ICI Pharmaceuticals Division

Medical Products

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Products

A review of their properties, indications and method of use

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Introduction

This booklet is intended as a concise guide to the range of ICI medical specialities and to the past, present and future activities of ICI Pharmaceuticals Division. Although the information on each product is generally sufficient for prescribing purposes, it is not intended as a substitute for more detailed literature which is available on request. The availability of some of the products, presentations and packs listed varies from area to area, as does the registration of some indications — particularly for the newer products listed. If in any doubt please consult our nearest associated company, branch office or agent.

We hope you find this publication useful, but any suggestions for its improvement will be greatly appreciated and acknowledged.

A Survey of Progress

About ICI

It will soon be apparent to the reader of this handbook that ICI Medical Products cover a remarkably wide range. They include representatives of many pharmacological groups of drugs. There are few branches of medicine or surgery in which they do not play useful and often prominent roles. And there are few places in the medical world to which recognition of their value and reliability has not already penetrated.

What kind of organisation has developed such a range of products? Achievement in the pharmaceutical industry is often associated with long traditions; many leading companies are justifiably proud of a lineage originating before the middle of the last century. But the history of ICI shows that such deep roots are by no means essential to success. For this, now one of the largest chemical companies in the world, was only founded in 1926 by the amalgamation of four British companies with interests in the alkali, dyestuffs, explosives and heavy chemicals industries.

Sustained and broad-based research, together with accumulated expertise, fostered technological innovation and widening interests so that today large semi-autonomous Divisions of ICI are devoted — to a diverse range of interests including agriculture, plastics, petrochemicals, fibres, general chemicals, paints, dyes — and pharmaceuticals.

Traditions are still comparatively short in ICI. But what is lacking in years only adds greater emphasis to some outstanding records of achievement. And this is particularly so in the Pharmaceuticals Division, one of the youngest but most successful of all the progeny of Imperial Chemical Industries Limited.

Birth of an industry

ICI Pharmaceuticals Division had its origins in a small but very active 'medicinal chemistry' team in the then Dyestuffs (now Organics) Division. This small group, inspired by the revolution in the chemotherapy of infection brought about by work on the sulphonamides during the 1930's, went on to synthesise 'Sulphamezathine' — regarded for many years as the best drug of this group for routine use. But other problems were demanding attention. During World War 2, shortage of quinine prompted a search for synthetic antimalarials, and resulted in the development of 'Paludrine' — still in use wherever malaria is endemic. Further work in this field led to 'Hibitane', a direct descendant of 'Paludrine', and excellent testimony to the value of careful screening of new compounds, for 'Hibitane' is not an antimalarial but one of the most useful topical antibacterials so far produced. In a completely different area of medicine, the development of 'Mysoline' yielded an effective anticonvulsant to protect thousands of epileptic patients against attacks and enable them to live more normal lives.

It was with these valuable contributions already to its credit that ICI Pharmaceuticals Division moved into its new Research Laboratories in Alderley Park in 1957.

The tip of an iceberg

It is a popular misconception that pharmaceutical research is the random synthesis of new organic compounds in the hope that the subsequent screening will reveal some item of therapeutic value. It is true that at Alderley Park several thousand new compounds are synthesised annually — but this is carried out according to carefully planned programmes suggested by existing knowledge. Clues are followed up, particularly in defined areas — such as cardiovascular disease and mental illness — where there are large therapeutic gaps.

For instance, the clue provided by dichloroisoprenaline, the first but clinically useless beta-adrenergic blocking agent, led to the synthesis of many congeners of this compound at Alderley Park.

ICI are world leaders in this new field of therapy and have made outstanding contributions to the modern treatment of several cardiovascular diseases, including hypertension, angina pectoris and a wide range of cardiac dysrhythmias.

Pointers in the quest for the structure-activity relationship, which facilitates the molecular manipulations leading to useful new compounds, can come from many sources. Sometimes fundamental research in biology or physiology is the stimulus and, in other instances, it may be a property of some natural animal or plant substance that triggers off the whole complex sequence that leads to a new drug. Very occasionally, serendipity — sheer good fortune — combined with constant vigilance, plays its part.

If it does prove possible to break the code of the structure-activity relationship of a group of compounds, further systematic molecular rearrangement may give the pharmacologists the properties they are seeking — and a new drug is born.

Below the surface

If organic synthesis and pharmacology are the more spectacular aspects of pharmaceutical research, a vast number of less well known but nevertheless essential activities are required to keep them afloat. In Alderley Park, fundamental research is carried out in Biology and Biochemistry in important areas such as parasitology, cardiovascular function, mechanisms in the central nervous system, the processes of allergy and inflammation, and the pathology of thrombosis. Physical Chemistry also plays its part in the investigation of molecular structure, and computers and advanced instrumentation are used in mass spectrometry, determination of nuclear magnetic resonance, microanalysis and spectroscopy. Computer systems are also used for storing details of 3-dimensional chemical structures and this 'Crossbow' technology gives comprehensive search facilities by whole molecular structure, fragments, or by atom-by-atom combination.

Information is clearly of major importance in the organisation, and the library, with its 23,000 books, also subscribes to more than 1,100 journals in several languages, while a specialised team of information scientists provide an efficient abstracting and documentation service.

Laboratory animals are essential to the biologist and pharmacologist, and the Breeding Unit at Alderley Park supplies 600,000 genetically sound, artificially reared, bacteriologically clean, disease-free animals every year. The Media Service provides 200 different types of biological media as well as 100,000 thin layer chromatography plates every year.

Operations of this magnitude involve a bewildering amount of glassware — and a correspondingly formidable washing up problem, but this is taken in its stride by a highly mechanised glass-washing service which handles 5 million pieces during the course of each year.

Research in perspective

All this activity takes place in some of the best equipped laboratories in the world, in a sylvan setting of some 150 hectares (360 acres) in mid-Cheshire. In these ideal surroundings, in an optimistic and vigorous atmosphere more like that of a university campus, some 40 per cent of the Division's employees are effectively involved in the research effort. One in five of them is of graduate or equivalent status, from a wide variety of disciplines, and bringing to the Company a diversity of skills and talents.

The cost of all this effort is high. Some £2 million is spent every year on materials alone. And the total investment in its Pharmaceuticals research programme by the ICI Group is currently of the order of £15 million per annum.

The final product

It is one thing to prepare a new drug on a small laboratory scale but quite another to transform the process into one that will operate safely and economically for production purposes. This is a science unto itself. Ideal formulations have to be considered — in conjunction with the medical advisers who are conducting clinical trials. Problems involving long-term stability, compatibilities, flavours, colours, packings, and many other matters have to be painstakingly resolved in order to maintain the reputation for pharmaceutical excellence of which the Division is justifiably proud.

The Division has its main pharmaceutical factory in Macclesfield near its research establishment. This factory has been designed to achieve maximum efficiency and economy in the large-scale production of the entire range — from basic materials to finished ICI Pharmaceutical Products. Complete factories or pharmaceutical processing facilities, in over 40 of the 130 countries supplied by the Division, provide a production system designed to meet world needs.

Rigorous testing at every stage in manufacture and processing ensures that the highest standards of quality and reliability are maintained. Doctors and patients can be certain that whenever these products are prescribed they will bring the full benefits of ICI's great contribution to pharmaceutical research.

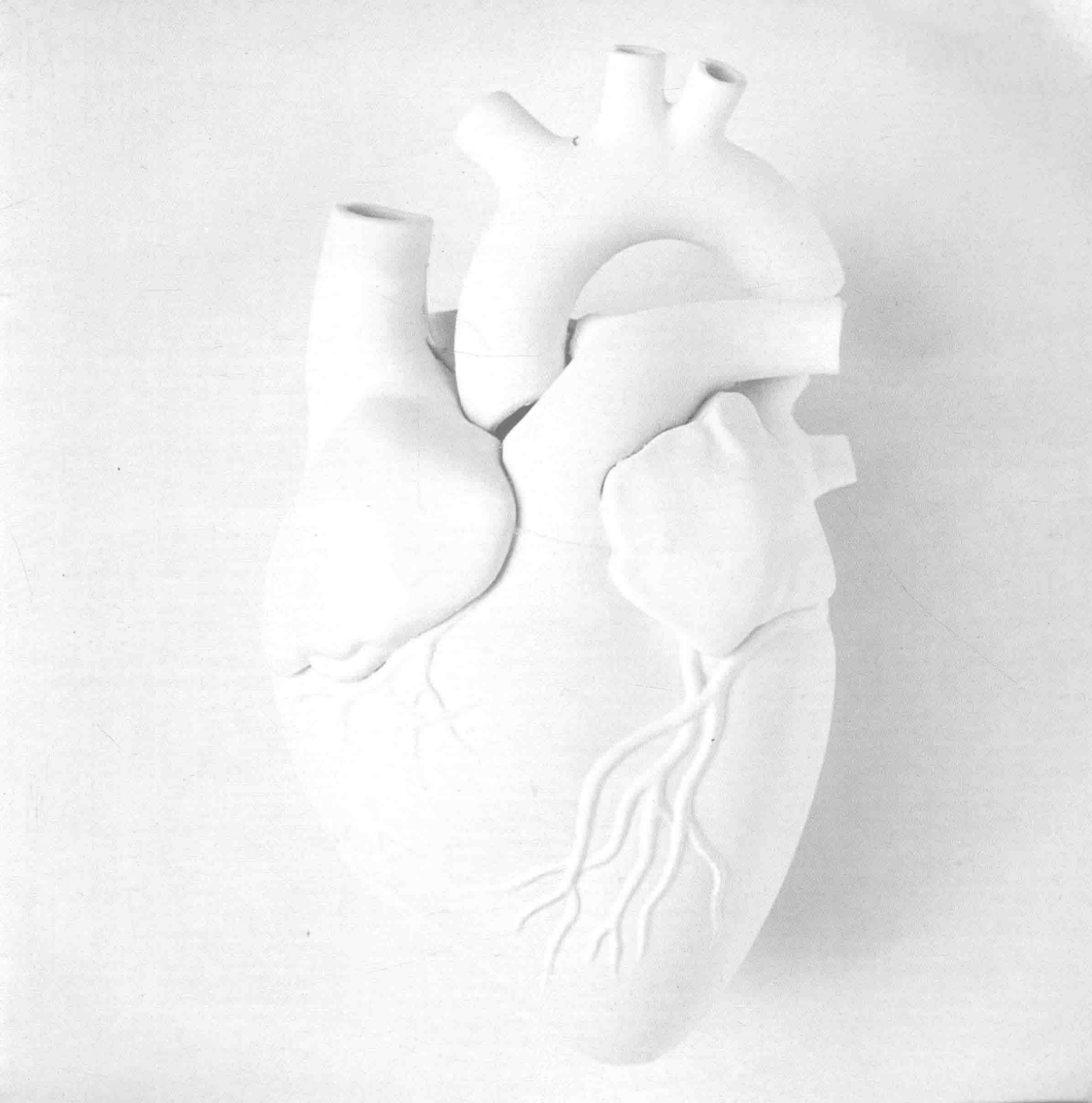
Cardiovascular Disease

In the U.K. six people die from coronary heart disease every hour. In the U.S.A. the situation is equally grave, one person dying every three minutes. What can be done to curtail this appalling death rate? Among research findings has been the fact that the early recognition of atherosclerosis has a vital bearing on coronary heart pathology.

For some time it has been known that abnormal lipoprotein patterns occur in the early stages of the disease. It is fortunate that they are easily detectable, for they represent a threefold increase in risk. It is encouraging too that in four out of the five groups of hyperlipoproteinaemias the ICI discovery 'Atromid'-S helps correct these abnormalities in a predictable and safe manner. By reducing hyperlipidaemia, therefore, and returning to normal thrombogenic abnormalities, 'Atromid'-S, an exceptionally well-tolerated drug, is making a major contribution to the long-term management of ischaemic heart disease.

Other important progress has been made in the treatment of cardiovascular disease. 'Inderal', for example, is of great value in the management of hypertension. It reduces blood pressure smoothly, gradually and as effectively as other major anti-hypertensive agents. Owing to its extremely specific and precise action on the sympathetic nervous system however, it is devoid of the adverse effects commonly encountered with other treatments. 'Inderal' does not cause postural or exercise hypotension, spares sexual function and enables the patient to pursue more normal activities.

In the management of angina pectoris 'Inderal' pioneered a new approach and today at least a million patients every day obtain the benefits of 'Inderal' therapy. The myocardium is protected against excessive sympathetic stimulation, performs less work and needs less oxygen. The available oxygen supply therefore goes further, the patient has fewer and less severe attacks of angina and exercise capacity is also increased.



Atromid-S

Clofibrate B.P.

antilipaemic agent

Indications

Where abnormal lipid patterns are observed such as:–
(i) Hypercholesterolaemia (Fredrickson Type IIa)
(ii) Hypertriglyceridaemia (Fredrickson Types IV and V).
(iii) Mixed hyperlipidaemias (Fredrickson Types IIb and III).

In hyperlipidaemia associated with diabetes.

In exudative diabetic retinopathy.

In the treatment of xanthomata which are frequently associated with hyperlipidaemia.

In patients with angina irrespective of their lipid levels (where patients have suffered a myocardial infarction 'Atromid'–S has not been shown to influence subsequent infarction rates).

Where fibrinogen levels are chronically raised in association with atherosclerosis.

'Atromid'–S has a marked and sustained lowering effect on elevated lipids and chronically elevated fibrinogen levels. (However, the drug does not reduce the acute rise in fibrinogen which follows severe trauma, e.g. infarction, major surgery or infection, and is not indicated for this purpose).

'Atromid'–S has been shown to reduce platelet stickiness and to prolong platelet survival time.

'Atromid'–S has been used continuously for periods exceeding ten years and in this time has been shown to be remarkably free from side effects.

Lipid and Fibrinogen Estimation
A useful aid to the estimation of plasma lipoprotein and fibrinogen levels has been the development of the Thorp Micro-Nephelometer. With this highly accurate, but simple-to-use instrument, biochemical estimations can be carried out in a fraction of the time taken by conventional methods.

Administration and Dosage

Three or four capsules daily divided into two or more doses taken after food.

Contraindications and Special Precautions

It is considered inadvisable, on theoretical grounds, to give 'Atromid'–S to patients during pregnancy or to patients who present with renal or hepatic dysfunction.

Patients taking anticoagulants concurrently with 'Atromid'–S should have the dose of their anticoagulant halved and adjusted later as necessary.

In patients with low serum albumin levels, for example in nephrotic syndrome, high levels of unbound drugs may give rise to myalgia with raised serum creatinine phosphokinase levels. Caution is advised in treating such patients.

Side Effects

The outstanding safety of 'Atromid'–S has been demonstrated by its widespread use extending over 12 years. Side effects are seldom seen but include transient slight upper abdominal discomfort, nausea and looseness of the bowels. It is usually unnecessary to discontinue treatment. Very occasionally myalgia has been reported (see Contraindications and Special Precautions above).

Liver Function: At therapeutic doses 'Atromid'–S does not enter the liver cell. In some cases slight and usually transient increases in serum transaminase levels have been observed. It is considered that these reflect adaptive responses of the liver. In large, long-term studies, even transient increases in transaminase levels have seldom been reported. 'Atromid'–S has not been shown to affect serum bilirubin or bromosulphthalein tests.

Experimental studies confirm clinical observations. The liver weight gain found in rats, dogs and monkeys probably represents an adaptive response of the liver and increased protein synthesis.

Due to its action on cholesterol metabolism, 'Atromid'–S may increase the lithogenicity of bile and there have been isolated reports of a slightly increased incidence of gallstones.

Cardiovascular System: There has been a published report of ventricular arrhythmia associated with 'Atromid'–S treatment. However, the patient had an unstable rhythm prior to treatment. One study in post-infarction patients showed an increase in some cardiovascular events; these were non-fatal and have not been confirmed in any other long-term studies.

Blood: 'Atromid'–S normally has no effect on the blood picture. Isolated cases of adverse effects include slight fluctuations in haemoglobin values and occasional reduction in white cell counts. There is no evidence of marrow toxicity but one case of agranulocytosis has been reported in a patient undergoing multiple drug therapy which included 'Atromid'–S.

No special measures are indicated in the treatment of overdosage – treatment should be symptomatic.

Presentation and Packings

Soft gelatin capsules containing clofibrate 500 mg in containers of 50, 100 and 500. The capsules should be kept in a closed container protected from heat.

Inderal

Propranolol Hydrochloride B.P.

antihypertensive
anxiolytic
antianginal
antidysrhythmic
migraine prophylactic
anti-tremor

Indications

Control of essential and renal hypertension.

Control of anxiety, and anxiety tachycardia.

Management of angina.

Control of most forms of cardiac dysrhythmias.

Prophylaxis of migraine.

Control of essential and senile tremor and the management of Parkinsonian tremor.

Management of thyrotoxicosis and thyrotoxic crisis.

Management of hypertrophic obstructive cardiomyopathy.

Management of phaeochromocytoma.

'Inderal' is a product of original ICI research and was the first adrenergic beta-receptor blocking drug (beta-blocker) to be introduced into clinical medicine. Although the pharmacology of 'Inderal' is complex, its most important effects are:

(a) reduction in raised blood pressure.

(b) protection of the cardiovascular system against excessive sympathetic nervous stimulation (whether this results from mental or physical activity) and the excitatory effects of catecholamines. This means that pulse rate, the force of cardiac contraction and cardiac output are reduced, resulting in a reduction of cardiac work and myocardial oxygen demand.

In *hypertension* 'Inderal' gives smooth, gradual reduction of blood pressure in essential and renal hypertension of all degrees of severity, particularly when it is important that there should be no interference with mental, physical or sexual activity. Effective control of blood pressure can be expected in more than 80% of patients when 'Inderal' is added to existing diuretic therapy. The drug does not interfere with normal mechanisms that adjust blood pressure to change in posture, physical activity or external temperature. For this reason, 'Inderal' gives on-going control of blood pressure, even when the patient is supine. Side effects are minimal: 'Inderal' does not cause sexual dysfunction, mental depression or lethargy, nasal congestion, or electrolyte imbalance.

In *anxiety* 'Inderal' has been shown to act in a different way from conventional sedatives and tranquillisers. It rapidly controls somatic symptoms by direct action, as well as relieving the psychic manifestations of anxiety. Because there is no widespread suppression of central nervous activity, 'Inderal' is unlikely to cause drowsiness.

In *angina pectoris* 'Inderal' gives continuous long-term prophylaxis, reduces the frequency and severity of anginal attacks and improves the patient's capacity for exercise.

In *cardiac dysrhythmias* 'Inderal' is remarkably effective in restoring normal cardiac rate and rhythm. It is successful in a wide range of supraventricular and ventricular dysrhythmias whether they arise spontaneously or are associated with anaesthesia, digitalis intoxication or thyrotoxicosis. In the anxiety tachycardia syndrome, 'Inderal' gives a sustained reduction in heart rate, controls other somatic symptoms of sympathetic nervous hyperactivity and improves capacity for exercise.

In many *migraine* sufferers, prophylactic 'Inderal' treatment has been shown to significantly reduce the number of migraine attacks.

Essential and senile tremor are alleviated by 'Inderal' treatment, and the drug is of value alone or as an adjunct in Parkinsonian tremor. Unlike other drugs used in tremor, 'Inderal' has no central depressant effect, and does not become ineffective by prolonged use.

Dosage and Administration

Oral

'Inderal' Tablets should preferably be taken before food. One of the pharmacological actions of 'Inderal' is to reduce the heart rate. Reduction of the pulse rate to 55–60 beats per minute indicates that dosage should not be increased.

In angina, hypertension, migraine, anxiety and tremor the standard starting dose is 40 mg two or three times daily increasing by the same amount at weekly intervals according to patient response.

An adequate response in anxiety, tremor and migraine is usually seen in the range 80–160 mg/day and for other indications 120–320 mg/day. In hypertension further reduction of blood pressure is obtained when diuretic and/or other antihypertensive therapy is given in addition to 'Inderal'.

In cardiac dysrhythmias, hypertrophic obstructive cardiomyopathy and thyrotoxicosis, most patients respond within the dosage range of 10–40 mg 3 or 4 times a day.

In phaeochromocytoma (used only in conjunction with an alpha-receptor blocking drug) pre-operatively: 60 mg daily for three days is recommended — malignant cases (non-operable): 30 mg daily.

When 'Inderal' is added to existing diuretic therapy in hypertension there is summation of antihypertensive effect.

(continued over)

Inderal
(continued)

Other antihypertensive drugs are not usually needed except in emergency or refractory cases when they may, if necessary, be given concurrently with 'Inderal'. These other agents can then be progressively withdrawn as control with 'Inderal' is established. Use of one of the rapidly acting antihypertensive agents is mandatory in hypertensive crisis because the gradual action of 'Inderal' will not produce the immediate fall in blood pressure demanded by this condition. Nevertheless, concurrent therapy as outlined above will enable the patient to benefit from the advantages of 'Inderal' once his blood pressure has been reduced to a safer level. Intravenous 'Inderal' will not produce a more rapid therapeutic fall in blood pressure than oral administration and must never be used in the emergency treatment of hypertension. 'Inderal' Intravenous Injection is intended only for the emergency treatment of cardiac dysrhythmias.

Intravenous
'Inderal' Intravenous Injection is for the emergency treatment of cardiac dysrhythmias only. Before injecting 'Inderal', atropine 1–2 mg should be given intravenously. The initial dose of 'Inderal' is 1 mg (1 ml) injected over one minute. This may be repeated at two-minute intervals until a response is observed or to a maximum of 10 mg in conscious patients and 5 mg in patients under anaesthesia.

Precautions and Side Effects
As with all beta-blockers treatment should not be discontinued abruptly.
'Inderal' should not be used in the presence of heart block; if there is a history of bronchospasm; after prolonged fasting; or in metabolic acidosis (e.g. in diabetes).

Patients with poor cardiac reserve may be heavily dependent on uninhibited sympathetic nervous stimulation for maintenance of adequate myocardial contractility. These patients should be given 'Inderal' only if myocardial contractility can be maintained and signs of failure fully controlled. The myocardial stimulating effect of digitalis is not impaired by 'Inderal'.
Prior to elective surgery, the anaesthetist must be made aware of 'Inderal' therapy in patients due to undergo general anaesthesia.
Like all other drugs, 'Inderal' should not be given in pregnancy unless its use is essential. There is no evidence of teratogenicity with 'Inderal'.
'Inderal' is usually well-tolerated. Minor side effects such as nausea, insomnia, lassitude and diarrhoea are usually transient and can often be avoided by gradual introduction of treatment. Isolated cases of purpura, erythematous rash and paraesthesia of the hands have been reported. In the rare event of intolerance to 'Inderal', manifested as bradycardia and hypotension, the drug should be withdrawn and, if necessary, treatment instituted as for overdosage:
In cases of overdosage, excessive bradycardia can be countered with atropine 1–2 mg intravenously, followed, if necessary, by a beta-receptor stimulant such as isoprenaline 25 micrograms intravenously or orciprenaline 0·5 mg intravenously.

Presentations and Packings
Tablets containing Propranolol Hydrochloride B.P. 10 mg — containers of 50, 250 and 1000.
Tablets containing Propranolol Hydrochloride B.P. 40 mg — containers of 50, 250 and 1000.
Tablets containing Propranolol Hydrochloride B.P. 80 mg — containers of 100 and 500.
Tablets containing Propranolol Hydrochloride B.P. 160 mg — containers of 50 and 250.
Injection Solution containing Propranolol Hydrochloride B.P. 1 mg per 1 ml — containers of 10 × 1 ml ampoules.

Notes
Worldwide registration of 'Inderal' for all of the above indications has not yet been completed. If in any doubt, please refer to local literature, or consult your ICI representative.

Skin Disorders

Problems posed by skin disorders are demanding an increasing share of the physician's time. It has been estimated that one in four visits to the general practitioner requires treatment for a skin condition. ICI has, therefore, developed a growing interest in this field and today offers a range of products which provides treatment for the majority of dermatoses encountered in general and hospital practice.

The introduction of 'Synalar' in 1961 marked a major breakthrough in steroid therapy.

The tremendous potency of fluocinolone, estimated at several hundred times greater than hydrocortisone, meant that for the first time there was available a low concentration, high efficacy steroid for topical use.

Today 'Synalar' is widely used in the treatment of a great many skin disorders.

The latest ICI product in this field, 'Metosyn', marks a further advance in topical steroid therapy. Its base is entirely synthetic, unlike traditional bases which consist of natural substances such as animal fats or vegetable oils. Consequently, it does not contain water, hydrolyse, deteriorate or support bacterial or fungal growth. Furthermore, as it needs no preservatives and does not contain lanolin or emulsifying agents, the risk of sensitization to these substances is eliminated.

The function of the base as a vehicle has also been improved and the design allows the steroid content of 'Metosyn' to be released consistently and completely into the epidermis.

Apart from the novel base, 'Metosyn' contains the latest development in steroid chemistry. The new steroid, fluocinonide, contains an acetate group in the 21 C atom position which has been found to influence favourably the partition coefficient in skin lipids. This factor, combined with the new transportation system, results in the most effective topical steroid yet devised.

The development of 'Fulcin' (griseofulvin) gave fresh hope to sufferers of recalcitrant superficial fungal infections. Formulated in fine particle size to ensure rapid and efficient absorption, this orally administered antibiotic obviates the need for messy pigments or sticky ointments and gives a degree of efficacy which makes it pre-eminent among antifungal medicaments.

No less spectacular on their introduction and still rendering sterling service after many years' world-wide use is the 'Lorexane' preparation for headlice, the sarcopticide 'Tetmosol', and 'Cetavlon' P.C., a liquid shampoo formulation of 'Cetavlon' for seborrhoeic dermatitis and seborrhoea capitis.

Finally, protection of the skin from the harmful effects of body fluids and water-soluble irritants is important, not only because inflammation and excoriation of the skin cause discomfort, but also because any injury increases the risk of infection. 'Siopel' Cream is a water-repellent silicone preparation specially designed to protect the skin, which contains 'Cetavlon' as an emulsifying agent and bactericide. 'Siopel' is finding increasing use in medical and surgical practice.