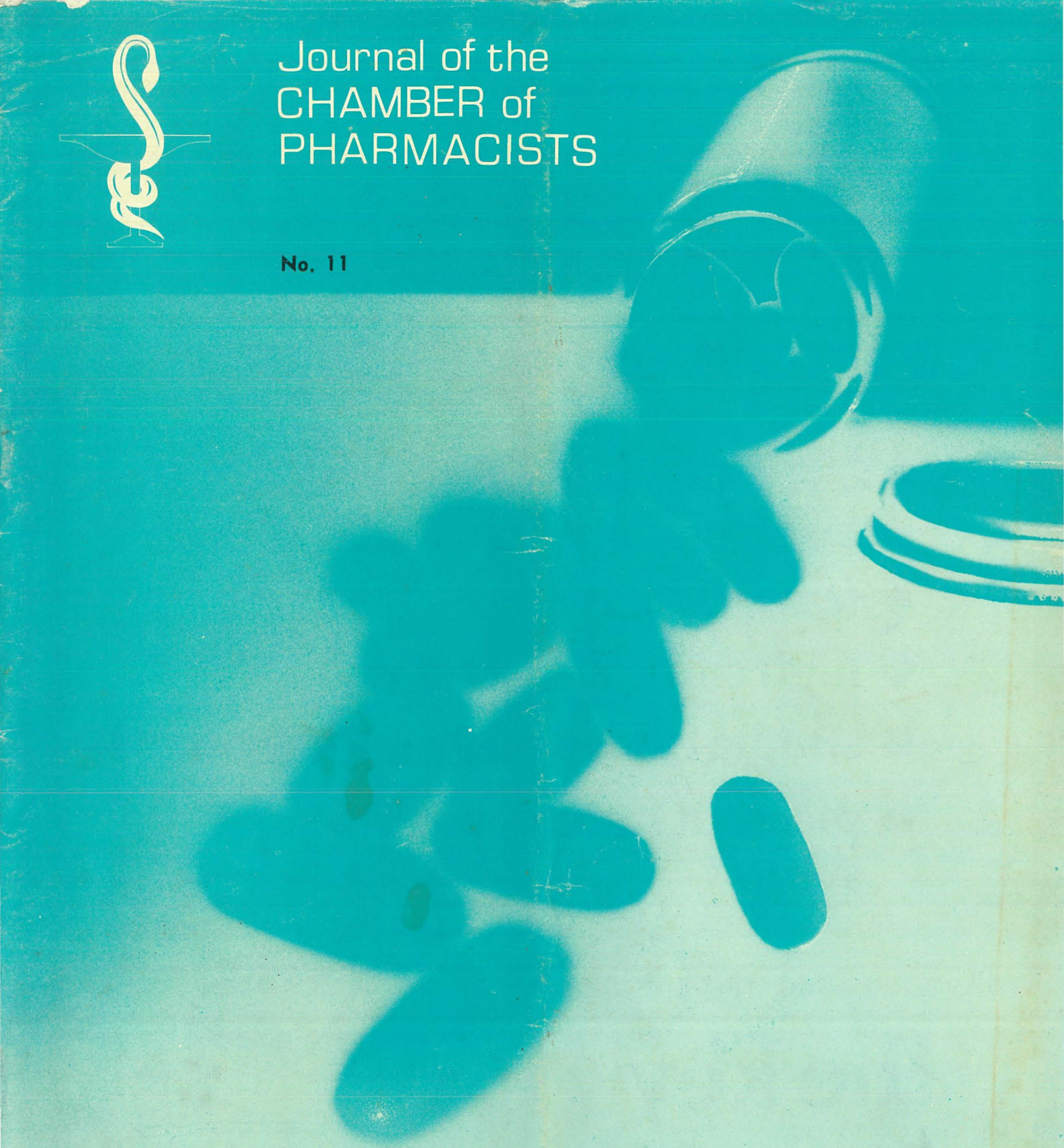
Journal of the
CHAMBER of
PHARMACISTS

No. 11



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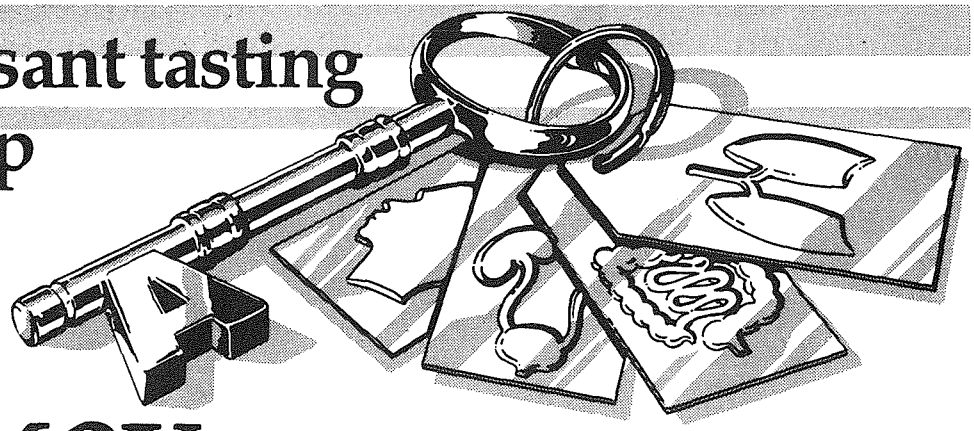

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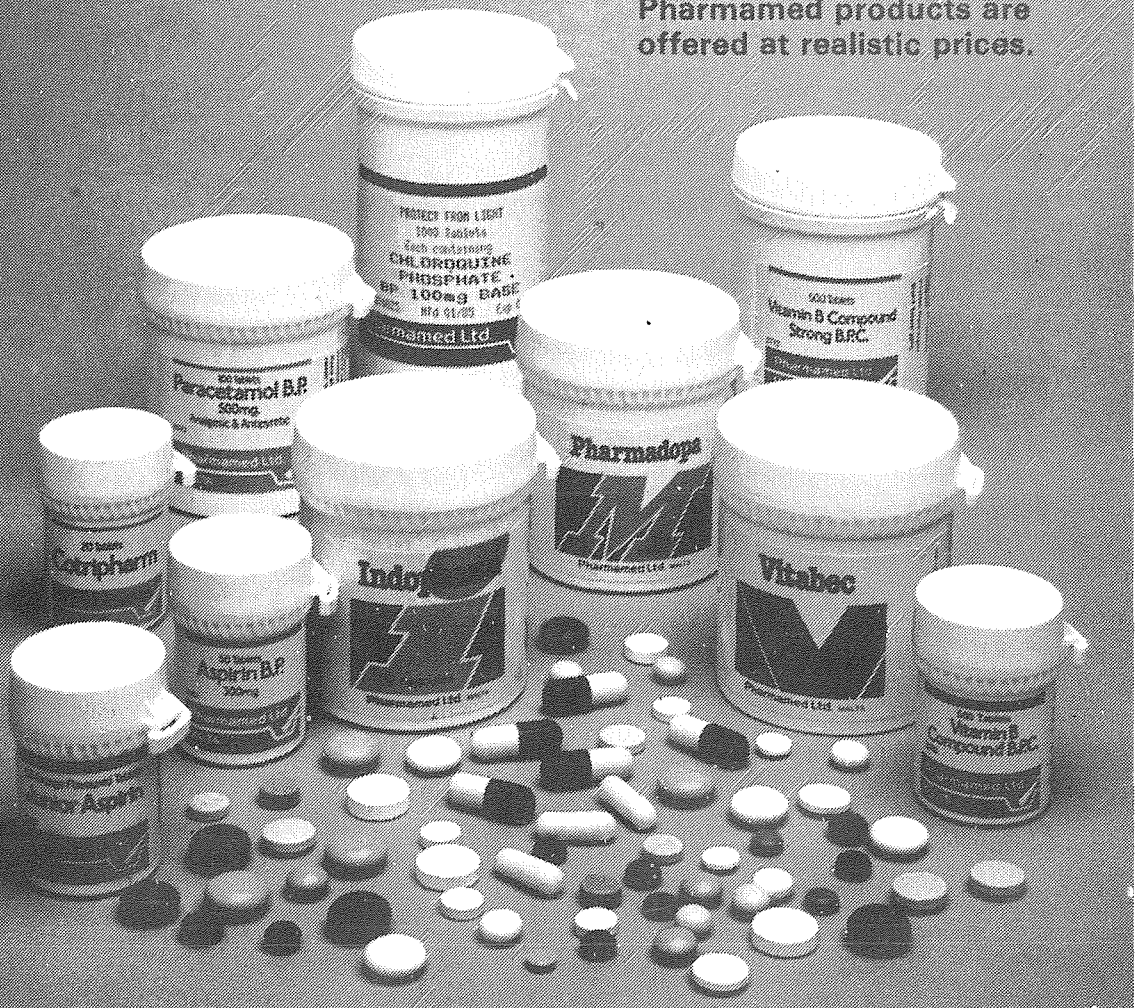


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# THE PHARMACIST

## JOURNAL OF THE CHAMBER OF PHARMACISTS — TRADE UNION

THE PHARMACIST is published by the Chamber of Pharmacists, 1, Wilġa Street, Paceville. It is sent free to all Pharmacists and distributed to doctors. Others may subscribe at an annual subscription of Lm1.50 or obtain copies from Sapienza's Library, Valletta.

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CONTENTS — No. 11, AUGUST 1985

**Ocular hypertension**
**Glaucoma chronicum simplex**
**Postoperative increase in pressure**

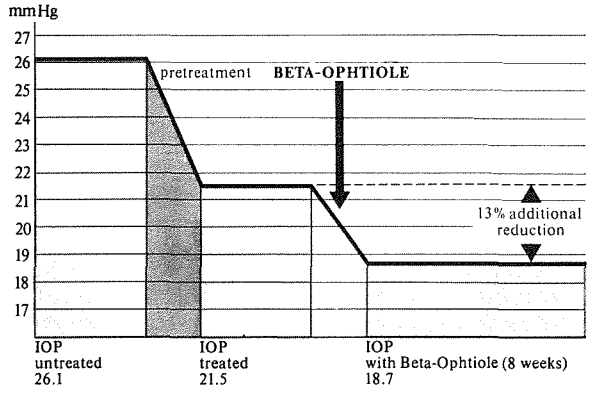
The answer to the problem is

# BETA-OPHTIOLE

0.1% 0.3% 0.6%
sterile eye drops

## Beta-blocking agent in glaucoma therapy

- **reliable longterm reduction in I.O.P. (Ø)**




- **no tachyphylaxis expected**
- **no relevant influence on circulatory parameters**
- **good corneal tolerance**

**Composition:** 1 ml of **Beta-Ophtiole 0.1%** contains metipranolol hydrochloride 1.118 mg (equiv. to 1.000 mg of metipranolol), benzalkonium chloride 0.100 mg. 1 ml of **Beta-Ophtiole 0.3%** contains metipranolol hydrochloride 3.354 mg (equiv. to 3.000 mg of metipranolol), benzalkonium chloride 0.100 mg. 1 ml of **Beta-Ophtiole 0.6%** contains metipranolol hydrochloride 6.707 mg (equiv. to 6.000 mg of metipranolol), benzalkonium chloride 0.100 mg. **Indications:** Increased intraocular pressure, chronic open-angle glaucoma, aphakic glaucoma, to reduce intraocular pressure after cataract extraction. Therapy is indicated in certain special types of glaucoma such as glaucoma capsulare, pigmentary glaucoma, juvenile and haemorrhagic glaucoma. **Contraindications:** Hypersensitivity to metipranolol, bronchial asthma, obstructive pulmonary diseases (constriction of respiratory tract), decompensated cardiac insufficiency, disorders of cardionector system (A-V block), dystrophy of the cornea. **Side effects:** Occasionally a slight, transient stinging may occur. At the beginning of treatment headache, which disappears within a few days, may occur. Treatment with Beta-Ophtiole should be carefully controlled by the physician in wearers of contact lenses, patients with reduced lacrimal secretion, asthmatic patients and in cases of bradycardia. So far results of treatment with Beta-Ophtiole during pregnancy and in children are not available. In such cases the expected benefits should be weighed against possible hazards and carefully controlled by physician. **Special remarks:** As with any glaucoma therapy the intraocular pressure and the cornea should be checked frequently (every 4-6 weeks). **Dosage and administration:** Unless otherwise prescribed, instil 1 drop of Beta-Ophtiole twice daily into the conjunctival sac. **Presentation:** Ophtiole (dropper bottle) of 4 ml.

Dr. Mann Pharma

**Dr. Gerhard Mann, Chem.-pharm. Fabrik GmbH, D-1000 Berlin 20 (West), Germany**

# Summer Sun, Heat and Holidays

Summer sun, heat..... they make a different demand on the pharmacists' professional expertise than do the winter months. Heat rashes, sunburn, prevention of sunburn, travel sickness, traveller's diarrhoea, become everyday problems. It is important for the managing pharmacist to see that his pharmacy is adequately stocked. Bronzing preparations for dark complexioned people and sunblocks for freckled red heads who burn more than tan are a must. The public often bases its choice of suntan preparations on adverts. However, people have little knowledge as to what their requirements are. The blonde requesting coconut oil for her first day out in the sun is probably worse off than using no preparation at all.

*The Pharmacist is the only health professional who is readily available for such advice.* Great awareness is necessary on the part of the pharmacist to identify people who underestimate their complaint. What may casually be described as sunburn may be second degree skin burn which requires medical attention. On the other hand, several people tend to misuse potent ointments and sprays for heat rashes and other heat related problems. The idea that there exist creams which are 'tajbin għal kollox' (good for everything) is unfortunately a popular misconception held by a fair section of the general public. *The pharmacist is a specialist on drugs and pharmaceutical products* and we must educate the public that it is wiser to seek advice first than to experiment with medication that may be available in the medicine cupboard or passed on by a neighbour.

Summer sun, heat..... holidays..... The pharmacist is no exception to think of taking a holiday. But, any such thoughts immediately bring to mind the very real problem of finding a locum pharmacist. A number of pharmacies are beginning to close for annual holidays. This practice cannot be discouraged but as this becomes more widespread it will be important for pharmacists to get together and plan their pharmacies' shutdown. The public *must always* be provided with a pharmaceutical service. Time off for the pharmacist is not a problem only in summer. Even working to within the weekly hour limits of the labour office requirements both for the pharmacist and other staff is a problem because of the long opening hours of a pharmacy. A solution has already been discussed for a number of years now :— *opening on Saturday afternoon by roster.* It is known that almost 100% of general practice pharmacists support the idea. It is hoped that the chamber will continue pressing with the matter.

.....And what better may could there be for bringing pharmacists together in such warm weather, than by organising a barbeque. This is precisely what the executive of the chamber did on Wednesday 14th August. For years now, the Chamber's sole annual social occasion has been the Christmas dinner or party. The need for more social occasions has long been felt among pharmacists. It is hoped that this will become another annual event for the Chamber.

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Editor: Ms. M.A. Ciappara B.Pharm.
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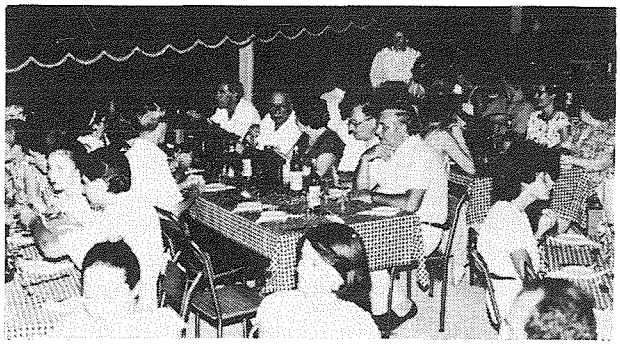
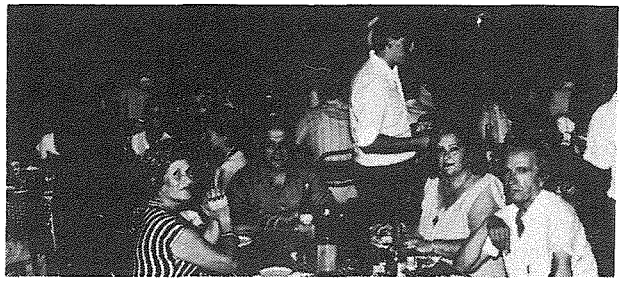
# *Barbeque at Lido San Gorg*





**Members and guests during the barbeque.**

Members of the Chamber of Pharmacists — Trade Union, and Pharmacy students together with their guests attended a barbeque at Lido San Gorg at St. George's Bay, St. Julians on Wednesday, 14th August.

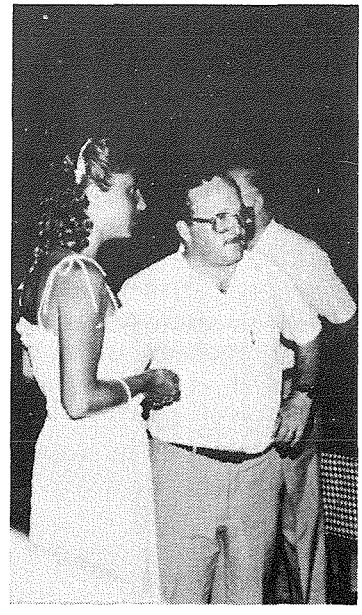
This highly enjoyable event was organised by the council members of the Chamber of Pharmacists and sponsored by Prosan Ltd.

Among those present were Mr. J. Gusman, representing Prosan Ltd., Ms. T. Wirth, P.R.O. of Prosan Ltd., Dr. R. Vella, President of the Federation of Professional Bodies, and Ms. L. Mintoff, Government Chief Pharmacist.

In her short speech, the President, Ms. M. Gatt thanked Prosan Ltd., for sponsoring the event and expressed her hope that this will become the annual summer event of the Chamber of Pharmacists.

(Photographs by Mr. E. Bugeja B.Pharm.).

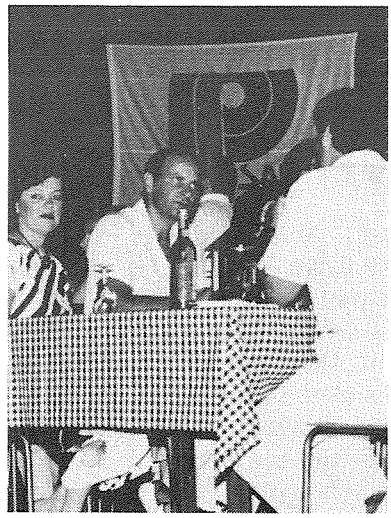
**Mr. J. Gusman left and Dr. R. Vella finding the choice of salads difficult!**

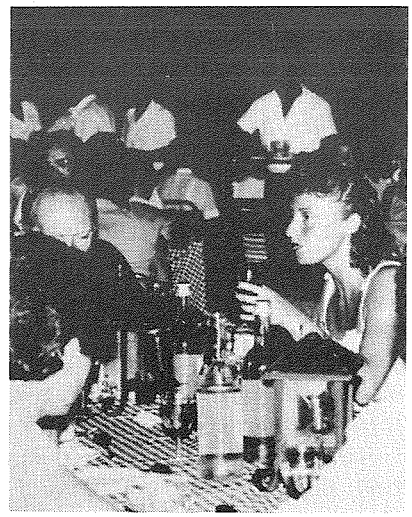


**Ms. T. Wirth, P.R.O. of Prosan Ltd., with Dr. A. Serracino Inglott.**

▶ Ms. L. Mintoff, Government Chief Pharmacist with Mr. A. Darmenia, former Government Chief Pharmacist.

▲ Some of the pharmacy students at the barbeque.





▶ Ms. T. Wirth and Mr. J. Gusman enjoying the company.

The council members with Mr. J. Gusman.

THE COUNCIL OF THE CHAMBER OF PHARMACISTS WOULD LIKE TO THANK **PROSAN LTD.**, FOR SPONSORING THIS VERY SUCCESSFUL EVENT.

## Annual General Meeting

The Annual General Meeting of the Chamber of Pharmacists was held on the 19th April 1985.

Compared to the extraordinary General Meetings the attendance was rather low. Perhaps, as the president said, they have so much confidence in the council that they did not feel the need to attend.

The annual report was presented in which were highlighted the various events of the past year, which included the yearly extension studies, two issues of 'The Pharmacist', and several extraordinary general meetings. This year the old tradition of a Christmas Dinner was revived with a very successful dinner which was held at Sardinella Restaurant, St Julians.

### Dispense or sell medicines?

In her address, the president, Miss Gatt asked: do we dispense or sell medicines? She quoted an incident which occurred during a meeting with Government officials. Some pharmacists were explaining the role of the pharmacist in society. He gives advice, is alert for drug interactions, etc. When they had finished the Government officials said: "But no one has ever told me anything whenever I purchased medicine from a pharmacy..." Recently, a young man was prescribed steroid eyedrops for inflammation caused by contact lenses. After six months of repeated use of the anti-inflammatory preparation, he developed glaucoma. Whenever he purchased a new bottle, no one ever advised him about the dangers of continuous use. The president stressed: 'Let us not forget to dispense and not to sell medicine in practise as well as in theory'.

The dispensing fee had been discussed several times during recent meetings and she was glad to note a positive change in attitude towards this subject.

### United we stand

In 1984 there were a good number of paid up members. Ms Gatt said it was very encouraging to see the support of members in difficult situations as was indicated by the good attendance at the Extraordinary General Meetings. However all pharmacists had to keep in mind that the Chamber of Pharmacists is **their** association and progress could only continue to be made in pharmacy, if pharmacists show continuous support of their association, by participating in the Chamber's activities.

The president concluded her address by thanking the council members and editorial board for their support in the past year, and the local pharmaceutical agents who supported the Chamber and its journal, 'The Pharmacist', through advertisements.

### Motions approved

1. The members present at the Annual General Meeting having agreed on the desirability to compare with international trends re the use of suitable containers, adequately labelled for the dispensing of medicinals directs the newly elected council to issue guidelines about this matter and establish a standard fee to cover the expenses involved.
2. In the light of the amendments made in the Drugs (Control) Regulations in 1984 introducing the use of special prescriptions for the dispensing of Narcotic and Psychotropic drugs. Aware of the fact that the new obligations, regarding the dispensing of these medicinals and the monthly return of all prescriptions duly filled with all the information required has considerably increased the work involved in the dispensing of these medicines, the members of the Chamber of Pharmacists at this General Meeting instructs the new elected council to make representations to the competent Authorities for the establishment of an adequate dispensing fee on the sale of such medicinals.
3. The members of the Chamber of Pharmacists gathered at this Annual General Meeting recognise the need that their Trade Union affiliates with a stronger body which would enhance its position in any trade dispute that might arise. The General Meeting assembled also agrees that the C.M.T.U. is an organisation that can provide this protection if the need arises. In view of this, the general meeting resolves that the council starts forthwith the proper negotiations for entry as a free member of the C.M.T.U.
4. The Annual General Meeting considers that the Pharmacy Board as presently constituted cannot fulfill the aims it was originally intended for and appeals to the competent authorities to re-constitute the Pharmacy Board in a manner which will ensure the adequate representations of the pharmacy profession so that the original objectives can be achieved.

## Health Education
## New Extended Role for the Community Pharmacist

Dear Madam,

Today a lot of emphasis is made on the prevention of diseases. Cardiovascular diseases, colon cancer and diabetes are largely preventable diseases. Of the major factors that influences their development is diet. Proper dietary habits are the best insurance against disease. Pharmacists, come in contact with a large percentage of the population. They are in a position to act as advisers and health educators to their clients.

Health education should form part of the practise of Community pharmacy. This was stated in the article 'Betablockers in the treatment of hypertension, angina pectoris and myocardial reinfarction' by M. Felice Sant Fournier.

In my view, through this new role, pharmacists can participate in the prevention campaign. This will add a new dimension to the practice of community pharmacists. In a recent exercise held by the Victoria Branch of the Pharmaceutical Society of Australia to discuss the future practice of community pharmacy, it was felt that the pharmacist's role should be drug and health related. Apart from advising and educating the public on medication, his role can be extended into general health problems, advising and educating on such matters as general health, nutrition, obesity, occupational health, etc.

Continuing education is vital for the implemention of this new role. A short specialised course organised by the University can provide the necessary knowledge and guidance necessary.

These health initiatives would require the cooperation of other health professional to ensure that they will not regard it as an intrusion into what they may think is their professional domain.

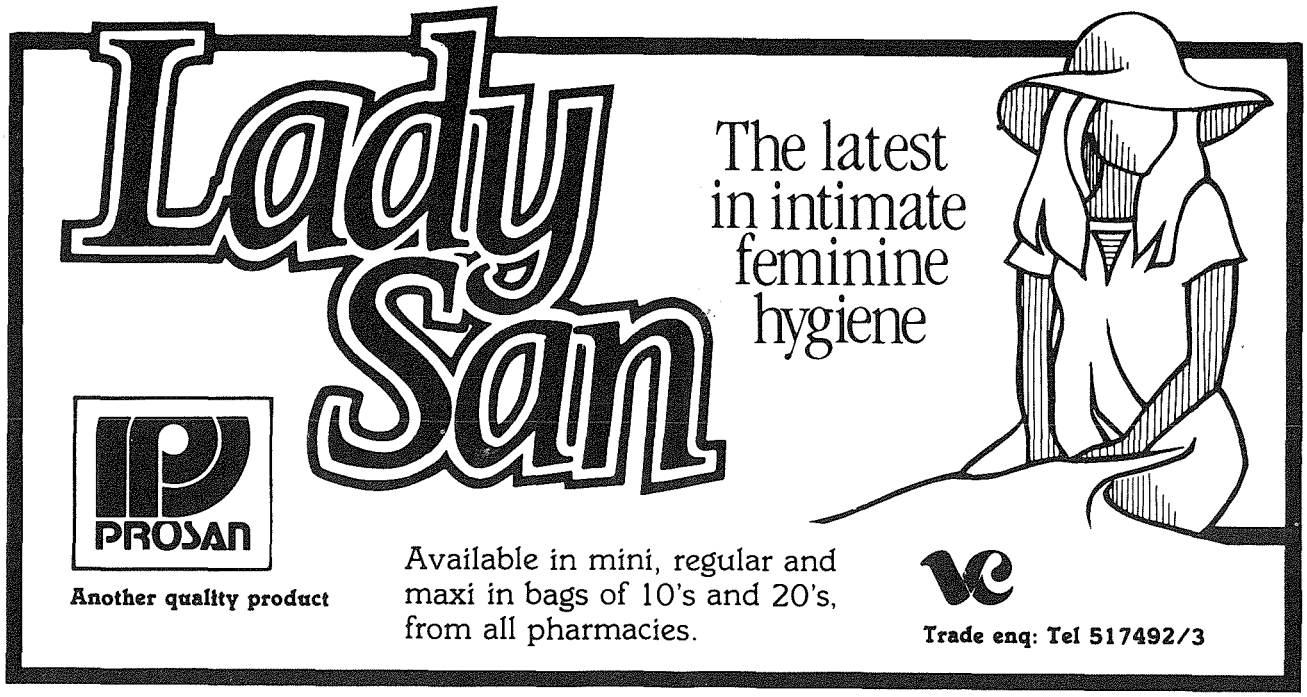
For the implementation of this new and existing roles of the pharmacist, a public educating campaign should be initiated to encourage them to make use of the professional services provided by the pharmacist. This will contribute to built up the image of our profession in Malta.

**References**

'Looking Ahead Ten Years Hence', The Commonwealth Pharmacist, Vol. 3, No. 2, 1984.

Felice Sant Fournier M.A., 'Betablockers in the treatment of Hypertension, Angina Pectoris, and myocardial reinfarction', The Pharmacist, No. 10, pp. 23-27, 1985.

Yours faithfully,
**Community Pharmacist**



## ISSX CONFERENCE

# *The many facets of foreign compound metabolism*

**A review of the ISSX first European Symposium on Foreign Compound (Xenobiotics) Metabolism held at the University of Malta between February 24th and March 3rd, 1985.**

**Mary Ann Felice Sant Fournier, B.Pharm., M.Phil.**

*This review is divided into two parts; the first part of the review appearing in this issue of 'Tha Pharmacist' deals with the proceedings of the first two days of the symposium mainly dedicated to Professor Eric Boyland and his work together with contemporary methods in drug metabolism studies.*

*The second part of this review which deals with the final two days dedicated to the role of disposition studies in the safety evaluation of consumer products, including agrochemicals and to oral and poster free communications will appear in the next issue of this journal.*

### INTRODUCTION

The local academic and industrial communities were in a unique and privileged position towards the beginning of this year because the International Society for the Study of Xenobiotics (ISSX) in cooperation with the University of Malta organized its first European symposium on Foreign Compound Metabolism at the Assembly Hall, University of Malta, Tal-Qroqq.

It was therefore with great pleasure and interested anticipation that I accepted to attend and report on proceedings on behalf of the Chamber of Pharmacists.

**Some of the 120 participants at the ISSX conference applaud one of the speakers at the main sessions. Prof. R.L. Smith is (2nd from right front row) and Dr. P. Johnson (4th from right) and Dr. J.W. Gorrod (6th from right).**
**Prof. A.H. Beckett is (1st from right second row).**
**Prof. D.V. Parke is (1st from left, fourth row).**

*(Courtesy of Allied Newspapers Ltd)*

About 120 participants from 12 countries including the U.S. and Japan attended the 4-day conference during which 25 papers were presented at the main sessions whilst there were 11 oral free communications; 19 poster free communications were also presented. All these contributed to various interesting discussion sessions between the speakers and their audience.

The organising committee included P. Johnson, chairman (Smith, Kline & French Ltd., England), L. Chasseud (Huntington Research Centre, England), V. Ferrito (University of Malta), G. Gibson (University of Surrey, England), J. Gorrod (University of London, England), R.L. Smith, President of ISSX, ex-officio (St. Mary's Hospital Medical School, England).

The programme committee was under the chairmanship of J. Gorrod and included G. Brooks (University of Sussex, England), D. Howes (Unilever, England), A. Renwick (University of Southampton, England), W. Ritter (Bayer, West Germany) and V. Ferrito and G. Gibson.

## ISSX PRESIDENT INTERVIEWED

During a most cordial interview, Professor R.L. Smith (Department of Experimental Pharmacology, St. Mary's Hospital Medical School, University of London, England), who incidentally is a pharmacist, now Biochemical Pharmacologist and the current President of ISSX, explained to your author the 'raison d'étre' of the Society. Indeed, ISSX is the 'umbrella' under which the ever-increasing research workers in the various disciplines involving the study of xenobiotics, be it, Biochemical Pharmacology, Toxicology, Cancer Research, the pharmaceutical, chemical, agricultural and food as also the perfume industries are to find a common ground for reference, discussion, possible problem solving, influencing changes in research trends, updating, and influencing regulatory bodies in formulating related legislation; indeed, conferencing.

The first ISSX symposium was held in Florida, California, USA in 1983; but, it was soon felt that a European conference would be more easily accessible to the many members interested in the study of xenobiotics which include drugs and also non-drug cmpounds.

## GLOSSARY

Xenobiotic: or 'foreign compound'... not necessarily a compound "not normally present in the diet" or "to which the organism is not normally exposed"; indeed, the food we eat and the air we breathe contain a formidable array of compounds which today are all described as 'foreign'; the term 'Xenobiotic' attempts to overcome the 'problem'; a generic term such as 'foreign compound' or some equally indefinable term as 'xenobiotic' is needed to refer to those compounds which by custom are classed as 'foreign'.

Biochemical Pharmacology: the field wherein not only the molecular aspects of a drug, i.e., a chemical substance, usually foreign, are explained but also the changes which they cause in biochemical systems and cellular strategy; indeed, it is devoted to research into the development of biologically active substances and their mode of action at the biochemical and subcellular level.

Detoxification, Detoxication: while metabolism often results in the conversion of xenobiotics to less toxic polar products, some metabolites may be more toxic than the parent compound resulting in tissue damage and even the initiation of carcinogenesis. Thus the word 'detoxication' used to describe the metabolic reactions undergone by foreign compounds is capable of giving rise to misconceptions concerning the nature of the processes involved in the metabolism of foreign compounds. Problems associated with the use of the term are now generally recognised.

Metabonates: chemical breakdown products of metabolism distinguished from metabolites, products of enzymatic degradation.

Phase I metabolism: or pre-conjugation metabolism including oxidative, reductive and/or hydrolytic reactions.

Phase II metabolism: further 'detoxication' by conjugate formation and subsequent excretion.

## PROFESSOR BOYLAND HONOURED

Amongst the many eminent personalities in their respective fields who were participating at the conference was Professor Eric Boyland, leading Biochemist, Toxicologist and Educator who was honoured by the University of Malta for his outstanding contribution to cancer research with the conferment of a degree of Doctor of Medicine and Surgery (Honoris Causa) at the start of the conference.

The conferment was made by The University Rector, Professor G.P. Xuereb; the Chairman of the Faculty Board of Medicine and Surgery, Professor E. Grech was the sponsor.

In an address during the conferment ceremony, Professor Victor Ferrito, Acting Head of the Department of Pharmacy, described the English Professor, who incidentally was celebrating his 80th birthday whilst in Malta, as a pioneer, founder and father of the study of xenobiotics. He said that Prof. Boyland has made several important observations, discoveries and postulations, later proved correct which had laid the foundations for the science of molecular toxicology.

Born in Manchester in 1905, Prof. Boyland graduated B.Sc., in 1926 and M.Sc. in 1928 from Manchester University.

Between 1928 and 1931 he was Grocers Co. Scholar and Beit Memorial Fellow at the Lister Institute for Preventive Medicine and at the Keiser Wilhelm Institute, where he worked on the biochemistry of muscle.

He was awarded the Ph.D. degree by London University in 1930 and was appointed Physiological Chemist to the Royal Cancer Hospital in 1931. In 1936, he was awarded the B.Sc. of the University of Manchester and was appointed Reader in Biochemistry. He was appointed Professor of Biochemistry of London University in 1945.

**Prof. E. Boyland receiving the degree of Doctor of Medicine and Surgery (Honoris Causa) from Prof. G. Xuereb.**
*(Courtesy of Allied Newspapers Ltd).*

Professor Boyland retired from his professorship at the Institute of Cancer Research in 1979 and became visiting professor in Toxicology at the School of Hygiene and Tropical Medicine at the University of London. He still holds this position.

Professor Ferrito said that Professor Boyland's suggestions, postulations and predictions on the **in vivo** behaviour of various types of xenobiotics were in advance of his time.

The 4-day conference started immediately after the conferment ceremony. The first day was devoted to topics related to Prof. Boyland's career in research and included the presentation of papers by several of his former students and research collaborators.

## SCIENTIFIC APPROACH TO CANCER RESEARCH THROUGH CHEMISTRY

The first session chairman, Prof. D.V. Parke (University of Surrey, England) introduced the day's work by presenting an appreciation of Prof. Boyland's Life and Work, which can be summarily described as a rigorously scientific approach to cancer research through chemistry.

### Appreciation of Prof. Boyland's Life and Work

Indeed, amongst other important breakthroughs, Boyland identified the link between nitrosamines and cancer, e.g. in the bladder and stomach; the relation between thiocyanate levels in the saliva of cigarette smokers and cancer during studies on tobacco alkaloids. In 1948, Boyland indicated the relation between alkylating agents and cancer; and on to glutathione conjugation, the cell's main defence against cytotoxic effects of electrophilic xenobiotics. The identification of glutathione-S-Aryl-transferase removed any doubt of the actual existence of this pathway in the metabolism of xenobiotics. Boyland **et al** (1957-58) also carried out useful work to unequivocally show the presence of mercapturic acids in the urine of experimental animals.

Thus in about fifty years of fruitful activity, Boyland has been ahead of his time in advocating today's accepted trend of Prevention of cancer by modification of social and personal customs, such as tobacco smoking and sunbathing and a decrease in the abuse and, or rather, the misuse of chemicals.

Boyland's elucidation of the metabolic pathways of polycyclic aromatic hydrocarbons without the benefits of modern characterization methods, such as High Performance Liquid Chromatography (HPLC), Nuclear Magnetic Resonance (NMR), Mass Spectroscopy (MS), etc. considered as essential today to workers in this field was described as 'more an art than science' by Prof. P.L. Grover (Chester Beatty Laboratories, Institute of Cancer Research, London) during the presentation of his paper entitled Metabolism and Activation of Polycyclic Aromatic hydrocarbons.

Following the isolation of Benzpyrene from coaltar in 1933, Boyland (with Levy, 1935) studied the metabolism of anthracene and (with Wolf, 1950) of phenanthrene. The existence of simple epoxides as intermediary metabolites of polycyclic hydrocarbons and as intermediates in the formation of dihydrodiols, phenols and glutathione conjugates was originally proposed by him in 1950. Such epoxides were initially regarded as being involved in detoxication but evidence now shows that epoxides of various types are also the reaction species responsible for the carcinogenic and mutagenic effects of the parent hydrocarbons; the cytotoxicity of polycyclic hydrocarbons may also be due to these epoxides, which, although not yet identified, recent work has shown that benz-a-pyrene diol-epoxide can be metabolized to an even more reactive species that reacts covalently with microsomal protein or with thiols and that may be a triol-epoxide.

### Metabolism of Aromatic Amines

Dr. J.W. Gorrod (Department of Pharmacy, Chelsea College, University of London) gave an overview of work carried out on the metabolism of aromic amines, which are widely used in the chemical, pharmaceutical, rubber and plastic industries and occur as natural sustances and/or their combustion products. Many aromatic amines are toxic — indeed, approximately 35% of neoplasms in workers in such industries as above are occupational — and hence, their metabolism has been extensively studied with a view to elucidating the mechanisms involved.

The oxidative metabolism of aromatic amines can occur at 3 sites on the molecule viz., the constituent nitrogen, the aromatic ring system, and the substituents on the amino group. These oxidative reactions are mediated by the cytochrome P-450 isozyme system although other enzymes may play an important role in organ directed toxicity. The parent amines and the primary metabolites can undergo conjugation with acetic, glucuronic and sulphuric acids or with glutathione. The conjugation reactions are reversible and in the case of acetylation this may influence the position of nuclear hydroxylation compared to the parent amine.

During the course of these metabolic processes reactive compounds are sometimes produced which may be involved initiating a toxic response in a biological system. Indeed, that N-hydroxylation of aniline leads to phenylhydroxylamine associated with methaemoglobinaemia was first shown by Kiese (1959). Cramer **et al** (1960) identified the carcinogen N-hydro-

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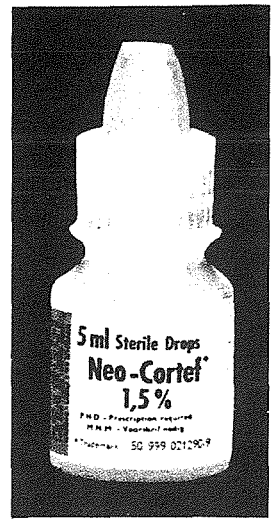


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xy-2-acetlyaminofluorene in rats after incubation of acetylaminofluorene. Japanese workers studying N-hydroxylation of heterocyclic systems have identified potent mutagens, now carcinogens, trace amounts of which may be formed after food pyrolises. Boyland and Levy have shown the relation between nitrosamines and bladder cancer.

It would be of interest to note at this point that Dr. Gorrod was the organiser of at least three symposia on the Biological Oxidation of Nitrogen in Organic Molecules at Chelsea College and had edited the proceedings of these international symposia. The Department of Pharmacy of the University of Malta had participated at the 2nd International Symposium on the Biological Oxidation of Nitrogen in Organic Molecules held at Chelsea College, University of London, U.K.,19-23 September 1977 and had presented a paper, published in the proceedings of the symposium, entitled 'The metabolism of pyrroles and Indoles: ring nitrogen oxidation' under the authorship of Prof. A. Jaccarini and Miss Mary Ann Felice B.Pharm., M.Phil.

**Metablism of Tobacco Alkaloids**

The metabolism of tobacco alkaloids was then discussed by Prof. Dr. A.H. Beckett, (Chelsea College, University of London) who has had longstanding connections with the Department of Pharmacy, University of Malta having examined many a B.Pharm. student (including the undersigned, also at M.Phil. level). Tobacco contains more than a dozen alkaloids containing the pyridine ring structure substituted in the 3-position with 5 and 6 cyclic ring systems containing the N-atom in the 2-position.

The important centres of primary metabolic attack are the pyridyl N-centre, and the second N-centre (aliphatic in most of the alkaloids) and its **alpha**-carbon-atom, which are then further metabolized or changed chemically to metabonates. The pyridyl nitrogen can be metabolically methylated but apparently not converted to the N-oxide unless the second N-centre is rendered virtually non-basic, i.e., as in cotinine. The aliphatic tertiary N-centre can be converted to the N-oxide metabolically e.g. in nicotine and N-methlyanabasine, whereas an aliphatic secondary N-centre can be oxidized metabolically to the corresponding hydroxylamine e.g., in anabasine, which is chemically changed to the metabonate nitrone.

Metabolite C-oxidation on the C-atom **alpha** to the aliphatic N-centre leads to chemically unstable alkanolamines and thus N-dealkylation or ring opening depending on which **alpha**-carbon atom is attacked. Metabolic oxidation of other than C-atoms **alpha** to the non-aromatic N-centre can also occur e.g., cotinine to hydroxycotinine. Stereochemical aspects are important; nicotine and many of the minor tobacco alkaloids contain an asymmetric centre.

**Metabolism of Anticancer Drugs**

The essential role played in determining both symptoms and antitumor selectivity by drug metabolism, for most clinically useful anticancer agents was pointed out by T.A. Connors (MAC Toxicology Unit, Medical Research Council Laboratories, Surrey, U.K.), during his presentation entitled 'Metabolism of Anti-Cancer drugs'. Examples of pro-drugs which are pharmacodynamically inert but which may be metabolized to active drug were given; their use to improve both pharmacokinetic properties and drug penetration in the tumour was also discussed. Other examples of anticancer agents where drug metabolism may lead to greater antitumour selectivity or conversely a poorer therapeutic index were made.

Indeed, a simple knowledge of drug metabolism is indispensable for positive cancer therapy although one must always bear in mind that the metabolism of anticancer agents may be responsible for unique toxic features.

**Conjugation Reactions Involving Glutathione**

The importance of the reducing and nucleophilic properties of glutathione (GSH) in the metabolism of xenobiotics was emphasized by Brian Ketterer (Courtuald Institute of Biochemistry, Middlesex Hospital Medical School, London). Indeed, 'Phase I' mixed function oxidations of xenobiotics produce both free radicals and electrophiles simultaneously.

As a reducing agent GSH plays an essential role by detoxifying oxidizing by-products of oxygen utilization through the agency of Se-dependant GSH peroxidase and certain GSH transferase isoenzymes. The success of GSH in the detoxification of electrophiles depends on: 1) the chemical properties of the electrophiles, e.g., their "softness" and "hardness"; 2) the extent to which their detoxification is catalysed by GSH transferase isoenzymes; and 3) the tissue under consideration since isoenzyme distribution differs from tissue to tissue.

**Perspectives and Horizons**

Rounding up the day's work, Prof. Boyland (TUC Centenary Institute of Occupation Health London School of Hygiene and Tropical Medicine, London) expressed the hope that means by which cancer could be prevented by modification or inhibition of metabolism of foreign compounds would be presented at the meetings; many carcinogenic compounds including polycyclic hydrocarbons, aromatic amines and nitrosamines are active only after 'metabolic activation'. The activating processes involve the misuse or incomplete use of 'detoxicating' reactions. Knowledge of the biochemical mechanisms by which these compounds are activated to cause initiation, promotion and progression was accumulated slowly over a number of years. Processes which involve induction of cancer are not removed by evolution.

## IMPORTANCE OF CONTEMPORARY METHODS IN DRUG METABOLIC STUDIES

At the present time, the identification of metabolites excreted in the urine continues to play a major role in the study of foreign compound metabolism, but with an important difference, namely, that powerful new investigative procedures have become available during the last 30 years or so.

### Extraction of Metabolites from Biological Fluids

The second day of the conference was dedicated to such contemporary methods; the first session, under the chairmanship of W. Ritter (Bayer, West Germany) was opened by M. Stewart (Royal Infirmary Drug Investigation Unit, Scotland), who discussed the extraction of metabolites from biological fluids.

It is generally felt amongst workers in this field, however, that the isolation and therefore, extraction of intermediates in metabolic studies still does present a problem; also, it is the extraction procedure which now contributes to the majority of imprecisions in a drug assay; yet, despite all this, relatively little effort has been put into methods for improving this stage of analysis. Although detection systems for drugs and toxins continue to improve rapidly in both sensitivity and specificity, radio or optical immunoassays now allowing the detection of drugs at levels of $10^{-12}$M, for positive identification, a specific method of extraction is necessary.

Solid phase extractions have considerable theoretical advantages over solvent extractions which are likely to contribute impurities to the final extract even after careful distillation and purification with losses in sensitivity once the final identification step is reached. Automated solid phase systems now exist which allow rapid processing of batches with minor operator involvement, thus also curtailing costs and increased time requests. Indeed, the Dupont Prep centrifugal extraction system described has been found to provide a flexible answer to a wide variety of extraction problems such as elimination of streaking as in solvent extraction, selectivity, a must in cathecholamine studies and of course, the extraction of metabolites in toxicological **in vivo** studies.

### Utilisation of Radiochemicals in Xenobiotic Metabolism

The utilization of radiochemicals in xenobiotic metabolism, especially the use of $^{35}S$-labelled inorganic sulphate to study effectively the formation, identification and whole-body disposition of sulphoconjugates was very interestingly described by Prof. G. Powell (University College, Wales) the only lady amongst the speakers at this symposium.

The usefullness of the isolated perfused liver system receiving continuous infusions of inorganic [$^{35}S$] sulphate and the formation of sulphoconjugates under steady-state conditions were given particular attention. The liver plays a control role in the formation of sulphoconjugates of both xenobiotics and naturally-occurring compounds and has also a role in the partitioning of suphoconjugated metabolites between bile and blood. By utilising [$^{14}C$] Leucine, the effects of xenobiotics on normal intermediary metabolic pathways such as the synthesis of proteins, glycoproteins, lipids, and cholesterol may be investigated.

### Electrochemical Methods in Xenobiotic Metabolite Analysis

Dr. H. Oeschlager (Institut für Pharmazeutische Chemie der Universitat Frankfurt, W. Germany) President of the Pharmaceutical Society of that country, showed how electrochemical methods, in particular, Differential Pulse Polarography and HPLC with ECD (Electron-Capture Detector) are approved for drug analysis **in vivo.** By functionalization reactions polarographically inactive molecules are accessible from electrochemical detection to a limit in the

range of 10ng/ml. Since pharmacokinetics influence the pharmacodynamic effect to a great extent, a successful therapy needs analytical data concerning plasma levels of an administered drug and its metabolites, as well as the concentration of these xenobiotics in the urine and faeces. One convincing advantage of polarography is the possibility to calculate the current signal if the reducation- or oxidation mechanism is known.

**HPLC: Limitations and Possibilities**

The need for analytical methods of increased sensitivity and stability in drug metabolism studies has coincided with the introduction of high pressure liquid chromatography (HPLC; also referred to as high performance or high speed liquid chromatography) as a routine method of separating and quantitating drugs and metabolites. K. Zech (Byk-Gulden, Pharmaceuticals, GFR) discussed the limitations and possibilities of this relatively "young" technique, an indispensable tool in drug metabolism studies particularly as: a) biofluids can be introduced directly onto the reversed phase column, without prior extraction, b) performance is at room temperature, permitting the analysis of thermally labile metabolites and c) it is non-destructive, permitting 100% recovery of all metabolites with optimized separation and detection systems.

Extensive use of different detection for sensitivity, as well as on line screening for drug metabolites by coupling HPLC with a diode array detector (DAD). Direct injections of large amounts of biofluids on an automated precolumn switching system may overcome such limitations as errors by loss of metabolites or formation of artefacts during routine analysis sample preparation.

Thin Layer Chromatography (TLC) is employed for various purposes in drug metabolism studies; for separation and purification of metabolites prior to their characterization by other analytical (spectral) methods; to help identify drugs of their metabolites if authentic reference samples are available for direct comparison of Rf values and in addition TLC has been used for quantitation of compounds which are not amendable to Gas Chromatographic analysis (GC) due to their instability or poor GC properties.

**Detection and Quantification of Xenobiotics and Metabolites by HPTLC**

During the session chaired by P. Johnson (Smith, Kline & French, England) W. Ritter proposed the use of High Performance Thin Layer Chromatography (HPTLC), an analytical procedure based on conventional TLC but considerably faster and much more reproducable and economical. High performance is obtained by combining the increased separation power of HPTLC plates coated with an optimized silica gel and the instrumental performance of sample application (up to 20 samples simultaneously) chromatographic development under controlled conditions and quantitation by scanning **in situ.** The speaker surveyed the advantages of HPTLC as a tool for separation, detection and quantitation of various types of xenobiotics, e.g., polycyclic aromatic hydrocarbons, preservatives, nitrosamines, antioxidants, insecticides, herbicides and phosphate pesticides, drugs and their metabolites with examples from recent literature and his own experimental studies in drug pharmacokinetics and metabolism.

**Spectral Methods in Metabolite Structure Elucidation**

T. Marten, (I.C.I. Pharmaceuticals, England) then reviewed the "array" of spectroscopies available to the researcher for use in metabolite structure elucidation. Indeed, although traditional methods for identification of metabolites are still used, they have evolved and though phase II metabolites consist of large, polar molecules, presenting special difficulties to the spectroscopist, developments in mass spectrometry, (MS), Nuclear Magnetic Resonance (NMR), Ultraviolet (UV), and Infra-Red (IR) spectroscopy have allowed many of these problems to be overcome, e.g., DAD's have made looking for metabolites in biological samples much easier and have provided structural information at the same time.

Judicious use of stable isotopes and corresponding spectroscopic technique has aided metabolite detection and identification particularly when looking at a specific problem such as the position of hydroxylation on an allycyclic ring NMR spectroscopy remains vital because it gives very specific information on structural and spatial arrangements of atoms and Mass Spectrometry remains one of the most important analytical innovations; electrical impact mass spectrometry (EIMS), chemical ionization mass spectrometry (CIMS) and — to a lesser extent, field desorption mass spectrometry (FDMS), are analytical techniques which are now routinely used in metabolism studies. If an electron impact or chemical ionisation mass spectrometer is coupled with a gas chromatograph and a data

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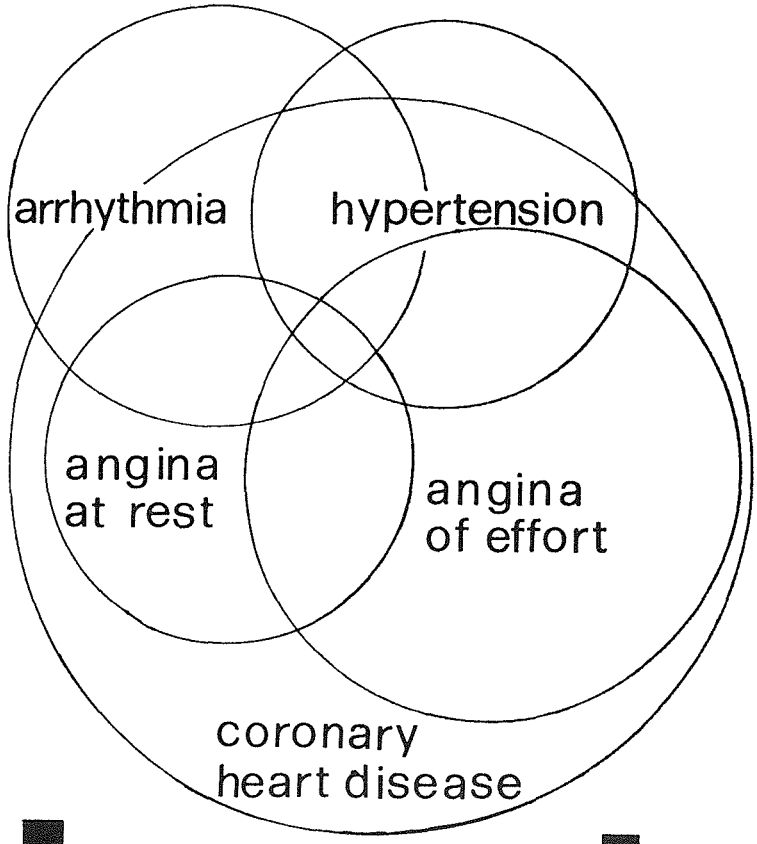


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system, the separation, identification and quantitation of minute amounts (nanograms or less) of drugs and their metabolites become relatively simple procedures.

Many examples of drug metabolism reactions involve stereoisomers (diastereoisomers or enantiomers) either as substrates or as products. The discrimination of isomeric subtrates is termed isomeric selectivity and the phenomenon is influenced by enzymatic factors as well as molecular properties. Since enantiomers differ only in their chiral properties (e.g., optical rotation, interaction with other chiral compounds) they are not resolvable by the usual chromatographic techniques.

### Analytical Methods in the Study of Stereoisomers

Prof. Bernard Testa's (School of Pharmacy, University of Lausanne, Switzerland) lecture on 'Analytical Methods in the Study of Stereoisomers' focussed on developments in the chromatographic discrimination of enantiomers using either chiral reagents or chiral phases. Reaction of enantiomers with an optically pure derivatization reagent leads to the formation of diastereoisomers which are separable by TLC, GLC, but emphasis was made on HPLC and its applications in the analysis of enantiomeric substrates and metabolites. Chiral bonded HPLC phases have been used for such separations.

### Use of Isolated Hepatocytes in Xenobiotic Metabolism Studies

W. Voelter (University of Tubingen, W. Germany), presented results after following the formation of metabolites from aminpyrine, 2-ethyl-3-(4-hydroxybenzyl) benzofuran, N-alkyl-substituted piperidiness, biphenyl and 3-(p-chlorophenyl)-1-phenyl pyrazole-4-acetic acid in different **in vitro** systems and **in vivo** experiments by HPLC. The metabolic pattern of these xenobiotics received upon incubation with a 10,000xg liver supernatent fraction, microsomes prepared by different methods and importantly hepatocytes, were compared with **in vivo** experiments of different species. The use of isolated hepatocytes was advocated, being relatively easy, and of low cost; it reduces animal experiments and circumvents trials in humans.

**(To be continued)**


### ACKNOWLEDGEMENTS

The author would like to thank Prof. V. Ferrito for making it possible for her to attend the conference and for his help, advice and hospitality during and after the sessions. A word of thanks to Drs P. Johnson, J. Gorrod and J. Caldwell for sparing some time in answering her queries.

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# *Labelling - Image of a Professionally Run Pharmacy*

**Maryann Ciappara B.Pharm., and Anthony Gatt B.Pharm.**

Labels were extensively employed in the not too distant past when the compounding of mixtures, powders, ointments and pills formed the day-to-day occupation of the pharmacist. The use of labels has gradually declined with the dispensing of mainly proprietary medicines.

Labels that are neatly written and carefully displayed on the container, and packages of proprietory medicines, strengthens the patient's confidence in the preparation and in the pharmacist.

The Medical and Kindred Profession Ordinance 16 Cap 51 of the Dispensaries (Licensing) Regulations 1984 which apply to the labelling of containers and packages of medicinal products state that:

1. All medicinals should be properly labelled.
2. For the purpose of this regulation proper labelling should include the expiry date, where in accordance with good pharmacy practice such date is indicated.

### Pharmacists Responsibility in Relation to Labelling

The patient or a distracted and worried parent or relative will remember very little of what he hears in a doctor's clinic or he may remember them incorrectly. Much advice given verbally by the pharmacist is soon forgotten. The patient needs to have the instruction in writing. By proper labelling the pharmacists can give the products they sell a unique added value in the form of advice.

### Advantages of Proper Labelling

— the writing of labels serves as an added check for the pharmacist
— gives more individual attention to each patient
— prevents confusion when the patient is receiving several medicaments
— no other record of the treatment may be available to a doctor called to see another doctor's patient
— encourages patient to understand his treatment
— increases patient complience.

**PROPER LABELLING**

1. Name of Preparation followed by the strength, form and the quantity of drug dispensed.
2. Directions for use.
3. Patient's name.
4. Prescription number.
5. Date on which medicine is dispensed.
6. Name and address of pharmacy.
7. Expiry date.
8. The route of administration in the case of pesseries, suppositories, nasal spray and drops.
9. If the product is an embrocation, liniment, lotion, liquid antiseptic or other liquid preparation or gel and is for external application, with the words "For External Use Only".
10. 'Keep out of reach of Children'. This was introduced in England in July 1979. This does not apply to medicinal products which are:
    i. in small containers or strip packs.
    ii. confectionary on a general sale list bearing no recommendation other than for coughs, colds or nasal congestion.
11. Storage conditions to ensure full potency throughout the period of treatment.
12. Warning of possible side effects.

### Source of Information about Drugs

The sources of information about drugs to the patient are many, yet many of these sources have their limitations. These sources include:—

1. Doctor
2. Other patients
3. Mass Media
4. Pharmacist
5. Labelling.

The most readily available source of information to the patient is the label on the container and package. Special instructions are necessary for individual preparations. (See Table 1).

## TABLE 1 — INSTRUCTIONS FOR INDIVIDUAL PREPARATIONS

| Instruction | Preparation |
|---|---|
| 1. May cause drowsiness (for children preparations) | e.g. antihistaminic syrups, cough syrup, diazepam syrup, amitryptyline syrup. |
| 2. May cause drowsiness — if affected do not drive or operate machinery, avoid alcoholic drink | e.g. antihistamines, sedatives, hypnotics, tricyclic antidepressants, some antihypertensives, codeine, some antiepileptics, some antiemetics, some muscle relaxants. |
| 3. Avoid alcohol | e.g. antidiabetic drugs, insulin, metroxidazole (due to flushing). |
| 4. Do not take antiacids at the same time as medicament. To be taken three hours apart | enteric coated tablets granule preparations, tetracyllines. |
| 5. Do not take iron preparation or milk at the same time as medicament. To be taken 2 hours apart | e.g. tetracyclines, penicillamine. |
| 6. Do **not** stop taking medicament unless advised by doctor | e.g. drugs whose therapeutic effect is slow e.g. antihypertensive drugs that if withdrawn may cause serious reactions e.g. steroids, heart preparations, beta-blockers, contraceptive pill, allupirinol, drugs that are immediately beneficial but the whole course has to be taken e.g. antibiotics. |
| 7. Avoid exposure of skin to light | e.g. amidarone, azopropazone, thiazides, frusemide, protryptilene, nalidixic acid, Moduretic. |
| 8. Avoid asperin preparation | e.g. anticoagulents, patients suffering from gastric ulcers. Uricosuric agents e.g. Probenic, sulphopyrazole. |
| 9. Dissolve or mix with water | Effervescent powders and tablets. |
| 10. Colouring of urine or faeces | Anthraquinons; phenolphtalein (e.g. Agarol, Alophen, senna); triamterene; levolopa, refampin, iron preparation; phenytoin, pyriduim, metronidazole. |
| 11. Keep away from flames | ether, alcohol, acetone; pharmaceutical aerosols. |
| 12. Dissolve under tongue. Discard eight weeks after opening | e.g. glyceryl trinitrate Angised). |
| 13. Do not take more than .... a day | e.g. drugs for treating migraine; anti-inflammatory drugs. |
| 14. To be taken with food | e.g. anti-inflammatory drugs, indomethacin, asperin, codeine; antiashmatics; iron preparations; pivampicillin, nitrofurantoin, griseofulyin. |
| 15. Take 1 hr. before food | ampicillin, erythromycin, tetracycline, nitronidazole; appetite supressants, enzyme preparations, antiacids, Peritrate; Persantin. |
| 16. To be sucked or chewed | e.g. antiseptic lozenges; antiacid tabs, Mintezol tabs; calcium gluconate. |
| 17. To be taken with plenty of water | e.g. in the elderly to avoid danger of tablets sticking in the oesaphagus; co-trimoxazole; methylcellulose. |
| 18. To be applied sparingly | e.g. steroid creams. |

It is not intended to write an essay on instructions on the dispensing container or package. However, writing one or two of these instructions will help the patient to comply better and can avoid serious consequences

Obviously writing some instructions on the dispensing container is time consuming and the introduction of a dispensing fee will then have more sense. No profession gives advices and time without financial return—pharmacy should not be an exception.


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# The importance of biochemical pharmacology in the interpretation of forensic toxicological analysis

**A. Serracino Inglott B.Pharm., D.Pharm., M. Zarb Adami B.Pharm. (Melit.), B.Pharm. (Lond.), M.R.S.H., D. Camilleri Novak B. Pharm., Ph.D.**

This paper was presented at the International Forensic Science Congress held at Oxford University in 1984.

Professor Francis Camps wound up the symposium on Forensic Toxicology held at the Chemical Defence Establishment, more than 10 years ago in 1972. Speaking on the future of forensic toxicology he said "This is easy: at the moment it has none". He made the proviso that Forensic Toxicology will have a future only if the basic knowledge of Physiology, Anatomy and Pharmacology is used to interpret the results of examination of autopsy specimens for drugs and poisons.

This paper presents some examples of how the interpretation of values of drug levels found in various compartments of the body requires an understanding of Pharmacology. In order to do this it is proposed to look at the following areas:—

a) the distribution of toxic substances in the body
b) individual variations
c) interactions
d) the possible significance of biochemical test

**Distribution of Drugs**

Toxic absorption of Digoxin resulting from a change in formulation sparked an interest in the phenomenon of bioavailability. Numerous studies have been carried out to find out how much of a particular drug is absorbed from various dosage forms. This involved the development of analytical procedures for the determination of drugs in low concentrations. Study of how the drug distributed in various body compartments in turn evolved into the science of Biopharmaceutics and Pharmacokinetics. This knowledge of the distribution of drugs can be important in the interpretation of forensic results.

For example a 22 year old tourist was taken to hospital in a coma but she was certified dead on arrival. Routine examination of the blood taken at autopsy revealed no toxic substances. However analysis of a liver sample yielded high concentrations of dextropropoxyphen. A bottle of 100 Distalgesic tablets dispensed to the patient on the previous day was later found empty among her personal effects. It was also later learnt that she had had a history of unsuccessful suicide attempts.

**LD50 in Humans!**

From blood level — time curves in animals one can determine the toxic level as well as the lethal level. The lethal level may be of more interest to the forensic scientist. These levels are influenced by the subject's individuality such as weight, age, sex, genetics and metabolism; drug interactions and tolerance could also change these levels. In the case of Theophylline the therapeutic level is 5ug/ml whereas the toxic level is 12ug/ml. In such a case can a forensic scientist decide that a patient has died from Theophylline overdosage if the blood level is say 20ug/ml? Questions often asked of a forensic scientist include:—

1) Was a drug or poison taken?
2) If yes, had the drug been used in that person for therapeutic purposes?
3) What was the dosage involved?
4) Can an estimate of the time of administration be given?

In clinical practice one might determine when a drug was administered from the biological half life of the drug. However in post mortem cases one often does not have sufficient details to give an interpretation of the results from a blood level determination. The problem that one has to consider is that the value for the lethal level cannot be fixed at a specific level for a particular drug. In other words one cannot fix the lethal level in a clear cut table for all drugs. In basic pharmacolgy an attempt was made to establish LD50. This in itself is limited as it only shows at what dose 50% of the animals are killed. One hopes of course that the day will not come when one could determine the LD50 for Humans! So the Forensic scientist has an added problem in comparison with the clinician in that controlled experiments on humans in the relevant dosage ranges cannot be carried out. It is difficult to relate in court the determined levels of a particular drug with the effect that those levels are likely to have had on the individual concerned.

**Individual Variations**

In the classical case of alcohol it is easy to say that a sample of blood had so many milligrams percent of alcohol. But it is much more difficult, if not impossible to answer such questions as "How much alcohol was drunk by the victim?", "When was it drunk?", "Was the victim in a state of intoxication?" As is well known this depends on a large number of factors including how tolerant the individual was, at what rate was it ingested, what were the stomach contents at the time of ingestion and so on; data which are usually not available to the Forensic Scientist. Has the victim had a massive haemorrhage? Has the individual been admitted to hospital and been given a large dose of I.V. fluilds? If the subject has been given medical treatment then this may well influence the interpretation of results. In fact there may be much to be said for the statement that the individual's ability to walk a straight line may be more relevant than GC results, if such a test can in fact be carried out on the individual.

Again, what is the lethal dose for Propranolol? Is the published figure of 10ug/DL in blood applicable to a patient who was previously suffering from bradycardia? Would it not be reasonable to suppose that in such a patient a much smaller dose would still be lethal? The same may be said for Digoxin in Hypokalaemia, for Tolbutamide in Hypoglycaemia and for Codeine, Morphine and Meperidine in the case of respiratory impairment.

It is worth considering the case of Trimethoprim and Theophylline. One could predict the dose from blood level standards on computer, provided that certain data are available, e.g. time when drug was taken. This hold well for Trimethoprim as there is little subject to subject variation. In the case of Theophylline per rectum the actual dose is not easily determined. This is due to the enormous subject to subject variation in rectal absorption. In fact in recent times it has become common practice that in order to keep a patient between the minimum effective concentration and the toxic level, the clinician "titrates" the necessary dose and schedule of administration for the particular patient by monitoring the blood level of the drug.

The factors which should alert the Forensic Scientist to possible problems in absorption include:—

a) a sparingly soluble drug used in large doses
b) long acting dosage forms
c) gastric contents or flora affect the drug
d) drug is absorbed by active transport
e) different formulations and dosage forms

**Drug Metabolites**

Another important aspect in Forensic Toxicological investigations is the question of drug metabolites. Beckett states that "the biological activity of a drug is frequently the result of a complex series of reactions involving both metabolites and the parent drug". Consequently in order to determine the toxic effects of a drug which could lead to lethal consequences, it is essential to have an understanding of:—

1) the metabolic routes involved in the change of drugs in the body
2) the physico-chemical and biological properties of the metabolites

The lack of stability of the metabolites in biological fluids especially in post mortem samples leads to great difficulties especially when quantitative analysis is required. In addition analytical artifacts could further complicate matters. On the other hand, a knowledge of the rate constants involved in the metabolic process together with a quantitative determination of metabolites could be of great value when interpreting results. Was the Victim under the influence of drugs during an accident? An evaluation of metabolites could assist in answering such a question. The amount of normeperidine in meperidine overdosage could help to show when the drug was taken.

In a recent murder case in Malta, the accused pleaded possible mental influence from lead poisoning. The accused was a lead worker. The Court ordered the examination of the accused in order to examine this plea. It is to be borne in mind that a toxic lead level at the time of examination does not necessarily imply that the same was the case at the time of commission of the crime. This is a case where the toxicology of lead presents difficulties. In such a case one has to determine lead values as well as consider the biochemical effects of lead, for example, the effect of lead on the biosynthetic pathway of haem. Delta amino laevulinic acid synthetase (d-ALA synthetase), delta aminolaevulinic acid dehydrogenase (d-ALA dehydrogenase) and haem synthetase are inhibited by lead. This leads to increased urinary excretion of D-ALA, coproporphyrin and sometime porphobilinogen and the accumulation of protoporphyrins in erythrocytes. Only the presence of these abnormalities points to slow lead poisoning over a period of time.

**Biochemical Tests**

It is interesting to see how the forensic scientist could use other biochemical data as signs of toxicity. A number of drugs can alter the normal values of biochemical substances and detecting the presence of such abnormalities will alert the investigator to look into the possibility of the presence of the drugs that cause them.

Examples of drugs altering Blood Urea Nitrogen and Serum transaminases and Phosphatases are given in the tables 1 and 2.

**Table 1 — DRUGS EFFECTING SERUM TRANSAMINASES AND PHOSPHATASES**

| | |
|---|---|
| Cabamazepine | Nicotinic acid |
| Methyldopa | Oral contraceptives |
| Tricyclic antidepressants | Papaverine |
| | Sulphonamides |

**Table 2 — DRUGS AFFECTING BLOOD UREA NITROGEN**

a) drugs changing protein metabolism
   i) anabolic: Thyroid, insulin Testosterone
   ii) catabolic: corticosteroids
b) drugs acting directly on kidney aminoglycosides and tetracyclines methoxyfluorane (autopsy revealed calcium oxalate crystals in renal tubles) diuretics

If postmortem studies are to be carried out to examine the effects of drugs on biochemical tests such as blood urea nitrogen (BUN) and serum transaminases and phosphatases, the effect of death itself on the normal values given by these biochemical tests must first be studied. A blood sample was taken from a rabbit and the BUN and VMA were determined. The rabbit was sacrificed and the blood samples taken at fifteen minute intervals from the time of death were analysed. No significant changes were observed up to three hours after death.

A number of drugs are known to increase VMA levels following administration. This may be useful both from the point of view of colloborating other evidence as well as a possible indicator of drugs to be looked for. It is difficult for example to establish death due to excessive isoprenaline in halation from the toxicological point of view. A patient found dead with two empty medihaler-iso by his bedside was shown to have a high value of VMA. This corroborated the evidence that a high dose of isoprenaline had been inhaled since increase in the VMA level is usually small when small doses are administered but may increase significantly with large doses. If a high VMA level is found it may be worth the effort to look for Insulin. Although the increase is not so large as to indicate Phaeochromocytoma, it is statistically significant.

The level of a xenobiotic in an organ and its relation to toxicity may differ from person to person, especially in cases of tolerance or genetic variation. In determining the cause of death, it would be of interest to the forensic scientist if a method could be found to establish whether the person had developed tolerance to the drug found in his body. Using a number of mice, it can be shown that mice which developed tolerance to morphine had higher concentrations of calcium in the brain than those which were given morphine for the first time.

**The Interpretation of Laboratory Results**

It is true that a routine analysis can never be replaced in Toxicolgy. The literature gives many examples of cases where there was no clue to the possible toxic substance present if any, and where the routine analysis lead to significant discoveries. However in some cases, the victims symptom's and history much be ascertained because a careful analysis of these may point towards looking for a specific poison or class of poisons. The absolute level of a drug found in a body fluid can be of very limited value if considered in isolation. What is of significance is the likely effect that such a level of drug would have had on the behaviour or physiological reaction of the particular individual. In a number of cases it is not easy to state unequivocally whether a level of a drug in a biological fluid is lethal, toxic or in the therapeutic range. This is the grey area where the interpretation of laboratory results is what really matters. This is the area which requires a good knowledge of physiology and pharmacology.

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# PHARMACISTS OF OLD

CHEV. J. BORG, K.M., Ph.C., L.P., F.R.S.H., F.I.N.T.Pet.

126. Pharmacist Vincent (Ċensinu) Caruana from Żejtun, where he was born in 1900. He obtained the warrant to practise the pharmaceutical profession on 20th September 1922 and opened his "Perellos Pharmacy" at "Casa Perellos" where he lived at Żejtun, but died very young aged 27 on the 17th March 1927. His brothers were the late Dr Anton Caruana, LL.D. (1916) who died on 3.1.1976 and Dr Joseph Caruana, B.Sc. (1918), M.D. (1922).
127. Dr Blanche V. Caruana neé Huber, who was born at Sliema in 1901, obtained the Pharmaceutical Diploma in 1921 and graduated M.D. in 1925. When she married Dr Joseph Caruana, B.Sc., M.D., whose Pharmacist younger brother Ċensinu died in 1927, she took the management of his "Perellos Pharmacy" in August 1927, and which she later transferred to No. 54, now No. 71, St Catherine Street, Żejtun as "casa-bottega". She died on 19th July 1942. There is a street named after her at Sliema.
128. Pharmacist Luigi Cutajar, from Rabat, who obtained his Pharmaceutical Diploma in 1927 and managed his father's pharmacy at No. 40, High Street, Rabat, after the death of the latter.
129. Pharmacist Carmelo Vassallo (see No. 79 of former list, cf. "The Pharmacist" No. 5 of January 1983), from Żebbuġ — Malta, where he was born on 6.5.1905 son of Mr Carmelo, Inspector of Schools and his wife Mary-Vincenza neé Psaila. He obtained his Ph.C. Diploma in 1927. He married Miss Giorgina Anastasi on 15.2.1930. He was employed at a private pharmacy in Floriana, then in 1937 entered the Government Service as Pharmacist at Central Civil Hospital Pharmacy and then as Analyst at the Customs Department Laboratory in 1944, whence he was pensioned in 1960 and died aged 65 years on 6th August 1970.
130. Pharmacist Carmelo Ellul, from Cospicua, who obtained his Pharmaceutical Diploma in 1927, managed "The English Pharmacy" at his native city and died aged 57 years in 1938.
131. Pharmacist Eric Carmel Mizzi, from Sliema. He made his Pharmaceutical studies at Modena — Italy and obtained his warrant in 1929. When he moved to Żabbar he opened here his "St Mary's Pharmacy" which was later named "Mizzi's Pharmacy". Mr Mizzi used to import several medicines especially from Italy, and during the last years of his life he served even as a member of the Pharmacy Board and as an examiner of the Assistant-Apothecaries' examination. He died aged 74 years on the 3rd September, 1980.
132. Pharmacist Joseph Gerard Debono, from Victoria — Gozo, was born on the 16th July, 1908. He obtained his Pharmaceutical diploma in 1930 and managed consecutively a pharmacy at Cospicua, "Pasteur Pharmacy" at Qormi so-named after that great microbiologist Louis Pasteur (1822-1895), the "Royal Pharmacy" of Republic Street — Valletta and lastly "Spinola Pharmacy" at St Julian's. He so much loved science subjects that he attended the appropriate course at the University whence he graduated B.Sc. in 1940. He died aged 61 years on the 20th August, 1969.
133. Professor Joseph John Mangion, M.D. (1934), B.Sc. (1931), Ph.C. (1930), D.D.S. (1940), F.D.S. R.C.S. (1948), born at Floriana on the 10th February, 1909. He was consecutively employed as Assistant-Resident Medical Officer at the Central Civil Hospital-Floriana (1934-1940), Medical Superintendent of same (1940-1945), Junior Dental Surgeon (1940-1954), Lecturer in Dentistry (1948-1954) and Professor of Dental Surgery (1954-1969). He run his own Dental Clinic at No. 156, Strait Street, Valletta. He had worked as Pharmacist during 1930-1934 at the "Floriana Dispensary" in No. 23, St Anne Street — Floriana. Professor Mangion died aged 71 years on the 1st November, 1980.
134. Pharmacist William Woodcock, who obtained his M.P.S. from London and who was employed during the 1930's at "Collis and Williams Dispensary" branch of No. 13 Sliema Wharf, Sliema but soon after at the "Junior Army and Navy Stores" of Strada Reale, now Republic Street, Valletta.
135. Professor Oscar Zammit, Ph.C. (1933), B.Sc. (1934), M.Sc. (L.pool), M.D. (1940), F.R.C.O.G., born on 7.12.1911, son of Mr

Vincent and his wife Maria-Stella neé Vella. When he became a Pharmacist he was employed as Managing Apothecary for three years (1934-1937) and during the summer months of those of (1938-1939) at Dr Sacco's "Marsa Pharmacy" at Marsa Cross Road, Marsa. He married his fellow student and Pharmacist Mary Zammit, Ph.C. (1933) of Vittoriosa on 19.10.1941 and they have two sons: Francois L. born on 17.8.1942 an Executive Civil Servant at the Labour Department and Etienne (sive Stephen) born on 13.4.1945 and is a Bank of Valletta official. Pharmacist Oscar was then employed as a Lecturer in Biology at the University and concurrently as Scientific Official in the Agricultural and Fisheries Department from 11.9.1939. He was later appointed Professor of Obstetrics and Gynaecology at the University from 1952 and Senior Accoucheur from 1.1.1954 at the Central Civil Hospital and died just over 51 years old on the 6.5.1963.

136. Pharmacist Mary Caruana, B.Sc., from Valletta was born on the 2nd April 1914. She obtained her Pharmaceutical diploma in 1933 and the B.Sc. degree in 1934. She was employed as Managing Apothecary of the "Central Pharmacy" of Republic Street — Valletta, but on 16th January 1958 she entered Government Service as a Family Welfare Officer. She also served as General Secretary of the Malta Catholic Action and was awarded the decoration P.E.P. (Pro Ecclesia et Pontifice — for services done in favour of the Church and of the Pope) on the 24th July, 1972. Her brother is Dr Salvino, M.D. (1943), Ph.C. (1936), B.Sc. (1937), who now lives abroad. She died aged 65 years on the 4th March, 1980.
137. Pharmacist Aldo Cherubino, born in Malta, the son of Italian parents who had settled here at No. 64, Old Mint Street — Valletta as the chief pharmaceuticals' importers from Italy under the trade and proper name "Ciro Cherubino". Aldo pursued his studies at Pisa University whence he was "Laureato in chimica e farmacia" in 1934. As far as I know he never managed any pharmacy but his chief concern was the importation of medicaments from Italy and to a much lesser extent also from England and from France. He died aged 65 years on the 16th October 1975 in Italy.
138. Pharmacist Carmelo Debono, from Mellieha, obtained the Governor's warrant to practise Pharmacy in 1936, when he soon set-up and managed his "Debono's Pharmacy" at No. 31D, Broad Street, Hamrun, later bought by our friend Pharmacist John Holland.
139. Pharmacist Henry Benjamin Formosa, who was born at Sliema on 18th August 1910. He obtained his diploma in 1936 and exercised his profession from that year up to 1941 when he was employed as a Civil Servant with the Government serving at one time as Research-Assistant and Cataloguer at the Public Library — Valletta (1956-1962). He served also as member of the Labour Party Executive Committee (1952-1957). In 1966 he wrote about a list of local murders in "The Sunday Times of Malta", and left unpublished a "Dictionary of Maltese National Biography including foreigners connected with Malta, or who died and are buried in Malta" which he compiled in 1958. He died aged 62 years on the 14th December, 1972.
140. Pharmacist John Raimondo, B.Sc., from Kalkara, who obtained his diploma in 1937. He managed "La Ripa Dispensary" at Kalkara. After attending a post-graduate course in Science at Manchester University he was appointed Practical Demonstartor i in Pharmaceutics at the University. He even entered politics on the side of the Labour Party and was elected to Parliament on the 13th November, 1945 but resigned "en bloc" with his other eight colleagues on the 12th September, 1946. He died on the 4th February, 1963. The new street off St Lawrence Street, Kalkara was named after him as per Notice No. 298 in the Malta Government Gazette of 27th May, 1983. (Photo page 31).
141. Dr Salvino Debono, M.D., B.Sc., Ph.C. (1939), from Vitcoria — Gozo where he was born on 4th November, 1914. He was employed as District Medical Officer first at Nadur — Gozo and later at St Julian's — Malta. He was pensioned on 26th August, 1970. Hence he acquired the "Strand Pharmacy" at the Ferries' Esplanade — Sliema first managed by his daughter Pharmacist Mary-Josette (married to Dr Joseph Degiovanni, M.D.) and later on as from the 24th February, 1971 by himself. He died aged 66 years on the 23rd November, 1980.
142. Pharmacist Salvino M. Xuereb, B.Sc., from Hamrun where he was born on the 21st March, 1910. Soon after becoming a Pharmacist in 1939 he was selected Demonstra-

**The nine elected Labour members of the Council of Government in 1945 with their guest of honour the British Lady Labour Minister of Education: (left to right, front row: Mr Dom Mintoff, Dr Paul Boffa, Dr Arthur Colombo, Dr Joseph Cassar and Mr Karmenu Vassallo; back row: Mr Robert Bencini, Dr Godwin George Ganada and Pharmacist John Raimondo).**

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tor of Practical Pharmacognosy at the University in 1941. He practised his profession in various community pharmacies: lastly at the "Economical British Dispensary" formerly in front of "Stella Maris"' Parish Church — Sliema. He was promoted Lyceum Head-Master at Gozo on the 17th December, 1962. He died aged 48 years on the 9th January, 1967.

143. Pharmacist Alfredo Pace of No. 106, High Street, Sliema. He was one of the University Students' Military Company established in 1941 during World War II and indeed a cadet. He was married to Miss Doris nee' Azzopardi. He did not manage any pharmacy but co-owned and jointly run with his brother Dr Tony LL.D. the "Mayfair Shoe Store" of "Kingsway Palace" in Republic Street, Valletta. He died on the 3rd September, 1981.
144. Pharmacist Salvino Degabriele, L.P. from Senglea, who obtained his Pharmaceutical and Legal Procurator's diplomas in 1942 and 1943 respectively exactly as myself and our confrere Wilfred Gatt of Sliema, as formerly had Augustine Levanzin (Vol. 5, No. 51), Joseph-Mary Borg of Lija and Nicola Spiteri of Qormi both mentioned in present list, and later our other confreres Major Joseph-M. Galea of Paceville and Aldo Camilleri of "Ta' Xbiex". Salvino usually worked as medical representative for Ciba pharmaceuticals. He died rather young aged 51 years on the 20th May, 1972.
145. Pharmacist Margaret Caruana Montaldo, B.Sc. She obtained her Pharmaceutical diploma in 1945. The Lord called her young because she passed to eternal life aged 42 years on the 22nd March, 1969. Both her sisters are fellow-Pharmacists: Miriam (Ph.C., 1948) and Antoinette (B.Pharm, 1952).
146. Pharmacist Charles N. Lanzon, from Sliema, who obtained his M.P.S. qualification from the Pharmaceutical Society of London in 1949. He managed a pharmacy in his native Sliema: the "Brown's Pharmacy" of No. 70, Tigne' Street until his rather early death on the 8th August, 1968 at the age of 56 years.
147. Pharmacist Joseph Tabone, "Peppi" to his relatives and fellow-Pharmacists, from Cospicua where he was born on 14.5.1928 son of Mr Leone and his wife Victoria neé Licari and brother of Dr Anton, Ph.C.

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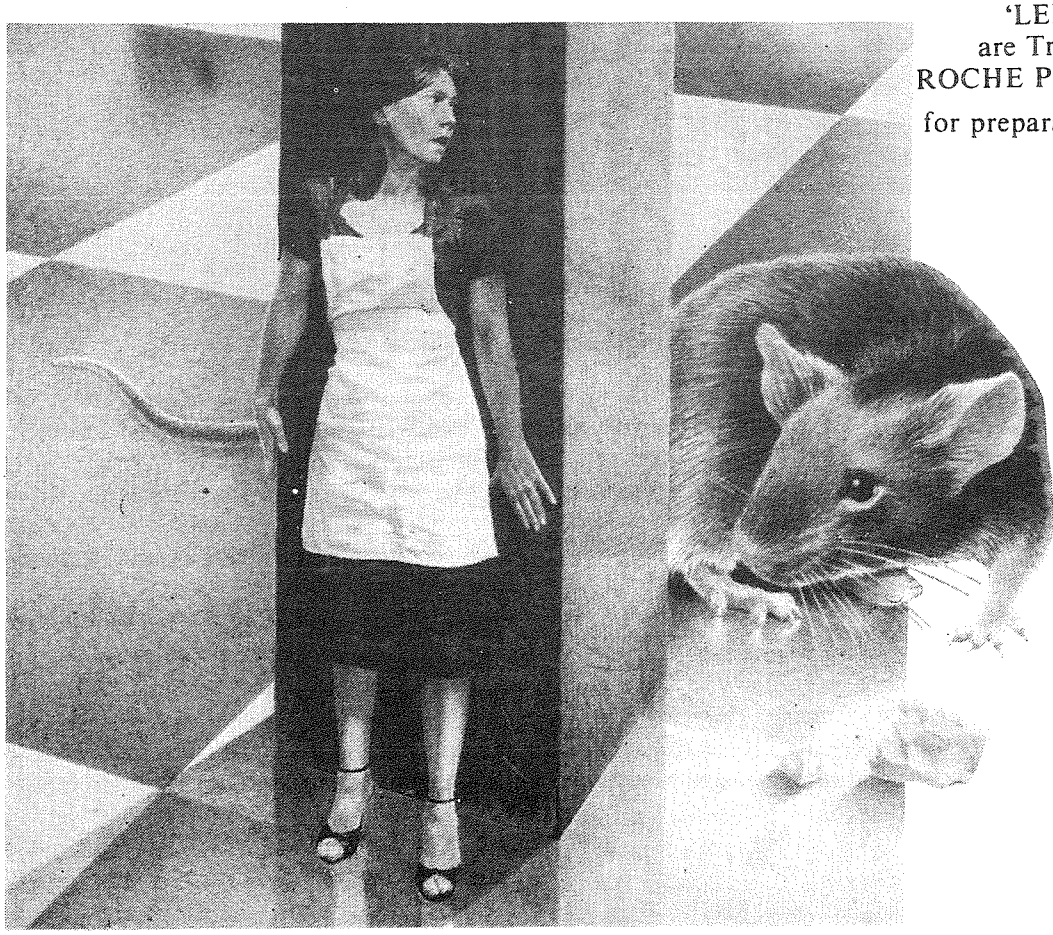

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**PHARMACISTS' DINNER AT "ROYAL HOTEL" — ATTARD ON 11.12.1950**

**1st row seated on steps: Anthony Bonello, Robert Aldo Tua, Queenie Gatt neé Gatt, Dr Oliver Azzopardi, B.Sc., M.D., D.R.C.O.G., Hilda Fenech neé Vella, Emmanuel Attard Bezzina, Chev. Oscar Vella, K.S.S., Eric C. Mizzi, Ondina V. Tayar and John B. Cassar;**

**2nd row standing: Joseph Ellul Castaldi, Joseph Gerard Debono, Joseph Debono, (seated: Dr Emmanuel Mizzi, LL.D., — Legal Adviser, Joseph Vassallo — President and Arther Mizzi — Secretary), Chev. Joseph Borg, K.M., L.P. and Angela Catania neé Frendo;**

**3rd row standing: Archangelo Agius, William Edward Felice, George Borg Barthet, Antoine Debono, Gaetano Farrugia, Ferdinand Felice, B.Sc., Lewis Anthony Wismayer, John Mifsud, Wilfred Gatt, L.P., Joseph Deguara, B.Sc., Lucy Portelli neé Demajo and Dr Joseph Portelli, M.D.**

(1948), M.D. (1952) and Capuchin Fathers now Missionaries in Kenya, Leopoldo ex-Parish Priest of "Our Lady of Lourdes" church at San Ġwann (21.1.1965 — 2.7.1983) and Krispin, ex-Provincial (15.7.1980 — 2.7.1983). He obtained his B.Pharm in 1953 and married Miss Antoinette née Muscat on 9.6.1966. He owned and managed "Martin's Pharmacy" at Birżebbuġa. He died aged nearly 56 years old on 26.4.1984.

148. Pharmacist George Galea, from Victoria — Gozo. He obtained his B.Pharm. degree in 1956. As far as I know he did not manage any pharmacy neither in Gozo nor in Malta. He entered politics with the Nationalist Party and was elected Member of Parliament in the 1962 elections and died in harness, so-to-say, after only 1½ years on the 5th July, 1963 at the very young age of 32 years. His brother is Dr Salvino, M.D., B.Pharm. (1955).

The Latins used to say "Finis coronat opus" — the fact that something begun is carried out to its end constitutes a satisfaction to its doer, or less poetically as we Maltese say "Kull bidu għandu t-tmiem" — every beginning has its end.

In conclusion, while saying that there were others of more than a century ago whose names are not known to me because I never read them anywhere, and not excluding that there may be some small mistakes or lack of information about some of those I am presently writing about, let me salute all our departed fellow PHARMACISTS and wish them ALL that much hoped-for better life in the eternal beatific sight of Our Most Blessed, Almight and Most Loving LORD and FATHER "Quod est in votis". Amen.

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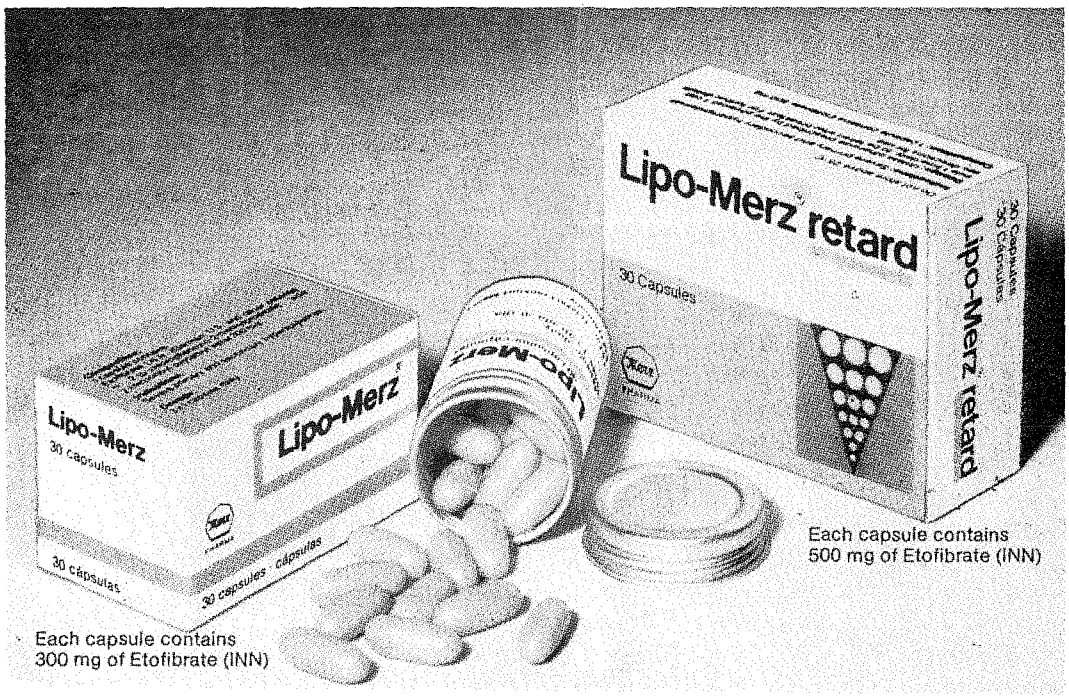


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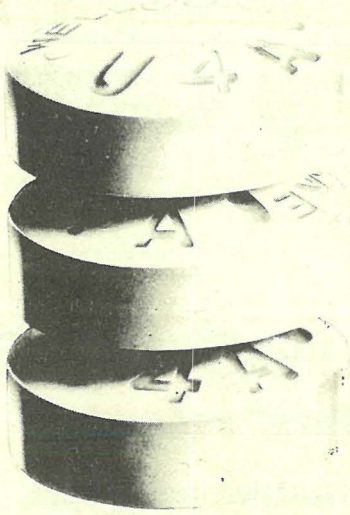

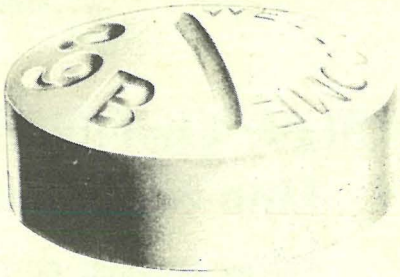

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