from an exogenous source. This concept has been validated by in vitro experimentation\textsuperscript{17} which is summarised below.

If XY foetal testicular cells are dissociated to form a cell suspension and then cultured under appropriate conditions, they will reaggregate to form long twisting tubular structures closely resembling seminiferous tubules. Similarly, dissociated foetal ovarian cells reaggregate to form spherical structures, resembling ovarian follicles.

It is possible to remove cell surface antigens from dissociated cells by a process termed lyostripping. Dissociated foetal testicular cells which have been lyostripped of their H-Y antigen will not aggregate into tubules but will form spherical follicular structures instead. Conversely, dissociated foetal ovary cells, if cultured in a medium rich in exogenous H-Y antigen, will bind the H-Y antigen and reaggregate into seminiferous tubule-like structures instead of follicles.

**True Hermaphroditism — H-Y Antigen Expression and Partial Receptor Failure**

True hermaphroditism is characterised by the coexistence of testicular and ovarian tissues and is usually accompanied by ambiguous genitalia. Over 80\% of true hermaphrodites have 46 XX karyotypes but serologically they express H-Y antigen, though possibly in reduced amounts. In this respect, they resemble XX males and the arguments relating to testicular development and the presence of occult Y chromosome material also apply. The new problem that arises here is that part of the gonad develops into an ovary in spite of H-Y antigen expression. This problem is similar to that of H-Y antigen positive ovarian dysgenesis and it therefore appears that receptor failure on part of the gonad is responsible for the ovarian development. In fact, it has been shown\textsuperscript{26} that the testicular portion of an ovotestis was H-Y antigen positive, while the ovarian portion was H-Y antigen negative. However, it remains a puzzling problem as to why receptor failure should involve only some of the cells.

**Conclusion - Mechanism of Gonadal Differentiation**

The evidence which has accrued from the study of the H-Y antigen in rare and frequently exotic anomalies of sexual development has considerably enhanced our understanding of the mechanism of gonadal differentiation, which is illustrated in Fig. 1.
It appears that the H-Y antigen, in fact the testis determining factor, controlled by the H-Y locus in the pericentric region of the Y chromosome. However, its expression is also dependent on other factors which are controlled by autosomal or X-linked genes. The H-Y antigen, whose synthesis is regulated by the H-Y locus becomes attached to the plasma membrane of all cells. Binding to a specific receptor site on the gonadal cells is necessary for the H-Y antigen to exert its inductive influence on testicular differentiation. Ovarian differentiation requires only the presence of one X chromosome and the absence of H-Y antigen. Further testicular and ovarian development are influenced by the sex chromosome complement because spermatogenesis cannot proceed in a germ cell line which has two X chromosomes and follicular degeneration occurs if a second X chromosome is lacking.

Development of the accessory genital organs depends on factors secreted by a functioning testis - Müllerian inhibiting factor, Wolffian duct stimulating factor and androgens.

References

This review is based on drugs used currently in Malta for the relief of pain in labour and during delivery. In my opinion the quality of analgesia offered in Malta during labour and delivery can be improved. The best possible anaesthesia is available for operative delivery as evidenced by the absence of maternal deaths associated with anaesthesia.

Identification of Drugs

For analgesia and anaesthesia the gas Nitrous Oxide holds pride of place followed by Trilene vapour and among the intravenous hypnotic agents used Thiopentone Sodium is the preferred drug (I would like to assert Thiopentone sodium as a hypnotic and not an anaesthetic agent as the doses we use locally of this potentially dangerous drug are so small as to induce sleep only). As a relaxant Succinyl choline is the one and only drug used both for intubation as well as for maintenance.

For analgesia alone, usually administered by the midwives under medical control, the drugs used are Sparine as an ataractic agent, Pethidine as a strong analgesic and a hypnotic agent and Trilene or Entonox as draw-over or demand analgesia vapours and gases.

For epidural and regional block Bupivacaine and Xylocaine (lignocaine) are used. Epidural techniques are an innovation to Malta but are gaining ground as more parturients are demanding this type of analgesia. It seems that the modern parturient wants to know more about what goes on and to participate, in an absolutely pain free interlude, during the whole of labour and delivery. But there remain a few Maltese who refuse any injection in the spine fearing a permanently painful back syndrome. Some may think that the description I have just delineated is extremely limited but one has to bear in mind the smallness of the Island, the limited monetary resources, the equipment available, and nursing and midwifery care and staffing. Indeed it is opportune to include a plea here for more qualified midwives and why not, anaesthetic nurses as well as resident anaesthetists. If a full epidural service is envisaged for the future a resident anaesthetist has to be provided for service round the clock. The annual birth rate stands at around 5000 so no one can object to the provision of a full 24 hours anaesthetic and analgesic service by a competent anaesthetist.

The Equipment

A basic technique demands very simple equipment. A simple anaesthetic machine as well as two sources of suction equipment, one based on electricity and one on a piped source of negative pressure.

A Manley Ventilator is at hand to take over some of the anaesthetist's humdrum work of bag inflation during a lower segment Caesarian section. A portable Entonox cylinder with a demand valve, to decrease losses of this costly gas, as well as a Trilene Draw Over Inhaler are available too. The usual intubating equipment and tubes are provided as well as small sized laryngoscopes and tubes for neonatal resuscitation. For epidural and regional blocks needles and catheters with proper filters are kept in stock.

Pharmacology of Drugs

1. Nitrous Oxide

Nitrous Oxide remains the original and surely the best gas for analgesia. It is used in different concentrations in the anaesthetic machine and as a 50/50 mixture with oxygen in a premixed state as Entonox. The popularity of this agent will increase as soon as a local firm is persuaded to start preparing the agent locally instead of depending on costly ready mixed cylinders imported from Italy. It is only since 1968 that Oxygen has proved possible so that one cylinder will supply a constant 50/50 mixture of both gases. A special demand type of valve is used to prevent unnecessary wastage of this drug so that the patient draws over the gas mixture of Entonox and no spill occurs to pollute unnecessarily the labour room.

The advantages of Nitrous Oxide are numerous as its action is limited to the time of inhalation only, no accumulation occurs in the patient's tissues as it is easily eliminated with a few deep breaths. So long as good oxygenation is maintained the effects of the mixture on the neonate or foetus are minimal. No metabolic breakdown by-products of the gas is known to occur in the tissues following its limited use during labour.

Also the liberation of catecholamines that the gas induces, keep the blood pressure slightly raised and so placental perfusion is improved. Other advantages...
include:

(i) The lack of irritant effects on the maternal tracheobronchial tree and gastrointestinal tract.
(ii) the safety of the method
(iii) the simplicity of equipment and administration
(iv) the minimal disturbance of consciousness allowing nearly full and constant patient participation and awareness.

These, in my opinion, fulfill the criteria for promoting the use of this agent.

2. **Trichlorethylene (Trilene)**

Trilene is the time honoured analgesic agent used for inhalation during labour and delivery. A graded dose of this bluish liquid is poured into a temperature compensated, constant delivery, portable apparatus. The patient holds the mask to her face while she breathes deeply at the start of a contraction and so draws air over the liquid vapourising it. The percentage obtained is set at 0.5% but can be reduced to 0.35% if labour is prolonged. When Trilene exerts its effect the drowsy patient releases her hold on the mask and so breaths room air once again. She wakes up ready for the next and other bouts of contractions and repeated Trilene inhalations. Trilene is a safe anaglesic with a sweetish smell and is non irritant. It does not lower the Apgar score of neonates. As it is effective and needs simple equipment I would encourage its use in Malta.

3. **Thiopentone**

Thiopentone (Pentothal) is a hypnotic and not an anaesthetic when used for obstetric purposes. It has to be used with great care, well diluted and parsimoniously injected IV to induce sleep. I still think a sleeping dose has not to be exceeded if one desires to avoid complications such as severe hypotension, vomiting, foetal circulatory impairment and babies born with a very low Apgar score. Calculating the dose according to the patient’s weight and giving it as a bolus IV has many pitfalls but this danger is not stressed enough in books. By injecting the drug slowly the acute tolerance described by Dundee of Wales is avoided and with a small dose one can really go a long way.

The time of starting off this hypnotic is also a subject under debate but in Malta an accord has been reached to delay the injection till the patient is draped and the operating obstetrician is ready with a scalpel in his gloved hands. Indeed it should be the only occasion in anaesthetic practice were the surgeon has to wait on the anaesthetist and not vice versa. A prerequisite for obstetric anaesthesia is a good, wide bore IV Cannula with a simple 5% glucose infusion running: and it is through this drip that thiopentone is to be given making sure that the drip flows easily into the vein.

A fall in blood pressure and a lowering of the cardiac output is to be expected, and combined with the pressure of the uterus on the big veins at the pelvic brim lead to an exaggerated hypotension. As in Malta we do not use special wedges under the patient’s back we rely both on a side tilt operating table as well as on the slickness of the operator to get the baby out in under three minutes and so avoid foetal hypoxia. In any case the minimal fall in blood pressure combined with dexterity of the operator helped by muscle relaxation ensures that no fall in Apgar score occurs when the baby is born. Muscle relaxation, besides allowing intubation of the trachea, lessens the incidence of laryngospasm due to thiopentone, protects against vomiting (as the abdominal muscles are relaxed, thereby avoiding pressure on the stomach) and ensures an uncluttered view of the operation field to the operating obstetrician.

4. **Succinylcholine**

Succinylcholine is the one and only muscle relaxant I recommend for use during a LSCS. It is to be avoided only in those patients who have had confirmation of low pseudocholinesterase activity. All pregnant women have rather lowered values of this enzyme and therefore the use of minimal dosage, usually 50 mg, is enough. This initial dose should be sufficient for intubation and also for delivery of the neonate, although occasionally an increment of 25 mg may have to be added on later. To avoid any bradycardia it is usual to administer Atropine 0.6 mg in the drip tubing at the beginning of the operation. It is to be mentioned that the big molecule of Scoline does not reach the foetal circulation as it will not pass through the placental barrier. Used in the doses recommended the muscarinic effects of the drug are mild and easily covered by atropine.

Occasionally some delay in reestablishing full muscle power and adequate tidal volume is encountered in patients with low pseudocholinesterase activity and in these cases ventilation is continued. Usually it is only a matter of time before full restoration of tidal volume occurs. A good fluid input combined with a quick acting diuretic given IV sees that the drug is eliminated soon and breathing restored.

In rare cases where the use of this drug is contraindicated due to familial pseudocholinesterase deficiency then the nondepolarising drug pancuronium is used.

5. **Narcotics**

Among the narcotic agents Pethidine or Pethilorfan have for the last forty years been used in Malta. Indeed there is hardly a parturient especially primipara who is being managed by IM analgesia who fails to have either. They are excellent drugs not only for their pain relief but also for their muscle relaxant effect. Abolishing pain means relaxation of anxiety and so also relief of muscle tension. This helps the cervix to
dilate and so lessens the duration of labour while the
tired mother can be pain free for a time. As they cause
smooth muscle relaxation they lower the blood
pressure. Accompanying the fall in B.P. is tachycardia
but this is rarely of a degree to warrant attention.
However, the patient who has had pethidine has to
remain lying down and cannot be allowed to walk
around throughout the duration of labour. As all
narcotics knock off the will power the patient’s
cooperation is not easily obtainable during delivery.

In the doses recommended pethidine will not
cause depression of respiration to occur to an
alarming degree in the mother but the drug should not
be given if delivery of the foetus is anticipated within
three hours because the drug easily crosses the
placental barrier and may cause depression of
respiration in the neonate. The recent arrival on the
market of Naloxone in neonatal doses (Narcan), a
specific antagonist, has eased this problem. Any
precipitate delivery after pethidine injection and
consequent birth of a respiratory depressed neonate
can within minutes be assisted with a single dose of
this wonderful antagonist that has put the old reversal
agents Lorfan and other convulsant producing drugs
out of use.

Although every student knows that narcotics can
cause addiction the development of such a condition
following the use of Pethidine for pain relief during
labour is unknown in Malta.

6. Promazine (Sparine)

Along with Pethidine the ataractic drug
Promazine (Sparine) is often used.

This drug, a development on Largactil, is a very
good sedative as it tends to dissociate the patient from
the surroundings and yet allows her to remain
responsive to orders. Sparine is preferred to Largactil
as its hypotensive effects are less. This minimal alpha
blockade does not disturb the blood pressure to any
great extent but lessens foetal heart responsiveness
to the contractions of labour. This drug is a strong
anti-emetic and in the rare patient who reacts to the
emetic effects of pethidine the concurrent
administration of sparine will stop retching and
vomiting, besides augmenting the pain relief effect.
Sparine is often used as a premedicant drug when the
patient is to undergo regional analgesia. Its calming
effect ensures a high degree of patient cooperation.
Sparine does not depress the respiratory drive in the
mother nor causes any acid-base imbalances.

Although the administration of this drug is usually
in the hands of the midwives it is the local custom to
ask for the advise of the resident doctor before
repeating the injection.

The Epidural or Regional Techniques

Two drugs are used in Malta for all epidural
blocks: Bupivacaine (Marcaine) and Lignocaine
(Xylocaine).

The quick onset of action, the calculated duration of
effect and lack of side effects make these drugs safe
for routine obstetric use. They are amino esters of
an aromatic acid prepared as a salt. Following
injection the tissue alkalinity liberates the free base.
This free base has a high oil/water solubility and on
penetrating the axon is transmitted to the inner wall of
the nerve cell where it blocks the enzymes responsible
for keeping the sodium channels open. Paralysing the
sodium channels easily leads to electrical impedance
and consequently the cell cannot be depolarised,
remains polarised at -70mV and so it is functionless and
nonconductive for a time. After a while this sodium
channel block is overcome by removal, through liver
breakdown, of the drug and the cell wall again allows
sodium through, so that the cell can be depolarised
and starts to conduct nerve impulses again. A central
sedative action is also described but is minimal in
importance in the doses used. Inadvertent spinal
injection is however accompanied by convulsions and
can also lead to central depression and death, through
respiratory failure, hence the importance of
continued medical attendance when continuous
epidurals are in use. All the precautions usually taken
with general anaesthesia are to be at hand and ready
for immediate use. All patients under a block are to be
carefully monitored for the first 15 minutes. Beside
central effect the local analgesics also have a blocking
effect on transmission at the autonomic ganglia due to
depression of acetylcholine release and also a
non-depolarising competitive block. This explains the fall
in blood pressure, the bradycardia and the muscular
relaxation. Smooth intestinal muscle is also affected
and is contracted so that the risk of vomiting is less,
bowel movements are decreased and the obstetrician
cannot complain that the Patient is pushing. This
same spasmolytic action is responsible for the
peripheral vasodilatation and lowering of the blood
pressure. Peripheral vasodilatation and fall in blood
pressure are due to multi-factorial causes and the
eventual degree of fall depends on physical factors
such as the patient’s position, age of the arteries (not
patient’s age... remembering the damaging effect on
the arterioles of diabetes mellitus), drugs the patient
has been on, such as B blockers, ganglion blockers,
and, of course, to the prevalent obstetric condition...
the pregnant uterus that presses on the soft vena cava
and causes the hypotensive syndrome. More use
should be made of the Wedge. This is a four feet long
plastic pillow cut in the form of a wedge that is inserted
under the patient’s back to push the heavy pregnant
uterus away from the soft collapsible veins that course
down the posterior pelvic rim.

Bupivacaine has been chosen for epidural blocks
because it has a high analgesic potency ratio
compared with many other locals (4 times as potent as
Xylocaine). As it acts quicker, lasts longer and
penetrates tissues at a fast rate, the maximum amount
injected at one dose has to be kept under 1 mg per kg
body weight.

Continued on page 37
Infertility is a condition that involves a man and a woman attempting unsuccessfully to conceive a child. A working definition of the problem is necessary to provide criteria for initiating an evaluation. As a practical guide, infertility is present when a woman fails to conceive after one year of regular, sufficiently frequent, unprotected intercourse. Since the male or female or both partners may have specific factors causing the infertility, both should be examined initially. Male subfertility accounts for 45% of all infertile marriages and contributes to a further 10% when both partners are subfertile.

Many more investigations have been conducted in human gynaecology than in andrology. The reproductive ability of men is characterized by several interacting anatomical and physiological phenomena. The presence of normal responsive testes and accessory glands are essential for normal male reproductive function, as is the presence of normal anatomy of excurrent ducts permitting free passage of the ejaculate. Normal testicular function is dependent of normal endocrine relationships outlined in Figure 1:1. Reproductive failure in men can result from a large variety of causes including anatomical, mechanical, vascular, neural, physiological, endocrine, immunological, genetic, psychogenic, iatrogenic or pathological factors. A working classification of causes of male subfertility is outlined in Table 1:1. The diagnosis of male subfertility relies on an accurate semen analysis supplemented by other investigations such as an endocrine evaluation. It is also important to take a complete history and perform a physical examination in sufficient detail to detect unsuspected underlying disease.

History
The physician should attempt to elicit by direct and specific questions symptoms related to various

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**Fig. 1:1 - The hypothalamic-pituitary-testicular axis showing stimulatory (+) and negative (−) feedback mechanisms. Testosterone and oestradiol are inhibitory to LH and FSH secretion, while inhibin is inhibitory to FSH secretion.**
### Table: A Working Classification of Male Subfertility

<table>
<thead>
<tr>
<th>A. Testicular Abnormalities</th>
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<tbody>
<tr>
<td>1. Primary hypogonadism:</td>
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<tr>
<td>1. Developmental, genetic,</td>
<td></td>
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<tr>
<td>traumatic, inflammatory,</td>
<td></td>
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<tr>
<td>radiation, thermal disorders,</td>
<td></td>
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<tr>
<td>cryptorchidism, retarded</td>
<td></td>
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<tr>
<td>descent.</td>
<td></td>
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<tr>
<td>2. Secondary hypogonadism:</td>
<td></td>
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<tr>
<td>hormonal disorders of</td>
<td></td>
</tr>
<tr>
<td>pituitary-hypothalamic axis</td>
<td></td>
</tr>
<tr>
<td>adrenal, increased</td>
<td></td>
</tr>
<tr>
<td>oestrogens, thyroid</td>
<td></td>
</tr>
<tr>
<td>disorders.</td>
<td></td>
</tr>
<tr>
<td>B. Accessory Organ Abnormalities (Prostate and Seminal Vesicles)</td>
<td></td>
</tr>
<tr>
<td>1. Congenital</td>
<td></td>
</tr>
<tr>
<td>2. Traumatic</td>
<td></td>
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<tr>
<td>3. Infectious</td>
<td></td>
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<tr>
<td>4. Immunological</td>
<td></td>
</tr>
<tr>
<td>C. Excurrent Duct Abnormalities</td>
<td></td>
</tr>
<tr>
<td>1. Vas deferens and</td>
<td></td>
</tr>
<tr>
<td>epididymis:</td>
<td></td>
</tr>
<tr>
<td>surgery or trauma, infective, congenital, cystic fibrosis.</td>
<td></td>
</tr>
<tr>
<td>2. Penile abnormalities</td>
<td></td>
</tr>
<tr>
<td>(a) anatomical - development or traumatic</td>
<td></td>
</tr>
<tr>
<td>(b) functional - disorders of erection or ejaculation</td>
<td></td>
</tr>
</tbody>
</table>

Conditions potentially causing the subfertility. This requires that a full review of childhood illness, organ systems, past medical history, occupational and dietary history be obtained. A family history of subfertility or hypogonadism may be particularly helpful. Full details regarding any known chronic illness should be recorded. A careful drug history is important. The male patient should be questioned carefully about prior fertility, either in another marriage or with an extramarital partner. The frequency of extra-marital experiences should also be elicited. A detailed history regarding frequency of intercourse is necessary. The physician should also attempt to determine by history that penetration actually occurs during intercourse and that ejaculation into the vagina takes place.

Testicular disorders account for about 60% of cases presenting with male subfertility. Cryptorchidism in childhood, even when corrected, is associated with a high incidence of subfertility. For this reason, the patient should be questioned about prior cryptorchidism and previous orchidopexy procedures. He should also be asked whether a scrotal mass has been previously noted. In addition, an attempt should be made to elicit a history of previous hernia, hydrocoele, surgery in childhood, mumps orchitis, testicular irradiation, cytotoxic drug therapy, excessive heat application to testes, or scrotal trauma. Since mild flu-like illnesses may result in temporary oligospermia, recent mild illness, testicular pain, or symptoms of urethritis should be asked about. Since testicular failure may result in androgen deficiency, pertinent questions should be asked about libido, frequency of shaving, muscle strength, endurance, potency or development of male pattern baldness. The age that the patient first noted pubic hair, penile enlargement, growth spurt and onset of shaving should be noted.

Anatomic obstruction to sperm egress usually in the epididymis and vas deferens account for approximately 8% of cases. A history suggesting epididymitis and venereal disease (particularly gonorrhoea) should be sought. Symptoms of frequent pulmonary infections may suggest a mild heterozygous form of cystic fibrosis which is associated with bilateral absence of the vas deferens. Prostatic disease may also cause mechanical obstruction and symptoms of prostatitis, penile discharge, pelvic pain on urination or defaecation, or prior prostatic or bladder neck surgery should be sought.

Approximately 9% of infertile men will be found to have pituitary or hypothalamic lesions as a cause. Two types of symptom complexes may be present in these patients. They may complain of symptoms referable to growing lesions (headaches or disturbances of peripheral vision) or alternatively they may have complaints suggesting endocrine abnormalities. Hyper- or hypofunction of the thyroid and adrenal glands have been implicated with subfertility in the male. Men with diabetes mellitus or other disease associated with autonomic neuropathy, as well as patients receiving antihypertensive medications, may experience retrograde ejaculation into the bladder. These patients may not appreciate that emission from the penis during ejaculation is absent. The only symptom may be a cloudy urine secondary to seminuria in the first voided urine after intercourse.

Psychogenic factors as a primary cause for subfertility may account for up to 5% of cases referred for a subfertility evaluation. Male impotence and
disorders of ejaculation are not uncommon. These disorders are frequently psychogenic in origin, but organic or iatrogenic causes must be ruled out. A number of clues suggesting psychogenic disorders may include:

1. sudden rather than gradual onset
2. retention of morning erections
3. potency in extramarital relationships
4. a prior history of premature ejaculation and
5. a history of a female dominant partner or prior homosexual tendencies

Stress factors at home or work may also contribute to the problem.

Physical Examination

A complete physical examination should be carried out to attempt to uncover unsuspected underlying systemic disease. General examination should aim at identifying psychogenic and endocrine causes for the subfertility. Careful measurement of height, arm span and pubis to floor distance may provide evidence of mild eunuchoidism. This finding is present when the arm span is two inches or more greater than the height, or the floor to pubis distance is two inches or more greater than the pubis to head distance. The overall androgenic effects in the patient are evaluated by observing the axillary, pubic and facial hair, penile size, muscle mass, and pitch of voice. A careful assessment of breast tissue should be made to exclude gynaecomastia.

The genital organs should then be carefully examined. The length and width of the testes may be easily determined with a millimeter ruler. The lower limit of testicular length and width in normal adult men is 3.6 and 2.1 cm respectively (length 4.6 ± 1.1 cm; width 2.6 ± 0.5 cm). Measurement of volume using a series of ellipsoids for comparison has been suggested as a more precise assessment of testicular size. An orchidometer has 12 models of definite shape and volume, eg. 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 15, 20 and 25 ml respectively. These sizes can easily be distinguished in the patient by palpation. Testicular consistency is also assessed. Hypogonadism secondary to pituitary disease is characterised by a softening of the testes as well as a decrease in size. Testicular masses should be also sought for. The presence of a varicocele in the scrotum should also be looked for. Dilatation of the veins in the upper portion of the scrotum are usually easily felt or are evident upon inspection when the patient is standing and performing a Valsalva manoeuvre. Signs of balanitis and balanoposthitis must be looked for and their aetiology identified. The epididymis and vas deferens should be palpated between the thumb and index finger. Nodularity, tenderness or masses may be indicative of previous epididymitis or granulomatous disease. The vas deferens may be congenitally absent. Inguinal and femoral hernias or scars of previous herniorrhaphies should be noted. Rectal examination allows assessment of the prostate and seminal vesicles. This examination should be directed towards determining overall gland size, consistency of the two lobes, irregularities of the surface or tenderness.
Physiological and Pathological Research at the General Military Hospital of Valletta, Malta, in the early Nineteenth Century*

DR. PAUL CASSAR MD, BSC, DPM, FR Hist. S,D LITT (HON. CAUSA)
HON. FELLOW OF THE UNIVERSITY OF MALTA

* The extended text of a paper delivered at a Medical Conference at the Medical School, G'Mangia, on 20th January 1984.

The theoretical and practical progress achieved by the biological sciences in our time contrasts very markedly with the tentative experimental studies in these fields in the early decades of the nineteenth century. Those distant years are of special interest to the historian of medicine as they formed the matrix in which the seeds of our present knowledge were sown and cultured.

Malta may take some pride in the fact that it has had a share - albeit a small one - in the series of steps leading towards the elucidation of the chemical, physiological and pathological perplexities of those formative years. This was possible thanks to the investigations and observations of Dr. John Davy carried out at the British General Military Hospital of Valletta- formerly the Holy Infirmary of the Order of St. John - between 1828 and 1835.

Biographical Note

Dr. John Davy (1790-1868) was the younger brother of Sir Humphrey Davy who invented the safety lamp for miners and was the first to record in 1800 the intoxicating effects of nitrous oxide and discover its anaesthetic properties.

John studied medicine at Edinburgh qualifying M.D. in 1814 at a time when London medical schools were still in embryo. He joined the Medical Department of the British Army, serving for a period of almost twenty-five years and finally rising to the rank of Inspector General of Army Hospitals. In 1834 he was elected Fellow of the Royal Society of London.

He was in the Mediterranean for a span of eleven years (1824-35), seven years of which (1828-35) he spent in Malta. He again visited the island towards the end of November 1840 while he was on his way to Constantinople to advise on the organisation of the medical corps of the Turkish Army. Two months previously, on the 28th September 1840, he was elected Honorary member of the Societa Medica d’Incoraggiamento di Malta (The Maltese Medical Society of Encouragement). This society was the only medical and scientific association in Malta at the time.

Apart from his professional commitments in the army, Davy was President of the Medical Committee which superintended the civilian medical services of the islands. He also had a busy private practice among residents in Malta and numbered several distinguished visitors to the island among his patients.

When Sir Walter Scott reached Malta on the 21st November 1831, he was an invalid as a result of an apoplectic attack which he had at Abbotsford in April of the same year. While he was in Malta, it was feared that another stroke was impending. Dr. Davy was called instantly. He found Scott with a flushed face, heavy eyes and great difficulty in speaking. He ordered the application of leeches to the patient's head - then the standard treatment - and Scott felt so much relieved the following morning that he was allowed to be driven into the countryside in the company of Mrs. Davy. The latter enjoyed an old family relationship with Sir Walter Scott as her parents resided near Scott's home in North Castle Street in Edinburgh; while Scott himself knew Dr. John Davy through his friendship with Sir Humphrey Davy.

Two years later Dr. Davy had occasion to treat another famous visitor in Malta. This was the Rev. J.H. Newman (later Cardinal) who had caught a very bad cold while undergoing quarantine at the Lazzaretto in January 1833. Dr. Davy recommended fifty drops of antimonial wine three times daily - a remedy which Newman found to be wonderfully efficacious.

Davy was an intimate friend of the Rt. Hon. John Hookham Frere who had settled in Malta and who endeavoured to arouse the interest of naturalists in continued on Page 23
PRESCRIBING INFORMATION

Presentation BACTROBAN ointment: A presentation of mupirocin 2% weight/weight in a white, translucent, water-soluble, polyethylene glycol base. Available in 15g tubes.

Activity BACTROBAN is a topical antibacterial agent, active against those organisms responsible for the majority of skin infections, e.g. Staphylococcus aureus, including methicillin-resistant strains, other staphylococci, and streptococci. It is also active against Gram-negative organisms such as Escherichia coli and Haemophilus influenzae.

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

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

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

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

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

Further information is available on request from Beecham Research Laboratories Brentford, Middlesex, England.
NEW SYRUP PRESENTATION

Augmentin (clavulanate-potentiated amoxicillin)

100 ml syrup in powder form
156 mg/5 ml clavulanate-potentiated amoxicillin

Augmentin is free from sugar.

PREScribing INFORMATION

Indications:
Chest, ear, nose, throat, genito-urinary, skin and soft tissue infections including those caused by β-lactamase producing organisms.

Dosage:
Adults and children over 12 years one AUGMENTIN tablet (125mg) three times daily.
Children 7-12 years 10ml AUGMENTIN syrup (312mg) three times daily.
Children 2-7 years 5ml AUGMENTIN syrup (156mg) three times daily.
Children 9 months - 2 years 2.5ml AUGMENTIN syrup

Severe infections these dosages may be doubled. Treatment should not be extended beyond 14 days without review.

Contra-indication:
Penicillin hypersensitivity

Precautions:
Safety at human pregnancy is yet to be established. Oral dosage need not be reduced in patients with renal impairment unless dialysis is required.

Side-effects:
Uncommon, mainly mild and transitory, eg diarrhea, indigestion.

If gastro-intestinal side-effects do occur they may be reduced by taking AUGMENTIN at the start of meals.

Presentations:
37.5mg AUGMENTIN tablets each containing 250mg amoxicillin (1) and 125mg Clavulanate acid (2).
156.25mg AUGMENTIN syrup. Powder for preparing fruit flavoured syrup. When dispersed each 5ml contains 125mg amoxicillin (1) and 3.125mg clavulanate acid (2)
(1) as the trihydrate, (2) as the potassium salt.

Not all presentations are available in every country.
A CHANGE FOR THE BETTER IN CHILDREN’S INFECTIONS

Broader in Spectrum

- A broader spectrum than ampicillin, erythromycin, co-trimoxazole and oral cephalosporins
- Excellent activity against Haemophilus influenzae, Strep. pneumoniae\(^1,2\) and Branhamella catarrhalis\(^3,4\)

Outstanding in Practice

- Rapid relief from symptoms
- Excellent success rates in ear, nose and throat infections\(^6,7,8,9,10\)
- Well tolerated, with a low incidence of side effects\(^6,11\)

AUGMENTIN

(General Practice isolates from Ear, Nose & Throat infections collected during 1979-80)\(^5\)

<table>
<thead>
<tr>
<th>Infection</th>
<th>Favourable Response</th>
<th>% Clinical Success</th>
</tr>
</thead>
<tbody>
<tr>
<td>Otitis Media(^9)</td>
<td>129</td>
<td>97%</td>
</tr>
<tr>
<td>Tonsillitis</td>
<td>106</td>
<td>97%</td>
</tr>
<tr>
<td>Pharyngitis(^9)</td>
<td>85</td>
<td>93%</td>
</tr>
<tr>
<td>Bronchitis(^9)</td>
<td>48</td>
<td>96%</td>
</tr>
</tbody>
</table>

References

1 Excerpta Medica. ICS 544, (1980), 173
2 Excerpta Medica. ICS 544, (1980), 19
5 Further analysis of data on file presented in summary form, Excerpta Medica. ICS 544, (1980), 173
6 Excerpta Medica. CCP4, (1983) 341
11 Excerpta Medica. CCP4, (1983), 347
12 Excerpta Medica. CCP4, (1983), 325

Further information is available from:
Beecham Research Laboratories
Brentford, Middlesex, England.
Flemoxin® E-tab
(amoxicillin)

The first amoxicillin effervescent tablet

- rapid effect
- sugar free
- no aftertaste

Sole Agent: EDWIN BUSUTTIL - Import/Export Agent
127, High Street, Hamrun,
Tel: 323366/220026

- extensive range of presentation forms:
drops, suspension, capsules, effervescent tablets

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<table>
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<tr>
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<tbody>
<tr>
<td>Drops</td>
<td>0-2 years</td>
<td>100 mg/ml (20 ml)</td>
</tr>
<tr>
<td>Suspension</td>
<td>2-10 years</td>
<td>125 mg/5 ml (100 ml)</td>
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<tr>
<td></td>
<td></td>
<td>250 mg/5 ml (100 ml)</td>
</tr>
<tr>
<td>Capsules</td>
<td>Over 5 years</td>
<td>100 x 250 mg</td>
</tr>
<tr>
<td>Effervescent tablets</td>
<td>Over 2 years</td>
<td>20 x 250 mg</td>
</tr>
</tbody>
</table>

**Indications** Flemoxin is indicated in the treatment of infections caused by amoxicillin-sensitive gram-positive and gram-negative microorganisms, e.g. respiratory, urogenital, gastrointestinal tract infections of the skin and soft tissues. In severe infections such as sepsis, meningitis, endocarditis, peritonitis, etc., parenteral administration (e.g. ampicillin) is to be preferred. Therapy initiated with parenteral administration may be continued with oral Flemoxin when parenteral therapy is no longer required.

**Contra-indication** Hypersensitivity to penicillins.

**Use in pregnancy** As far as known, this drug can be taken safely during pregnancy.

**Side-effects** Macular or maculopapular rashes may occur. Typical allergic reactions, such as urticaria and purpura are less common. An anaphylactic reaction following oral administration of penicillin or one of its derivatives has only very occasionally been reported. Gastro-intestinal side-effects, such as nausea, vomiting and diarrhea are sometimes observed, but are generally not serious and of a transient nature.
the fauna, plant life and fossils of the Maltese Islands. Davy kept up a correspondence with Frere on the natural history and geology of Malta even after his departure from the islands. He also wrote extensively on the agriculture and climate of Malta in his *Notes and Observations on the Ionian Islands and Malta* published in London in 1842. In this work he produced excerpts from a publication by the Professor of Botany at our university, the Rev. Fr. Carlo Giacinto (1805-24), issued in Italian in 1811 under the title of *Saggio di Agricoltura per le Isole di Malta*.

Davy conducted a number of experiments to find out whether the bright moonlight of Malta had any heating, chemical or magnetising powers. The belief was then current, in some Mediterranean countries, that moonlight had a harmful effect on health but Davy’s inquiries failed to support this concept. Indeed he ascribed - and rightly so - the ill-effects on health to malaria which he found to be more frequent in those who slept exposed to the night air though he admitted that the agent causing malarial fever was *enveloped in profound mystery*. In fact the malaria-cycle and the role of the mosquito (that bites at night) in the spread of the disease was only elucidated in 1897.

The provisions of measures to counteract the effects of the summer heat and to ensure a restful sleep at night engaged his attention in August 1830. A series of thermometric experiments led him to suggest the construction of an apartment *made as much as possible of glass* and provided with thick wooden shutters lined on the inside with cotton wool and painted white on the outside. These shutters were to be kept closed during the day and opened only after sunset.

From a study of the smallpox epidemic that raged in Malta in 1830-31, Davy became convinced that vaccination gave adequate protection against smallpox. The beneficial results of vaccination were amply demonstrated by the comparative exemption from the disease of the vaccinated British troops then in Malta. Thus Davy was able to show that, while among civilians one in every twelve was attacked, the proportion among the military was one in one hundred eighty-eight.

He endeavoured to promote the treatment of needy civilian sick on an out-patient basis so that the individual could receive the necessary medical attention without going to hospital. For this purpose he suggested the setting up of a dispensary in Valletta which was eventually opened on the 14th April 1832. He made over to the new dispensary sundry surplus utensils from the General Pharmacy of the British Army. This is how the Government Dispensaries in our towns and villages - known as *il-berga* - originated.

There were two government institutions which called forth Davy’s criticism - the Foundling Hospital and the Quarantine System. He disapproved of the Foundling Hospital because, in his view, it afforded a cloak to *licentiousness and the deadening of moral principle and natural affection* and because of the high mortality among its infants due, most probably, to dietetic errors. He favoured the mitigation of the quarantine laws but did not advocate any alteration in the regulations in force in his time before a searching inquiry into the whole subject had been carried out. What he wished to see established was a restrictive system which, while protecting the public health, caused as little vexation to individuals and to commercial intercourse as possible.

John Davy died on the 24th January 1868.

**Davy’s Research Work before coming to Malta**

By the time he came to Malta in 1828, Davy had already shown great interest and gained fruitful experience in chemical and anatomical research. In 1811, three years before graduating, he tried to determine the proportional quantities of organic and of calcareous matter in bones of different animals and of human beings of various ages. In the same year he joined the Royal Medical Society of Edinburgh to which he read a dissertation *On the Diseases Peculiar to Different Climates* - a suitable exercise for his future overseas service on the medical staff of the army. He later became President of the Society (1812-13) together with Richard Bright - of Bright’s Disease fame - of whom he was an intimate friend.

He was the first to prepare phosgene gas (COCl₂) in 1812 by exposing a mixture of equal parts of carbon monoxide and chlorine to sunlight. Phosgene found its chief use in the manufacture of aniline dyes and of pharmaceutical products, such as creosotol, but ironically enough what should have contributed to the welfare of humanity was turned into a lethal weapon of destruction by Germans one hundred years later when they made use of the toxic properties of phosgene to spread death by asphyxiation on the Western Front in December 1915.

During a voyage from England to Ceylon in 1816 he took the opportunity to observe the temperatures of men and animals in different latitudes and relating them to variations in the temperature of the atmosphere, diet, exercise and state of health. While stationed in Ceylon (1816-20), he studied the anatomy of the urinary organs of various amphibians and experimented with the effect of poisons from twenty different species of snakes. When he was transferred to the Ionian Islands (1825-27), he investigated the effects on the human skin of the sun’s rays and of the fluid exuded from he cuticle of the toad (*Rana bufo*, L).

He commenced the practice of keeping notes of every autopsy he performed from May 1821 to 1838. These post mortem examinations were carried out mostly on soldiers dying in British military hospitals but, in some foreign stations, also on the native population especially in Malta where he discovered that the Civil Hospital offered an ample field of research. Thus in a period of seventeen years he did no less than seven hundred and eighty six autopsies of which three hundred and seventeen were held in Malta.
Observations on the Temperature of the Human Body after Death (1828-29)

A topic which engaged Davy's attention in Malta in 1828-29 was the rise in temperature which is noticed in the deep seated parts of the cadaver at autopsy - a phenomenon about which, to his knowledge, no precise observations had hitherto been made.

His series consisted of ten cases of death occurring at the General Military Hospital or Station Hospital at Valletta. His study extended over a period of six months from July 1828 to the following January. The bodies were all of British soldiers serving in Malta. Immediately after death the bodies were removed "to a large, airy and comparatively cool room, the old laboratory of the hospital of the Knights, where they were to be examined and where they were generally covered merely with a sheet and placed on a table of wood". As the onset of putrefaction was hastened by the hot weather of the Mediterranean, in fact the autopsies were carried out sooner than usual and *almost immediately after death*, the time varying from three to seventeen hours after the decease. One obstacle to this haste was the question - then very much on men's minds - as to whether the individual was really dead or only apparently so. To exclude the possibility of vitality in the cadaver or of suspended animation, Davy took the very prudent precaution of excluding such an eventuality by ensuring that the body did not react when a small incision was made in the cutis, when the eyes were exposed to light and when the platysma myoides was punctured.

He found that the difference in temperature between that of the air in the room and the internal parts of the cadaver varied from twelve to as much as thirty-three degrees F. As these observations were recorded in a *comparatively warm climate* (Malta), later on in the same year, he compared them with an additional series of observations made at the General Hospital at Fort Pitt, Chatham, on ten bodies of soldiers and found the same range of increase in the internal temperatures of the cadaver relative to that of the room in which the examination took place.

As no putrefaction had taken place in the cadavers examined, Davy concluded that the high internal temperatures were generated before death, as happens in febrile diseases and in those persons living in the tropics where Davy ascertained that the temperature could rise to 101°F in the living *without damaging health*.

He realised that thermal phenomena could be of practical use in medical jurisprudence in arriving at a *tolerably positive conclusion, in doubtful cases of death, as to the time which may have elapsed between the fatal event and the post mortem examination* after taking into account the *circumstances likely to modify temperature*. He did not, however, follow this line of research any further and left other openings for curious and perhaps useful inquiry to others.

Experiments on the Tissues of the Human Body (1828-30)

**Desiccation**

The question of the proportional quantities of solid to fluid matter in the body was still unresolved in Davy's time. According to some research workers the proportion of solids to fluids was as one to six; and according to others as one to nine. He tried to throw some light on this question by desiccating eighty-two samples of human tissues (cartilage, bones, internal organs, etc) taken from the bodies of British soldiers dying at the General Military Hospital of Valletta but he found it extremely difficult to come to a definite conclusion as the number of samples examined was not large enough to furnish him with accurate data.

**Action of Corrosive Sublimate**

Davy felt on surer ground in his experiments with corrosive sublimate on human body tissues. The property which corrosive sublimate possesses of preserving animal tissues has been known for many years and anatomists had taken advantage of this feature both in the dissecting room and in pathological museums. However, Davy felt that not enough dependable research had been carried out. He applied himself to this inquiry in the summer of 1828 with the following positive results:

(a) *Confirmation of the general antiseptic power* of corrosive sublimate for the purpose of making dried preparations and for its employment in the dissecting room;
(b) corrosive sublimate arrests the fermentation of juice of grapes;
(c) corrosive sublimate prevents putrefication of animaland human tissues and arrests it when it has already started.

**Action of Lime**

In Davy's days, it was a commonly held belief that lime had a corroding and destructive action on animal matter and that, therefore, animal tissues exposed to it decomposed and disappeared rapidly. Accordingly it was recommended to add lime to burials where a quick decay of corpses was desirable as during the prevalence of pestilence.

From many experiments which Davy conducted in Malta in 1829-30 he concluded that this belief was erroneous and that far from destroying animal tissues, lime preserved them through its antiseptic property and enabled them to resist putrefaction whether they were placed in air or plunged and kept in common water. Lime, however, softened skin, nails and hair and finally destroyed them and it was perhaps this destruction of these particular tissues that led to the idea that lime exercised a destructive action on animal substances generally.

In the course of trials with other chemicals he found that ammonia, magnesia and potash had a similar preservative effect as that of lime.
**Boiling of Body after Death**

Davy found that the boiling of the human body after death aided its preservation if the boiled parts were immediately placed in receptacles containing spirit of wine (proof spirit)\(^1\).\(^7\).

**Action of Air on the Putrefaction of Various Tissues**

These experiments were carried out during the summer season. The rapidity of putrefaction varied from one type of tissue to another, being most rapid in the brain and slowest in bone. The process was attended by an elevation in temperature. A circumstance that accelerated the putrefactive process and the evolution of heat was the presence of maggots of various kinds of the genus Musca. Davy gives a very vivid account of the activity of these creatures. It is curious, he wrote, to watch the progress of these animals in their growth and still more so in their operations. When their food is very nutritious, the almost microscopic ova, in forty-six hours, are converted into large maggots. When they have nearly attained their full size they feed with extraordinary voracity as if aware that their lives depended upon their activity. The whole of a numerous brood might be observed, side by side erect, with one extremity in the ammoniacal poultacious mass, pumping up nourishment, and with the other narrower extremity in the atmosphere, the orifice of its canal dilated, seeming to pump down air\(^1\).\(^8\).

**Maceration in Water**

Anatomists had been hampered in their investigations on the maceration of the human body because of difficulty in procuring corpses, the time required for maceration to take place, the disgusting nature of the operation and the risks to the health of the investigator. These hurdles, however did not deter the inquiring mind of Davy from engaging in research on this topic while in Malta in July 1828. The experiments, he wrote, were all made in the laboratory of the General Hospital - formerly the hospital of the Knights - a room by its equable temperature well adapted for the purpose. The investigations extended over a period of twelve months. The water used was the potable water conveyed to Valletta by the Wignacourt Aqueduct. The parts were macerated in glass jars varying in capacity from one to two gallons and were kept in the water for eight to twelve months. The specimens were removed from the bodies of twelve British soldiers, varying in age from eighteen to fifty-six years, who died in hospital from such varied conditions as fever, tuberculosis, dysentery, etc\(^1\).\(^9\). The organs used included the heart and pericardium, lungs, the brain and its membranes, spleen, pancreas, kidneys, alimentary canal from mouth to rectum, sexual organs, muscles, cartilage and bones. Davy found that the rate of maceration varied from one type of tissue to another being most rapid in some but less so in others. He refrained from giving a minute account of his findings as otherwise a volume would be required to contain them but he wrote in sufficiently great details on the more important results obtained.

He attributed the changes produced by maceration to:

(a) chemical reactions,
(b) the activity of the unicellular *infusoria* of Linnaeus, today known as protozoa, feeding on the specimens,\(^2\)
(c) the larvae of the common gnat of Malta which were very abundant and active as destroying agents performing a role in water similar to that of the larvae of flies on dead animal matter in air, and,
(d) the operation of those obscure plants belonging principally to the *confervae* or *algae* *aquaticae* of Linnaeus, i.e. fine velvety-like mosses\(^2\).\(^1\)

**Observations on the Blood (1828-35)**

John Davy graduated from Edinburgh with an inaugural dissertation on the composition of the blood based mainly on the views current in Edinburgh and on the research work of the eighteenth century physiologist William Hewson who established the essential features of the coagulation of the blood.

In later years Davy returned to the same subject with special regard to the specific gravity and the coagulation of the blood. His experiments were conducted on lambs, turtles, sharks and human beings and took place at intervals and in various places where he happened to be staying at the time i.e. 1811 (Edinburgh), 1818-19 (Ceylon) and 1824-35 (Mediterranean, chiefly Corfu and Malta).

While in our island, he was led to inquire into the effects of various physical and chemical agents on blood coagulation. He studied this phenomenon in two hundred and forty-nine cadavers of soldiers of British regiments serving in Malta. He found that in only one hundred and five cadavers was the blood coagulated. He tried to establish a correlation between this feature and the type of disease from which the patient died but in his time, knowledge about the composition and functions of the blood was still elementary. Yet the question was of practical importance because of the use of bloodletting, by leech and by the lancet, as a remedy for the abatement of pain and the relief from the feeling of oppression in the chest accompanying certain illnesses. Physiologists differed considerably in their interpretation of the few facts then known while they were still trying to unravel the effect of oxygen and of carbon dioxide on the blood; and they were not yet sure whether blood was a *living* or a *dead* fluid. It is no wonder, therefore, that Davy, in spite of his investigations, had to confess that the subject of the blood in all its bearings was for him one of great obscurity and that all speculation concerning it required to be received with much caution and examined with all possible rigor (sic)\(^2\).\(^2\).
The Preservative Action of Vinegar and Spirit of Wine (1818-39)

Davy's attention was initially directed to devise methods for preserving anatomical preparations in 1825 when the Director General of the British Army Medical Department called on Medical Officers in overseas stations to contribute specimens to the Pathological Museum at Fort Pitt which was then in its formative phases.

In response to this request, Davy, who was then serving in the Ionian Islands (1825-27), made trials with a solution of sulphurous acid gas in water which he found to be effective for at least three years. It was besides, cheap and allowed a clear view of the minute structures of the prepared specimens.

When he came to Malta in January 1828 he carried out experiments over a period of six months with vinegar as a preservative for specimens. He used a solution of distilled vinegar diluted with water, the solution being almost colourless and with a specific gravity of 1.06. The specimens were suspended in this solution which was poured in jars covered with bladder at their mouths to exclude air. All the specimens thus treated were found to be in perfect preservation when they were inspected three years later.

Davy ascribed the preservative properties of vinegar to its antiseptic quality and for this reason he suggested the use of distilled vinegar in surgery for clearing foul ulcers and washing out deeply seated abscesses. He also recommended it for the preservation of table food thus preventing wastage of food.

In the hottest weather, states Davy, during the summer in the Mediterranean, when cold meat became tainted and unfit for use in twenty-four hours, or even in a shorter time during the prevalence of the damp scirocco wind, I have had slices of roast and boiled meat, of fish, poultry, etc put into vinegar... and they were preserved perfectly good and fit for the table for weeks. It is well known how long vegetables may be thus kept. He was not so convinced, however, about the efficacy of the pungent fumes of vinegar as a means of fumigating rooms and hospital wards for which purpose the fumes of vinegar were still commonly employed in his time.

By 1839 his experience in the field of preservation had been enriched by further trials during a stay of eleven years in the Ionian Islands and in Malta when he experimented with spirit of wine (Alcohol) as a preservative. He found that a mixture of seventy parts of proof spirit and thirty parts of rain or distilled water answered the purpose quite well. He stressed the need of using rain or distilled water because water containing carbonate and sulphate of lime produced a precipitate that prevented a distinct view of the specimen in the jar. Following these experiments he seems to have dropped the idea of using vinegar as a preservative for he declared that spirit of wine had proved to be better adapted for the preservation of moist preparations than any other liquid yet tried. One wonders whether Davy was aware that spiritus vini (alcohol) was first tried experimentally as a preservative of animal tissues as early as 1662 - although it was not until 1740 that it came into use as a museum preservative in England.

Animal Electricity (1831)

In 1831 Davy was engaged in experiments on the extraordinary property which the Torpedo (fish) possesses of imparting shocks similar, as far as sensation is concerned, to those of the Leyden vial.

Since the seventeenth century the Torpedo had become of special interest to anatomists because of its electrical functions. Stefano Lorenzini had written a monograph on the Torpedo in 1678 while an account of its electrical organ was published by R.A. Ferchault de Reaumur (1686-1757) in later years.

Davy, who was familiar with the literature on the subject, embarked on his enquiry at the request of his late brother Humphrey Davy who had shown great interest on this topic about which he had published a paper in 1829. Humphrey had used an apparatus, apparently of his own devising, which he suggested John should use in further researches but which John later found that it did not answer so well.

John commenced the anatomical studies of the Torpedo in Rome while his brother Humphrey was still alive, the kinds of fish which he dissected being the tremula and occhiatella; but his electrical experiments on the living fish were entirely made in Malta, the first one being carried out on the 3rd of September 1831 at eleven o'clock at night. It was not made earlier because on his return to Malta from Rome in June 1829, John was informed that the Torpedo was not known in the sea around Malta; but in the summer of 1831 he found out that he had been misinformed and that with a little trouble the fish could be procured alive at all seasons of the year.

As a result of his investigations he determined that the discharge from the electrical organ of the Torpedo could magnetise a needle and that a needle poised on a pivot in a multiplier made half a revolution. With regard to those investigations meant to ascertain whether the electricity of the Torpedo could produce light or had the power of igniting or passing through air, his experiments were attended by less satisfactory results. However he succeeded in confirming Michael Faraday's idea that heat was evolved during the passage of electricity as indicated by a very sensitive spirit thermometer.

In a number of electro-chemical experiments he found that the electricity of the Torpedo affected such chemical substances as common salt, silver nitrate and sulphuric acid with the evolution of gas and the precipitation of the metal. From these observations he deduced that the undersurface of the Torpedo corresponded to the copper or negative extremity of a
voltaic battery and the upper surface to the zinc or positive end. He called the sensation imparted by the shock of the Torpedo to the human body the physiological effect.

John Hunter had dissected the electrical organ of the Torpedo but Davy considered that this organ deserved a more minute investigation than Hunter had devoted to it and he proceeded to record his own observations in the course of dissection conducted with considerable care. In fact he traced the course of the cerebral, cervical and spinal nerves to their terminations in the various organs of the fish. He established the fact that when the brain of the Torpedo was removed entirely, the fish lost its power to give shocks. With regard to the electric organ, an examination with a simple lens magnifying more than two hundred times, suggested that it was formed of nervous tissue - an observation which Davy confirmed by microscopical examination. Concerning the mode of production of the electrical discharge, he admitted that it was unavoidably enveloped in great mystery.

Apart from the electrical phenomena of the Torpedo, Davy tried to investigate the breeding habits of this fish. While in Malta he examined more than two hundred Torpedos with this aim in view but only in five of them he found foetal Torpedos at full term. He therefore, inferred that the gravid fish was rarely met with in Maltese waters; in fact it was only after the lapse of twelve months that he could procure a fish with its young though he had offered to pay the fishermen two hundred times the market price of the fish. Even the non-pregnant ones were difficult to procure as they came into shallow water quite irregularly and sometimes he had to wait for as long as two to three weeks to obtain a specimen. The species which he met with in Maltese waters were the T. ocellata (oculata D) or Cramp Ray and the T. marmorata (diversicolor D) or Marbled Torpedo. They were known in Maltese as Haddiela (sic) (Haddiela) from the verb signifying to paralyse or benumb. To preserve the fish alive he recommended that it should be kept in an earthenware vessel, that the purest sea water should be used and changed daily; and that the vessel should be maintained in the coolest place available where the sun never shines.

Davy published the results of his experiments in the Philosophical Transactions (Part II for 1834) under the title Observations on the Torpedo with an Account of Some Additional Experiments on its Electricity, dated from Malta, March 4, 1834.

The conclusions he drew from his experiments were-

(a) the electricity of the Torpedo acted electro-chemically in separating the elements of compound bodies.
(b) it affected the needle in the multiplier and imparted magnetism to iron; and
(c) it generated heat.

It must be borne in mind that it was only during the first half of the nineteenth century that scientists began to gain a clear understanding of electrical phenomena and that up to Davy's time the investigation of electricity was still limited mostly to static electricity produced by a manually operated generating machine and that, though the Leyden jar had been in use since 1746, the Voltaic pile and battery were developed in 1800.

**Aqua Binelli for the Arrest of Bleeding (1831)**

The year 1831 found Davy occupied with less academic pursuits than the electrical phenomena of the Torpedo - none other in fact than the arrest of bleeding from the large arteries. The occasion arose in 1831 when he embarked on a number of experiments to test the styptic properties claimed for a proprietary medicine - *Aqua Balsamica Arteria* - produced by an Italian Doctor Fedele Binelli from Piedmont. A case of several bottles of this preparation, imported from Naples, was sent to Davy by the British Governor of Malta, for the purpose of having its qualities fairly investigated at the Military Hospital, Valletta.

Davy tried it on superficial cuts in the skin but found that it did not stop the bleeding at all. He decided that the preparation was an imposition on the public and deserved no further investigation. Two years later his attention was recalled to the subject by a medical practitioner in Malta who had studied in Naples. This practitioner invited Davy to witness the effect of a preparation, which was reputed to be identical with *Aqua Binelli* in composition and effect, on the severed carotid artery of a goat. The experiment was unsuccessful. Davy, however, tried to check the alleged styptic properties of the preparation himself by experiments on dogs. In every instance, however, he found that moderate compression of the cut artery with several folds of linen dipped in water succeeded in arresting bleeding and resulted in the healing of the artery after some weeks; these effects being due not to the water but to the moderate pressure exercised on the severed blood vessel. Would the same means of moderate compression operate as effectively in the case of wounds of the large arteries in human subjects? Davy did not know as he had not ascertained this possibility experimentally but he thought that the result would be the same. It was a point worth determining, in his view, especially for military surgery particularly on the field of battle where the number of wounded men required attention always exceeded the means of surgical intervention for the suppression of bleeding by ligating the cut blood vessel.

**Chemical Studies (1833-34)**

During these years Davy was busily occupied with chemical, physiological and pathological studies. His earliest paper, dated May 8, 1833, dealt with *Some Experiments and Observations on the Combination of Carbonic Acid and Ammonia*. His experiments confirmed the correctness of the results obtained by Louis Joseph Gay-Lussac (1778-1850) and other
contemporary workers and showed where his brother Humphrey had been deceived in some of his experiments on the salts of ammonia30.

In some observations on phosphorus he examined the varying gradations in the intensity of luminosity of phosphorus when placed in oxygen gas at different temperatures31.

His third paper is made up of two unrelated studies both of which are dated March, 1834. Part I entitled some observations on a note of M.A. Van Beek purporting to point out an error in the Bakerian Lecture of the late Sir Humphry Davy on the relations of electrical and chemical changes is a defence of his brother's theory concerning the protective action of zinc on copper when this latter metal is exposed to sea water. The question was of great practical interest for marine engineers because the rapid decay of the copper sheathing on the bottoms of British ships constituted a serious problem before zinc was found to be a satisfactory preservative to the copper sheathing.

Part II deals with some observations on eucloreline relative to the question of its decomposition. Following a series of experiments Davy concluded that eucloreline was a mixture of chlorine and deutoxide of chlorine (a combination of oxygen and chlorine) and not a pure or true chemical compound32. Off prints of the three papers were presented to the University Library by Davy, each title page being inscribed in ink for the University Library from the author. The texts contain a few corrections of misprints in the author's hand33.

Experiments on animal heat (1833-34)

The problem of the source and maintenance of animal heat had been the subject of a prolonged controversy in the early decades of the nineteenth century34. It first engaged Davy's attention in 1814. He returned to investigations on this subject in 183335.

While dissecting a tunny fish (Thynnus vulgaris, Cuv. & Valen) he was struck by the fact that its temperature in the deep seated muscles was higher than that of the surface of the sea, from which it had just been taken, by no less than 18 degrees and a half (99° and 80.50° F.). A careful inquiry among Maltese fishermen with a wide experience in the tunny fishery convinced him that the tunny was a warm-blooded creature. He tried to extend his investigations to other fish of the same family but he was unable to repeat his temperature experiments as he could not procure any of these fish alive. He was, however, able to carry out a dissection of the nervous system of various species of tunny caught in Maltese waters, but he could not suggest what accounted for the great difference in temperature between the tunny and its surrounding medium so that nineteen years after his initial attempts to understand the phenomenon of animal heat he humbly confessed that until physiologists learned more about all the sources of animal heat and the circumstances for its preservation no explanation was possible26. In fact this understanding of the factors involved in the temperature regulation of the body came much later.

Observations on the vascular system of the human body.

John Davy had shown interest in the pathology of the cardiovascular system as early as 1823 when he carried out experiments on the power of resistance of the heart muscle and the large vessels when he came across a fatal case of rupture of the heart and aorta in a man due to a fall of 50 to 60 feet deep in a chalk pit in Chatham. He again directed his attention to the cariovascular system when he read about Sir Astley Cooper's experiments on the dog and the rabbit by which Cooper demonstrated that the carotid and vertebral arteries can be occluded by tying with survival of the animal. This was due to the continuation of the blood circulation to the brain by the process of anastomosis. Davy had met with many instances, at autopsy, of atheromatous occlusion of the larger arteries in men where it had never been suspected during their lives. These fatalities had occurred in soldiers of active habits who died of acute diseases of short duration but which were unconnected with the morbid condition of the artery as found at post mortem; in fact the circulation had not been impeded in these cases owing to the expansion of the arteries involved or of adjoining ones. This, however, was not always what happened and in 1834 he came across an instance where the train of events was of a quite different and contrasting kind. A soldier of 36 years first experienced some difficulty in breathing at the beginning of 1833 but he remained on duty until he was admitted to the Military Hospital at Valletta on the 18th February 1834 when he came under the observation of John Davy. The main signs were paroxysms of tumultuous action of the heart, breathlessness, temporary loss of vision and occasional syncope. The pulse could not be felt in either wrist and brachial arteries but was strong in the femoral. He gradually became worse with continuous and severe dyspnoea, a livid hue of the face and great agony of suffering. He died suddenly on the 2nd June. At autopsy, Davy found hypertrophy of the heart and an enlarged arch of the aorta with thin plates of bone under the inner coat and complete obstruction of the left carotid and subclavian arteries by dense white matter.

His interest in the arteries of the human head did not flag in subsequent years. He was well aware of the existence of the anatomical peculiarities in the structure of the basilar artery in man but in June 1837, while at Fort Pitt, he came across a peculiarity that to the best of his knowledge had not yet been noticed by any anatomist. It consisted of a congenital band of fibres in the interior of the vessel, attached to its sides and intersecting it near the junction of the vertebral arteries37. During a period of seventeen months he met it in ninety-eight autopsies held at the General Hospital of Fort Pitt. In two instances he also
observed another hitherto unnoticed anatomical anomaly i.e. the presence of a narrow opening between the two vertebral arteries in the septum formed by their juxtaposition posterior to the basilar artery\(^38\).

His concern with these anatomical variations stemmed from the fact that in his time structural rarities had continued, as in previous epochs, to hold the interest of the dissector over what was common in anatomical investigations.

**Davy’s Laboratory**

Among the problems that beset the experimental investigator in Davy’s time was the dearth of laboratory equipment because the range of instruments and technical aids then available was very limited apart from being of a rudimentary kind and not very efficient. Davy, therefore, had to work with the simplest of tools. One must bear in mind, for instance, that tissues were still examined unstained under the microscope while the microtome and the embedding of tissues had not yet become diffused. Indeed a microtome capable of sectioning soft animal tissues was developed in 1856 and a method of staining bacteria in tissues was first described in 1875 - seven years after Davy’s death.

Davy had the advantage of being familiar with the laboratory equipment of his time for he was a member of the Apparatus Committee, set up in 1796, of the Royal Medical Society of Edinburgh. Several rooms of the premises of this society were reserved for the performance of physiological and chemical experiments by its members; and dogs, calves and rabbits were made available for the investigation of the effects of temperature on the body, for transfusion experiments and for the study of the respiratory system\(^39\).

Davy must have assembled many of laboratory tools himself as none of the apparatus which he mentions in his publications is known to have been held by the Holy Infirmary or by the Military Hospital before his time.

His instruments comprised a galvanometer, Coulomb’s electroscope, Harris’s electrometer, a Leyden jar, a Voltaic cell and an electrical machine - probably a generating machine i.e. a contrivance worked by hand for the production of static electricity, the charge thus produced being then stored in a Leyden jar. He also had his brother’s apparatus in a little box for studying the electrical phenomena of the Torpedo but which did not answer so well in John’s experiments. Of great help was a powerful lens and a microscope constructed by the excellent maker Mr. Ross with an object lens of one-eight inch focal distance. Mr. Andrew Ross (d. 1859) was one of the foremost microscope makers at the time of Davy’s researches in Malta. Ross was engaged in the construction of achromatic lenses and succeeded in obtaining a good quality image and a fine focusing mechanism in his instruments, so that it is likely that Davy’s microscope incorporated these advanced refinements\(^40\). Other items in Davy’s laboratory were glass retorts and tubing, spirit lamp, air pump with receiver, steam baths, mercurial baths (for raising the temperature to 170°F), bottles with glass stoppers, wires of gold, silver, platinum and copper, pieces of steel obtained from pianoforte wires, litmus paper, fine absorbent paper for wrapping salts and fine cambric (white linen) for drying glass tubes.

His range of chemicals was modest and included alcohol, ammonia, Black Manganese Oxide (for producing chlorine), camphor, Carrara Marble (pieces) for the production of carbonic acid by the action of dilute muriatic acid, chlorate of potash, distilled vinegar, iron filings from the blacksmith’s shop (for the production of hydrogen by the action of sulphuric acid), hydrocyanic acid, mercury, muriatic acid (hydrochloric acid or spirit of salt), nitrous oxide gas, oil of turpentine (solvent of phosphorous), silver nitrate, sulphuric acid, sulphuric ether and water solutions of chlorine, iodine and bromine\(^41\).

**Clinical Instruments**

In Davy’s days the clinical instruments available for the physician were very few. In 1823 the stethoscope had not yet been introduced in the General Hospital at Fort Pitt, Chatham. Davy saw this excellent instrument in the autumn of the same year in Edinburgh and began to use it. He was enthusiastic about it. Whoever employs the stethoscope, he wrote, though he may not appreciate its merits in the same high degree as the ingenious inventor of the instrument did, yet he cannot fail to derive instruction from its use, and to become better, more minutely, more discriminatively acquainted with the diseases of the chest.

Davy was no less appreciative of the value of Leopold Auenbruger’s method of diagnosis by percussion of the chest. Indeed he was in favour of every method of clinical investigation which directs and fixes the attention - drawing it away from vague and unmeaning generalities, the bane of knowledge, to precise and significant particulars -which are its essence -and which are equally important whether we have in view, during life, the symptoms of disease by the bedside of the patient, or, after death, on the dissecting table, the organic changes, the effect of diseased action.

Davy had been using an oral thermometer since 1816\(^42\).

**Davy leaves Malta**

Davy left Malta in 1835 but was here again for short periods after the 15th April 1838, in 1839 and, in transit, in November 1840. In the intervening years he was at Corfu and Chatham, occupying himself with the microscopical study of human pus cells, anatomical research work on the male generative organs of the Torpedo, common ray, and other fish. It
may be of interest to learn that Davy had already (1838) examined microscopically the human spermatic fluid after death while at Chatham from twenty cadavers. The spermatic animalcules were first discovered in man by John Ham in 1677 and confirmed by A. Leuwenhoeck in the same year; yet Sir Everard Home maintained that spermatic animalcules had no real existence. Davy not only opposed Home's view but confirmed their presence in the spermatic fluid and also realised their medico-legal importance in certain doubtful criminal cases where the microscopical examination of the fluid may reveal their presence and thus lead to decisive evidence. He found that though the spermatic fluid soon become putrid when exposed to air, the animalcules resisted change in a remarkable manner. In fact he claimed to have detected them microscopically in putrid fluid which had been kept for ten weeks and, in another specimen, which had been kept for a year and a half.

In January 1838 he carried out observations on the body temperature of mental patients under care in the Lunatic Asylum at Fort Clarence, Chatham, to check the notion - then current - that the temperature of mental patients was below the average of normal people. He found that this belief was erroneous. His studies confirmed the well established fact that the insane bear degrees of heat and cold - which would be disagreeable to sane persons - without complaining. He also noted that certain organic disease in mental patients, such as pulmonary tuberculosis, may be unaccompanied by the usual symptoms of cough and breathlessness but will show a raised temperature and a rapid pulse - two points of importance for the early detection of phthisis.

Discussion

John Davy commands our attention and respect because he endeavoured to discover truth and lay it before his colleagues in an objective and meaningful manner in over one hundred and fifty memoirs and papers; and because, thanks to his experimental work, he consolidated various innovative findings in the field of biological research of his time. In fact his merits lie mainly in his questioning the findings and deductions of previous investigators, in testing the accuracy of the results obtained by his contemporaries and checking the soundness of their speculations and clearing up uncertain ties in the areas of physiology and morbid anatomy; and finally, in the fact that the researches he undertook were not a mere quest for knowledge but were directed to practical ends.

Davy was a blend of physician, chemist and pathologist at a time when none of these practitioners had as yet emerged as distinct from one another and attained the status of specialists in their own rights. As such he was a representative of a new generation of doctor-scientists that appeared on the medical horizon at a time when pathology was still groping its way to gain an insight into the causes of disease and to explain clinical findings in terms of the underlying tissue changes revealed by post-mortem examination; for although Gio. Batta Morgagni (1682-1771) and other workers had laid their knowledge and experience of pathological anatomy for the medical world of the eighteenth century, the study of gross and minute pathology had much farther still to go.

In fact pathology came into its own in the final years of Davy's professional life. It happened after Robert Virchow (1821-1902) applied the cellular concept (1839) of Theodor Schwann (1810-82) to his cellular pathology (1858); and after the rise of the new science of bacteriology, the staining of bacteria in tissues by carmine in 1871 and methyl violet in 1875 and the artificial reproduction of lesions in experimental animals had become established procedures.

To appreciate Davy's efforts we must bear in mind that the state of medical knowledge was so poor in the mid-nineteenth century that medicine was being criticised for being rudimentary and involving much guesswork; and the President of the college of Physicians of England was regarded as being so nearly on a level with the meanest herbalist.

With regard to physiology, it must be borne in mind that Davy was engaged in such research, years before the founder of modern physiology - Claude Bernard (1813-78) - came on the scene. In fact the year when Davy qualified as a doctor and started his experimental work (1814) was almost the same year in which Claude Bernard was born so that by the time that the French scientist had become renowned and was doing the best part of his work between 1840 and 1870, Davy was coming to the close of his medical career.

Davy prepared himself with a wide and varied reading of the literature then available. This comprised, apart from such contemporaries as Astley Cooper, Charles Bell, Lorenzo Spallanzani and R.F.H. Laennec, the naturalist and medical pioneers of the seventeenth and eighteenth centuries as Gio Batta Morgagni, John Hunter, William Harvey and A. Van Leuwenhoeck. His journals included the Edinburgh Philosophical Journal and the Annales des Sciences Naturelles.

The medico-legal experts of his time were in his debt for elucidating some of the problems in forensic medicine such as the action of insect larvae in determining the rate of putrefaction of bodies exposed to the air or immersed in water; the detection of spermatic animalcules in cases of alleged sexual assaults; and observing the temperature in the cadaver to determine the time elapsed between death and the necropsy.

His idea of antisepsis, to which he alludes when discussing the preservative action of corrosive sublite and of lime on pathological specimens, is also worth noting in view of the fact that it shows that he had already grasped the significance of that concept before the age of bacteriology. This is not to say that he was among the first scientists to employ...
the word **antisepsis** because it had already come into use by 1712 (if not earlier) but his reference to the notion of antisepsis amply shows that he was receptive to the new concepts that heralded the germ theory of disease of Antonio Bassi (1773-1856), Louis Pasteur (1822-95) and its practical application by Joseph Lister (1827-1912) in 1865-68.

To what extent did Davy's work influence the study of chemistry, physiology and pathology in Malta? He certainly knew Dr. G. Aquilina, Professor of Chemistry at our university (1834-59), who had set up a **regular chemical laboratory** in that institution and whom Davy had judged to be a competent candidate for the professorship in 1834; Davy even honoured him, when he was in Malta in 1840, with his presence at one of Aquilina's lectures on chemistry with which he expressed himself very satisfied.

Physiology and pathology were taught by Dr. Stefano Grillet (1815-31) and, after a gap of two years, by Stefano Zerafa (1833-56). It is very likely that these two teachers were acquainted with Davy and his work. However that may be, there is no doubt of the influence exercised by British physiology on medical teaching in Malta in the late sixties. Indeed Dr. W.B. Carpenter's **Principles of General and Comparative Physiology**, then acclaimed as the first English book which contained adequate conceptions of a science of biology, was the textbook of physiology in the course of Medicine at the University of Malta.

Davy was well known for his active interest in the medical school of the island which was always his **favourite object** and to which he donated some books on chemistry and surgery (Appendix III). He had been appointed member of the University Council on the 1st November 1828 and in 1834 was invited to participate in a discussion on the planning of the medical curriculum and to examine the students in medicine. Even after leaving Malta in 1835 his interest in the medical school did not wane; so much so that when he passed through Malta for a few days in November 1840 on his way to Turkey, he made it a point to visit the university. On that occasion he mixed freely with the students and declared himself so very satisfied with the **improvements that had been introduced** that it was thought likely that he would suggest the training of medical students from Turkey at the Malta medical school. I have, however, found no indications so far that any young men came to Malta from Turkey to study medicine. We have not been told what the **improvements were**; they certainly did not include a collection of pathological specimens at the Civil Hospital of Valletta - the teaching hospital of the medical school - because the **Societa` Medica d'Incoraggiamento di Malta** was requesting the setting up of a Pathological Museum (gabinetto patologico) and an **ad hoc** Dissection Room in the hospital in July 1848. The absence of these features, however, does not mean that no pathological dissections were being performed at the Civil Hospital for teaching purposes for Davy himself has recorded that his **talented friend** Dr. Charles Galland, professor of Anatomy at the university (1839-58), had examined no less than six hundred and fifteen bodies of civilian patients dying from various diseases during the period December 1840 - December 1841. Unfortunately none of Galland's work was published and it is not known whether their manuscript records have survived and still await discovery.

**Davy's Relevance To-day.**

Apart from enriching the historical tie of the magnificent edifice of the Holy Infirmary, now the Mediterranean Conference Centre, with its medical past, Davy provides us with scientific principles that remain of fundamental value in the pursuit of the study of pathology in spite of the passage of almost one hundred and fifty years. In view of their soundness and their emphasis on thoroughness of examination and on attention to tidyness, they bear recalling for the benefit of our present generation of medical men.

(a) The main objects of pathological dissection are:-

(i) the detection of the effects of disease on the human body and of the cause of death;

(ii) the removal of diseased parts from the cadaver for preservation in a museum;

(iii) the acquisition of general anatomical knowledge.

(b) Every dissection should be carried out methodically with neatness and cleanliness. Thus conducted it promotes the dexterity of the hand for surgical operations on the living and trains the eye to distinguish between what is sound in structure and what is diseased.

(c) Parts of the body meant for preservation should be dissected out so as to be seen to the best advantage when mounted and in order to appear by themselves as intelligible as possible and to require very little explanation.

(d) Specimens should be freed from extraneous tissues at once; washed in running water and immersed immediately in strong spirit and mounted as they are intended to remain for display. The spirit should be changed after a month for fresh spirit and the mouth of the jar or vessel should be firmly secured.

(e) We must cultivate a cautious attitude of mind regarding the speculations and opinions of research workers who preceeded us in the field lest we are misled by the uncritical acceptance of their views and conclusions.

As has already been mentioned, Davy's experiments were performed at the erthswhile Holy Infirmary of the Knights of St John at Valletta, which had already become memorable in the time of that hospital Order as a house of healing (1575-1798) and as the cradle of the Medical School of Malta (1676). In 1800 the Holy Infirmary was turned into the general hospital of the British Military garrison stationed in Malta (1800-1920).

Very likely Davy's laboratory, where he also
performed some of his dissections, was none other than the pharmacy laboratory of the Knights which still existed in his own time. It occupied one side of the so-called Upper Quadrangle of the hospital abutting on Merchants Street. The building suffered extensive destruction by air bombing by the Axis powers during the Second World War and all traces of John Davy’s laboratory were erased. The site is now occupied by a block of flats.

By recording his investigations and experiments from this hospital in his two volumes of Researches Physiological and Anatomical, John Davy adds a novel role to the historical record of the ancient Holy Infirmary as a pioneering source of physiological, pathological and chemical research in the early decades of the nineteenth century.

Appendix I
Medical and other literature quoted by Dr. John Davy

W. Harvey. Exercitatio Anatomica de Cordis et Sanguinis Motu, Rotterdam, 1648.
S. Lorenzini. Osservazioni intorno alle Torpedini, Firenze, 1678.
A. Monro. The Structure and Physiology of Fishes, Edinburgh, 1785.
G. Rondoulet. Libri de Piscibus, Lugduni, 1554.

Appendix II
RESEARCHES
PHYSIOLOGICAL AND ANATOMICAL

By
JOHN DAVY MD FRS
Assistant Inspector of Army Hospitals
In Two Volumes
London.

SMITH, ELDER AND CO. 65, Cornhill, MDCXXXIX

The work is dedicated
TO
THE DIRECTOR GENERAL
OF
THE ARMY MEDICAL DEPARTMENT
AND TO THE
MEDICAL OFFICERS OF THE ARMY

THESE VOLUMES ARE RESPECTFULLY INSCRIBED.

Illustrations.
Volume I. There are thirteen plates drawn on stone by Mr. Ford from specimens preserved in spirit or from drawings of specimens in the fresh state. Twelve of these plates illustrate parts of the anatomy of the Torpedo fish. The thirteenth plate shows the anatomical variations of the basilar and vertebral arteries described in the text; the carotid artery of the dog in three stages of healing after being partially divided; and the microscopical appearance of the fluid of the human seminal vesicles.

Volume II. It contains three plates showing peculiarities of structure of the common biliary duct; the male genital organs of the Torpedo and of the thornback; and the microscopical appearance of pus globules.

Appendix III
Papers and books donated by Dr. John Davy to the University Library.

6. Lavoisier, Anton. Elements of Chemistry in a New Systematic Order. Translated by Robert Kerr, 3rd Edition, Edinburgh, 1796. Anton Lavoisier (1743-94) was a French chemist who stressed the importance of accurate observation and of testing theory by experiments in search for scientific truth. The Elements of Chemistry contains a number of plates showing equipment and instruments used in chemical investigations.

This is a pocket book intended as an aid to refresh the memory of the
student regarding the main topics in anatomy, physiology and chemistry of body fluids; in fact it consists of a series of questions and answers - a sort of catechism - on osteology, musculature, special senses, nervous system, internal organs etc; on the chemical composition of mucus, milk, urine, inspired and expired air, etc.

The author wrote in Latin because books on medicine were still being written in that language in his time and because he wished to encourage students to cultivate Latin because of its "elegance" of expression.

8. Velpeau, Alfred Armand Louis Marie. Nuovi Elementi di Medicina Operatoria, Milano, 1833. This Italian translation of Velpeau’s work on operative surgery, besides 941 pages of text, contains twenty copper engravings showing various surgical instruments and operative procedures. Velpeau (1795-1867) was a surgeon of great experience and women in childbirth.

All these books and papers are inscribed in Davy’s handwriting For the use of the Medical School, Malta, from J. Davy or Presented to the University Library by Dr. Davy; or For the University Library from the author in the case of his four papers, the first three of which contain corrections of a few misprints in the text in the author’s hand. They all bear a rubber stamp with the words Public Library Malta or Malta Government Library or Royal Malta Library.

References

37. Edinburgh New Philosophical Journal, April, 1834.
44. Fort Pitt was built between 1805 and 1819. It was adapted as a hospital in 1824. It was closed down in 1860 but was again used as a hospital during the 1914-18 war. Col. (Retd) A Tennuuci, RAMC Historical Museum, Aldershot. Personal communication 1983.
45. J. Davy. Researches etc., Vol. I, Plate XIII, fig. 2.
57. Appendix I.
60. L’arte, 7 February 1863, pp. 4 & 5.
62. Il Barth, 23 December 1871, p. 72.
63. Il filologo, 17 November 1840, p. 170.
70. Appendix II.
Asthmatic Child and Sport

Motto. If from running, gymnastic exercise, or any other work, the breathing becomes difficult it is called asthma. The symptoms of its approach are heaviness of chest, difficulties of breathing in running or on a steep road.

Aretaeus the Capadochian, 2nd Cent. A.D.

Paradoxically, 1800 years had to elapse before the condition, so graphically described by Aretaeus, achieved international prominence a gold medal winner in 1972 Summer Olympic Games was disqualified for having taken an ephedrine containing bronchodilator prior to swimming.

Most people with asthma, experience an attack when they exercise, which is symptomatically and physiologically quite similar to asthmatic attacks induced by other stimuli. At the peak of an attack the person is coughing, dyspnoeic and wheezy and a variety of pulmonary functions, if tested, are abnormal. Although exercise-induced asthma (EIA) is almost a universal finding in asthmatic subjects if sought intensively, it is largely seen in children, probably because they exercise more than adults and because of the prevalence of allergic asthma in them. The condition is so frequent in children that it alone can be used as a simple diagnostic test (EIA occurs also in approximately 40 per cent of those who have only allergic rhinitis or hay fever). It is most likely EIA to be a clinical problem in school children as it interferes with their physical education activity and games. What can be done to prevent it? The most obvious solution would be to avoid exercise and that was what the asthmatic children were advised to do up to some 8-10 years ago. Since then the attitude has changed towards the physical activity in asthmatics, thanks to a substantial body of knowledge concerning EIA acquired during the previous 15-20 years; and the increasing participation of asthmatics in competitive sports, many with distinction, clearly indicate that most asthmatics should not be considered physically handicapped. So, nobody familiar with children and young adults will advise them to abstain from physical exercise at a time when psychosocial growth depends on interaction with peers and interaction centers around physical activity. Yet, even today, because of the restrictive symptoms of EIA and anachronistically overprotective attitude of some parents and teachers, the asthmatic child may choose inactivity while the doctors are asked to cover it by writing excusing notes. In the light of the increasing demand placed upon paediatricians and family physicians for authoritative opinion concerning their asthmatic patients’ ability to be engaged in individual or team sport activity, it is timely to try to answer the question: Where do we actually stand with regard to the physical activity in young asthmatics? The series of excellent contributions presented recently at a symposium on specific problems facing athletes with asthma, provides us with the most up to date answer to the question1. Though the issue reached us in the wake of the 1984 Olympic Games, the symposium was held on the eve of the Los Angeles events. Eight years ago, while in Paris studying the ventilatory effects of physical exercise in asthmatic children2, I profited a great deal from the proceedings of a similar symposium which was a prelude to the 1976 Olympic Games3. By comparing these two reviews, which reflect the state of the art of today and that of eight years ago, one realizes how far our knowledge of the EIA has advanced in a relatively short period of time. Though many of the facts established by 1976 have remained unchallenged, in the past 8 years we have begun to understand better some of the enigmas surrounding EIA. New advances in the understanding of the underlying pathophysiological mechanisms involved in EIA have paved the way for its pharmacological control, which enables asthmatic children to live as normal a life as possible, asthmatic athletes to compete effectively in their respective sports, even to win gold medals in Olympic Games.

Exercise is an integral part of the life of asthmatic children and youths. Physical education, individual athletics and team sports activity interact with asthma in many ways and are thus a legitimate area of interest for present and future physicians. I feel that it is therefore, worth here to reiterate some of the basic points of the phenomenon of EIA.

EIA is characterized by a post-exercise bronchospasm with maximal fall in lung function some 5-10 minutes after stopping the exercise. At the beginning of exercise there is usually some mild bronchodilation that is replaced by the onset of bronchospasm after 4 to 8 minutes. Different types of exercise of identical severity result in different amount of EIA. Free range running causes the most severe asthma, cycling somewhat less and swimming least. The variable effects of different activities are an important factor to stress the young asthmatic patients who want to compete in athletics. Swimming is their sport of choice and no wonder that of 5 asthmatic gold medalists in the 1972 Munich Olympic Games, 3 were what the asthmatic children were advised to do up to some 8-10 years ago. Since then the attitude has changed towards the physical activity in asthmatics, thanks to a substantial body of knowledge concerning EIA acquired during the previous 15-20 years; and the increasing participation of asthmatics in competitive sports, many with distinction, clearly indicate that most asthmatics should not be considered physically handicapped. So, nobody familiar with children and young adults will advise them to abstain from physical exercise at a time when psychosocial growth depends on interaction with peers and interaction centers around physical activity. Yet, even today, because of the restrictive symptoms of EIA and anachronistically overprotective attitude of some parents and teachers, the asthmatic child may choose inactivity while the doctors are asked to cover it by writing excusing notes. In the light of the increasing demand placed upon paediatricians and family physicians for authoritative opinion concerning their asthmatic patients' ability to be engaged in individual or team sport activity, it is timely to try to answer the question: Where do we actually stand with regard to the physical activity in young asthmatics? The series of excellent contributions presented recently at a symposium on specific problems facing athletes with asthma, provides us with the most up to date answer to the question1. Though the issue reached us in the wake of the 1984 Olympic Games, the symposium was held on the eve of the Los Angeles events. Eight years ago, while in Paris studying the ventilatory effects of physical exercise in asthmatic children2, I profited a great deal from the proceedings of a similar symposium which was a prelude to the 1976 Olympic Games3. By comparing these two reviews, which reflect the state of the art of today and that of eight years ago, one realizes how far our knowledge of the EIA has advanced in a relatively short period of time. Though many of the facts established by 1976 have remained unchallenged, in the past 8 years we have begun to understand better some of the enigmas surrounding EIA. New advances in the understanding of the underlying pathophysiological mechanisms involved in EIA have paved the way for its pharmacological control, which enables asthmatic children to live as normal a life as possible, asthmatic athletes to compete effectively in their respective sports, even to win gold medals in Olympic Games.

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Games, all of them were swimmers. While the severity of the attack augments in linear fashion with the magnitude of the refractiveness diminishing during the next 3 to 4 hours. This suggests that either the ability of bronchial smooth muscle to respond to stimuli is diminished or that mediators were released through mechanisms that require a definite time to reactivate. Thus running through phenomenon, although poorly understood, allows asthmatic youths to participate successfully in games, such as basketball, hockey or soccer, which involve interrupted exercise which is less likely to cause EIA than are continuous endurance events. As a matter of fact, a series of short sprints is a useful technique for inducing a refractory period of EIA. Furthermore, the warm-up techniques used by all athletes tend to induce a measure of refractoriness.

8 years ago it was widely accepted that EIA was caused by the release of mediators from mast cells through some unknown exercise-related mechanism (hyperventilation was invoked among many other possible triggering mechanisms). At that time it was not clear why swimming, even if of severe intensity, failed to induce bronchospasm. Later on a Boston group of investigators noted that breathing humid air attenuated EIA and this could explain the low asthmogenicity of swimming. They advanced a theory which postulates that cooling of the airways is the primary stimulus for the onset of EIA. Physical exertion produces an increase of minute ventilation to provide sufficient oxygen for the metabolic needs of working muscles. This results in large volumes of incompletely conditioned air being inspired, drying and cooling the upper airways as heat and water are transferred from their surface. The total quantity of heat exchanged varies directly with minute ventilation and inversely with the temperature and water content of the inspired air. Variations in temperature and humidity of inspired air accounts for differences in asthmogenicity of such tasks as running, cycling, and conditions and choose swimming rather than skiing (or ice skating, or ice hockey) as his preferred sport. In this context it might be of interest to know that some 8-10 per cent of the Australian Olympic Team were asthmatic in 1976 and 1980 and of those slightly more than a half were swimmers.

Increased bronchial reactivity is the fundamental abnormality in asthma. The underlying cause of this abnormality is uncertain but the most widely accepted hypothesis attributes it to imbalance of autonomous control with predominance of excitatory (cholinergic and alpha-adrenergic) or deficiency of inhibitory (beta-adrenergic) control. Very recently this concept has been modified by involving the recently discovered third autonomous, non-adrenergic non-cholinergic (NANC) nervous system. It postulates that non-adrenergic inhibitory nerves may exert a braking effect on bronchoconstriction and a functional defect, presumably present in asthmatics, would lead to exaggerated responses to constrictor stimuli. Their neurotransmitter, vasoactive intestinal peptide (VIP) has been shown to relax smooth muscle in vitro and is bronchodilator in both animals and man. The results of very recent studies provide further evidence that VIP given intravenously or inhaled may have a place in the treatment of severe bronchospasm. The demonstration of non-cholinergic substance P-containing nerves in human lungs is also clinically relevant since this peptide can produce bronchoconstriction, bronchial mucosal oedema and mucus hypersecretion, all of which are features of asthma. On the other hand, cells other than mast cells and mediators other than histamine and neutrophil chemotactic factor (NCF), such as leukotriens and prostaglandins, must certainly play some role in the production of hyperreactivity of the airways in asthmatics.

What concerns the young asthmatic athlete on this point is that severity of EIA depends on the degree of bronchial reactivity which can be influenced by the release of mediators from mast cells through some unknown exercise-related mechanism. A previous contact with the causative allergens during naturally occurring asthma or in bronchial challenge tests, renders them more hyperreactive to exercise. The same applies to the atmospheric pollutants, such as ozone, sulphur dioxide and nitrogen oxide, which enhance bronchial activity and cause more severe EIA.

It has been shown recently that the level of ionization of the air can also affect EIA. In the existing polemics over the use of negative ion generators in the treatment of asthma, this makes their prescription even less justified.

Despite all the advances made to improve our understanding of the pathophysiology of EIA, the mechanisms by which exercise produces acute episodes of bronchoconstriction has not been worked out. It has been established, however, that EIA can be prevented by several pharmaceutical agents. The most important point with regard to managing patients with EIA is to emphasize the fact that it can be controlled
and they should not refrain from normal physical activity.

Numerous drugs have been tried as modulators of the bronchial response to exercise. Some of them have established themselves as effective or partially effective in prevention of EIA, others have already been discarded as ineffective while trials with the third ones are still under way.

EIA can be prevented by Beta-adrenergic drugs, theophylline and cromolyn sodium. Beta-sympathomimetic agonists, especially the more recent selective Beta-2 agents, are generally agreed to be the most effective. (They act through adenyl-cyclase to increase intracellular concentrations of cyclic adenosine monophosphate - c-AMP) Most researchers suggest that the inhaled route is the most practical as the drug is effective when used immediately before exercise. Oral sympathomimetics are equally effective but should be taken at least 1 hour, and preferably 2 hours before exercise. There is also an agreement that cromolyn and theophylline are less effective than Beta-2 selective agents administered by aerosol (Methyl-xanthines act through inhibition of phosphodiesterase which degrades c-AMP). On the other hand disodium cromoglycate (DSCG, cromolyn) has the advantage of preventing both the immediate and delayed type of response and is virtually free of side effects. The precise mode of action of DSCG is still unclear. It is difficult to account for all its properties on the basis of mast cell stabilization since relatively high concentrations of the drug are required to inhibit mediator release from sensitized human lung fragments, challenged with specific allergens. An important aspect of bronchial asthma is bronchial hyperreactivity and it has been suggested that the drug might have a direct influence on smooth muscle tone. This action is, probably, responsible for the most important therapeutic effect of DSCG, the ability of the drug to reduce bronchial hyperreactivity in the long run. Alternatively or in addition, the drug may act on certain neurological/vertical pathways, such as irritant receptors. For patients regularly being treated by cromolyn it is worth taking an extra dose, alone or with Salbutanol, immediately before strenuous exercise. The need for a dose of Salbutanol would also apply to patients under regular treatment with theophylline which seems to have a similar efficacy to DSCG in prevention of EIA.

Atropine and its isomer Ipratropium bromide (Atrovent) appear to be effective in selected patients, especially in those with chronic bronchitis which condition is rare in young asthmatic patients. These drugs may have a place for the treatment of those patients unresponsive to Beta-agonists but are unlikely to be useful for the athlete with EIA. The same applies to the newly introduced preparation Duouvent, in which Ipratropium bromide is combined with the bronchoselective Beta-agonist Fenoterol.

Although steroids are effective in chronic asthma and in restoring Beta-agonist responsiveness in acute severe asthma, their benefit in protecting against EIA is minimal. However, a recent study of Budesonide, a new steroid aerosol, showed protection against EIA after 4 weeks treatment. But, further evaluation will be needed before any definite recommendations are to be made.

While classical antihistamines are ineffective in preventing EIA, prophylaxis by Ketotifen, an orally active antihistamine with cromolyn - like anti allergic effects, has been controversial. According to a very recent study, Terfenadine, a new potent histamine receptor antagonist, has been shown to be effective in prevention of EIA.

Some Alpha-adrenergic blocking agents have been shown to be effective in EIA protection (Indoramin, Phentolamine. Isoxsuprine). These drugs may be of particular benefit to patients with both asthma and coronary disease, though it is hardly to expect such patients to participate in more strenuous sport activities.

The intracellular concentration of free calcium ions regulates many functions of the cells, including secretion, contraction, transport process, and mobility among others. All the pathogenetic processes in asthmatic airways are calcium dependent phenomena: excitation - contraction coupling in smooth muscle, stimulus - secretion coupling in mast cells and mucosal glands, nerve impulse initiation and conduction, and development of inflammatory infiltration. The intriguing concept of the possible role of calcium ions in the development of hyperreactivity of the airways in asthma has already led to therapeutic trials with calcium channel blockers, such as niphedipine and verapamil. Although they may effect EIA, airway tone, mast cell mediator release and experimental anaphylaxis, given the existing evidence, it seems unlikely that present agents will play a major role in the treatment of asthma. Maybe a new generation of calcium ion antagonists will find better place in management of asthma, including the prevention of EIA.

The philosophy of total rehabilitation of the asthmatic child aims at enabling him/her to live as normal a life as possible, comme tout le monde et avec tout le mondt, as the French nicely put it. The present body of knowledge concerning EIA and the existing pharmacologic arsenal for its prevention make this goal feasible.

References


Continued from page 14

In Malta plain Xylocaine is used for local infiltration prior to perineotomy but the dose has to be less than 3 mg per kg body weight.

Conclusion

Improvement in the control of labour pain by inhalation methods can be enhanced if midwives cooperate, and ensured if an anaesthetist is present in the labour ward. If we are to venture into the field of routine epidural blocks for labour and delivery, adequate budgeting has to be done beforehand in the provision of manpower, in terms of both nurses and doctors, so that the same good results can be obtained in regional analgesia as in general anaesthesia.

Errata Corrigendum

Issue No. 8 1986

A few misprints have appeared in the 8th Issue of Medi-Scope. Hence:

Page 17 Col. 1 line 16: "having" should read "have"

Page 18 Col. 1 line 45: "carriers" should read "caries"

Page 18 Col. 2 line 47: please insert word "Plaque", before "neglect".

The slogan in the Giuseppe Restaurant should have read The Restaurant for Doctors at Large

We apologize to our readers for the appearance of these errors in our publication.
GUIDELINES FOR AUTHORS

Authors are encouraged to submit material for publication in Medi-Scope hoping that the work is original and is not intended for publication elsewhere. All authors must give signed consent to publication. The Editor retains the customary right to style and, if necessary, to shorten material accepted for publication.

Acceptable material includes review articles, reports of studies mostly those carried out in Malta, case presentation, aides memoires for students, articles on practical subjects not usually well discussed in standard text-books and quiz material. Manuscripts should not be lengthy: one may consider that three type-written pages on A4 size paper, with one inch margin on either side and double spacing will occupy one page in the journal.

The number of authors should be kept to one or two; further acknowledgements can be added to the text. The authors’ appointments and qualifications at the time of writing the article should be given to the Editor. It should be made clear on the manuscript which author is responsible for correcting gally proofs and answering queries and correspondence. His/her address and telephone number must be stated. Proof corrections must be kept to a minimum; sizeable alterations should be discussed with the Editor.

A summary of about 80 words should precede the article giving the main argument or findings. The manuscript submitted MUST be typed with double spacing and one inch of margin on either side of the text. Articles should be typed on only one side of the paper; sheets should be numbered and the end of the article denoted by a double line. Authors are strongly advised to keep a copy. Acceptance of material sent for publication is at the sole discretion of the Board.

Drugs should be given their approved name. Abbreviations may be used provided that what they signify is clearly expressed at least once, on their first appearance in the article. Scientific measurements should be given in SI units with traditional units in parenthesis if necessary.

References:

References should be limited to approximately half a dozen. They should be in alphabetical order of the Authors’ names and should conform to the following style:

Articles in Journals:

Authors’ names and initials; year of publication; title of article; title of journal; abbreviated to the style of Index Medicus: volume number; first and last page numbers e.g.:


Books:

Authors’ names and initials; year of publication; title of book; publisher; place of publication; pages of reference e.g.:


Illustrations:

Tables, illustrations and graphs should be submitted on separate sheets of paper from the text proper. A reference must be made clear and highlighted in the text. Each should be accompanied by a caption. Graphs must contain all the relevant information in a properly labelled axes. Line drawings and rough sketches may also be supplied. Photographs are most useful in the form of prints rather than slides. The top left hand corner should be marked. Patients shown in photographs should have their identity concealed or should give their written consent to publication. Photographic material will only be returned to the authors if specifically requested in writing on submission of manuscripts. If any charts or illustrations submitted have been published elsewhere, written consent to republication should be obtained by the author from the copyright holder (usually the publisher) and the authors.

Letters:

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

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


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