RES MEDICA
Journal of the Royal Medical Society

Contents

ISSN: 2051-7580 (Online) ISSN: 0482-3206 (Print)
Res Medica is published by the Royal Medical Society, 5/5 Bristo Square, Edinburgh, EH8 9AL

Res Medica, Autumn 1959, 2(1): 5
doi:10.2218/resmedica.v2i1.334

Volume II, No. 1 Autumn 1959

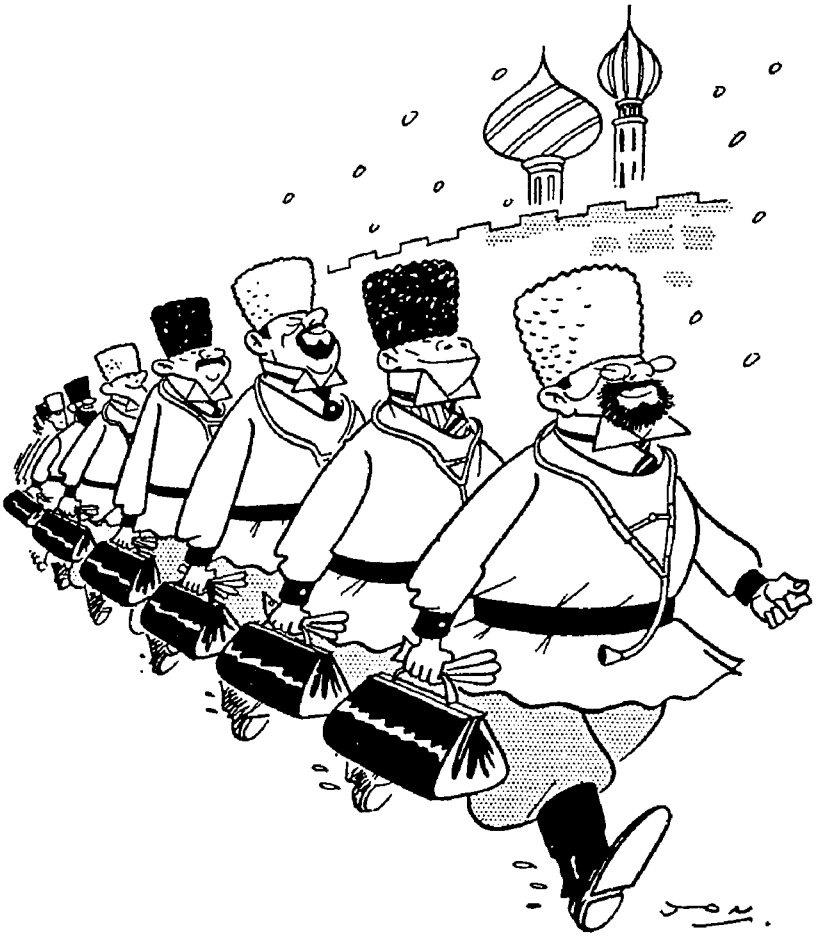
RES MEDICA

THE JOURNAL OF THE ROYAL MEDICAL SOCIETY

Contents

PUBLISHED AT 7 MELBOURNE PLACE, EDINBURGH

PRICE ONE SHILLING



346,000 DOCTORS

The country with the most doctors is the U.S.S.R.
with 346,000 or one to every 598 persons

(*Guinness Book of Records. P. 85*)

5,000,000
GUINNESS
are enjoyed every day

(*another Guinness record*)

G.E.3249.B

MILESTONE IN DERMATOLOGY

Griseofulvin is a Glaxo research development. In extensive trials conducted in Britain, the USA and Austria, griseofulvin, given by mouth, has demonstrated quite remarkable and consistent activity against dermatophyte infections of the skin, hair and nails. Infections even of many years duration have made a striking response to this unique substance.

"A new era in the therapy of many of the common mycotic infections of the human skin, hair and nails may be at hand with the discovery of the almost unbelievable therapeutic effectiveness of the oral antibiotic, griseofulvin"

Sulzberger, M.B. and Baer, R.L. Milestones in Dermatology XXXIX Griseofulvin. An Oral Antibiotic for the Treatment of Many Common Fungous Infections of the Skin, Hair and Nails. Excerpta Medica, 1959, 13 (Section XIII) 145.

GLAXO LABORATORIES LTD, GREENFORD
MIDDLESEX BYRON 3434
Subsidiary Companies or Agents in most countries
GRISOVIN IS A GLAXO TRADE MARK

RES MEDICA

THE JOURNAL OF THE ROYAL MEDICAL SOCIETY

Editor:
E. A. W. SLATER

Editorial Committee:
H. C. DRYSDALE · N. WRIGHT · N. A. BOYLE

SYLLABUS FOR THE 223rd SESSION

	1959		
Fri.	Oct.	16	INAUGURAL ADDRESS. Professor John McMichael, F.R.S., M.D., M.B., Ch.B., F.R.C.P.Ed., F.R.C.P. "From Genesis to Revelation in Research."
Fri.	,,	23	Dissertation: George E. Mawer, Esq., B.Sc. "Drugs which Lower Arterial Blood Pressure."
Fri.	,,	30	Dissertation: T. M. Kennedy, Esq. "Rheumatoid Arthritis."
Fri.	Nov.	6	TALK: Dr R. E. Verney, M.B., Ch.B., D.R., F.R.C.P.Ed. "The Problems of Student Health."
Fri.	,,	13	Dissertation: David Doyle, Esq. "Hydrocephalus."
Tues.	,,	17	PRESIDENT'S ANNUAL DINNER. Royal College of Surgeons, 7.15 for 7.30 p.m. Guest of Honour: Sir Stanley Davidson, B.A.(Camb)., M.D., F.R.C.P.Ed., F.R.C.P., M.D.(Oslo).
Fri.	,,	20	Dissertation: R. F. Rintoul, Esq. "Investigations into Vomiting."
Fri.	,,	27	Debate with the Glasgow University Medico-Chirurgical Society in Edinburgh. Motion to be arranged later.
Fri.	Dec.	4	ADDRESS: W. Ritchie Russell, Esq., C.B.E., M.D., D.Sc., F.R.C.P.Ed., F.R.C.P. "Brain Mechanisms and Social Problems."
Fri.	,,	11	Dissertation: W. Ritchie Russell. Esq. Bright and Bright's Disease."
	1960		
Fri.	Jan.	15	Dissertation: J. G. Clark, Esq. "Portal Hypertension."
Fri.	,,	22	Dissertation: N. Campbell Smith, Esq. "Caesarean Section."
Fri.	,,	29	ADDRESS: Professor L. B. Davis, M.D., F.R.C.P.Ed., F.R.C.P., F.R.F.P.S. "Pernicious Anaemia."
Fri.	Feb.	5	Dissertation: Bernard Canavan, Esq. "Prostatic Neoplasm."
Fri.	,,	12	TALK: details to be arranged.
Fri.	,,	19	Dissertation: G. W. K. Donaldson, Esq., B.Sc. "Hypertension."
Fri.	,,	26	ADDRESS: Professor Robert Cruickshank, M.B., Ch.B., M.D., D.P.H., F.R.C.P.S., F.R.F.P.S., F.R.C.P. "Immunity—Specific and Non-Specific."
Fri.	Mar.	4	Dissertation: G. E. D. Urquhart, Esq., "Chronic Bronchitis."
Fri.	,,	11	President's Valedictory Address.
Wed.	,,	16	Annual Extraordinary General Meeting.

Private Business at 7 p.m.

Public Business at 8 p.m. unless otherwise stated.

Clinical Meetings, Film Meetings, and Industrial Visits will be arranged during the Session. Due notice of these will be given.

The date for the Society's ANNUAL BALL will be announced later.

JOURNAL

of the

ROYAL COLLEGE

of

SURGEONS

of

EDINBURGH

Published quarterly: October, January, April, July

Annual Subscription: 21s. post free

EDITOR: John Bruce, C.B.E., T.D., P.R.C.S. Ed., Hon. F.A.C.S.

HYPOTENSIVE DRUGS

By G. E. MAWER
B. Sc.

Based on a Dissertation read before the Royal Medical Society on Friday, 23rd October 1959.

The arterial blood pressure is controlled by the autonomic nervous system. Information about the level of the arterial pressure is obtained by the stretch receptors of the aortic arch and the carotid sinus. An increase in pressure is registered as an increase in sensory discharge frequency and vice-versa. The sensory impulses reach the medulla by the carotid sinus nerves, the cardio-aortic nerves and the vagi. The central nervous mechanisms are such that changes in the arterial pressure evoke compensatory changes in the dynamics of the circulation. A fall in carotid sinus pressure, for example, evokes peripheral arteriolar constriction, an increase in venous tone and an increase in heart rate. Generalised arteriolar constriction increases total peripheral resistance. An increase in venous tone tends to increase the venous filling pressure and the stroke volume of the heart. The combined increase in stroke volume and heart rate produces a rise in cardiac output, which, together with the increase in peripheral resistance, restores the original arterial pressure.

The circulatory adjustments which regulate arterial blood pressure require a normally functioning sympathetic nervous system; peripheral arteriolar constriction is brought about by the release of noradrenaline from sympathetic nerve endings or by the release of adrenaline from the adrenal medulla; the same mechanisms are also responsible for the increase in venomotor tone and in part for the increase in heart rate.

The patient with early essential hypertension has compensatory reflex mechanisms which function in the normal way. The difference between him and the normal man is in the actual level of arterial blood pressure. The "setting" of these mechanisms has become altered so that the pressure level which they maintain is above the normal range. Immediately the pressure is lowered to a physiological level the homeostatic mechanisms act to restore the hypertensive state. Sustained lowering of the arterial pressure can, however, be obtained by the use of drugs which prevent the normal functioning of the homeostatic reflexes. The anatomical pathways for these reflexes can be interrupted at many points:—

1. Carotid sinus and aortic arch.
2. Central nervous system.
3. Sympathetic ganglia.
4. Sympathetic post-ganglionic nerves.
5. Peripheral adrenergic receptors.

1. Drugs Acting on the Carotid Sinus and Aortic Arch

Plants of the genus Veratrum contain alkaloids with characteristic properties. Selective extraction yields the mixture of alkaloids known as Veriloid and further purification gives the pure crystalline alkaloids protoveratrine A and B.

The intravenous injection of protoveratrine is followed by a rapid fall in blood pressure. This is accompanied by bradycardia and persists for one to three hours.

The veratrum alkaloids can be given orally and they have been used in the treatment of moderate hypertension and in pre-eclampsia. They suffer from several disadvantages, however. The duration of the effect is short and there is a low therapeutic ratio. The dose which lowers blood pressure is only slightly less than the dose which produces vomiting.

The veratrum alkaloids produce a fall in blood pressure by actions on sensory receptors in the heart, lungs and carotid sinus. Probably the pressure receptors are sensitised so that a given sensory discharge frequency is produced by a lower arterial pressure. If this is the case, the veratrum alkaloids can be described as "re-setting" the pressure regulating mechanisms so that they control the blood pressure at a lower level. Theoretically a drug which acts in this way is the ideal hypotensive agent; the pressure regulating mechanisms are not abolished, they are re-adjusted to a physiological level. It is unfortunate that the veratrum alkaloids have such a short action and are so liable to produce undesirable side effects.

2. Drugs which act on the Central Nervous System

The normal functioning of those parts of the central nervous system which regulate the circulation is modified by a large number of drugs.

Normal sleep is associated with a fall in arterial blood pressure. This occurs in both normal and hypertensive people and when the sleep is drug-induced. To this extent the hypnotics are hypotensive agents.

The acute rises in arterial pressure associated with emotion or excitement are prevented or reduced by the sedatives and tranquillisers.

During surgical anaesthesia the blood pressure is lowered; the total peripheral resistance is reduced by a direct effect on the arterioles and by a remote effect on the vasomotor centre. The force of myocardial systole is also reduced. Certain general anaesthetics, notably halothane, appear to block transmission in the autonomic ganglia. Slight increases in the concentration of halothane inhaled are often associated with abrupt falls in arterial blood pressure.

The administration of a medium-acting barbiturate, for example sodium amytal, to a hypertensive patient often produces a marked fall in arterial blood pressure.

3. Drugs which act on Sympathetic Ganglia

Special interest is attached to this synapse because it is a point on the vasoconstrictor pathway which is vulnerable to specific blockade.

Although ganglionic transmission is a continuous process, for convenience of description it may be divided into several stages:

1. Saltatory conduction in the pre-ganglionic nerve fibre.
2. Non-saltatory conduction in the non-myelinated terminal fibrils.
3. Release of acetyl choline at the boutons terminaux.
4. The crossing of the "synaptic gap" by acetyl choline.
5. The adsorption of acetyl choline at the receptor sites on the post-synaptic membrane.
6. Depolarisation of the membrane and the initiation of a propagated action potential.

Transmission may be blocked at each stage by the use of suitable

pharmacological agents. Stages 5 and 6 are interrupted by nicotine, the tetra-alkylammonium compounds, the methonium salts, mecamylamine and pempidine. Special interest is attached to this group because it includes the most specific ganglion blocking agents.

Langley in his classical studies on the anatomy and physiology of the autonomic nervous system, made extensive use of nicotine. He was able to demonstrate the presence of peripheral synapses which were selectively blocked by nicotine. Low doses of nicotine stimulate sympathetic ganglia and provoke the release of adrenaline from the adrenal medulla. The drug has important actions on a large number of other sites and is not suitable for clinical ganglion blockade.

Burn and Dale in 1914 showed that tetraethylammonium bromide closely resembled nicotine. The tetraethylammonium ion was shown to block ganglion transmission without preliminary stimulation. However, the latter suffered from several disadvantages; it had to be given by injection and the hypotensive effect was short. In addition the drug produced neuromuscular blockade. Nevertheless tetraethylammonium bromide was used in the emergency treatment of acute left ventricular failure secondary to hypertension and as a diagnostic tool to predict the response to sympathectomy.

Barlow and Ing in Oxford, and Paton and Zaimis in London developed the methonium compounds, which consist of two quaternary ammonium groupings linked by a polymethylene chain. The pharmacological properties are determined by the length of this chain. The members of the series with 5 or 6 methylene groups are very active as ganglion blocking drugs, but do not prevent neuromuscular transmission.

The penta- and hexa-methylene compounds, pentamethonium, and hexamethonium, were tested on hypertensive patients. They were very effective hypotensive agents but absorption from the alimentary tract was poor and unpredictable. The drugs were given parenterally and hypertensive patients were taught self-administration.

A large number of structural analogues was prepared. Among these was pentolinium (Ansolysen) which is closely related to pentamethonium but better absorbed. In many cases it was possible to obtain adequate control of blood pressure with oral pentolinium. However quaternary ammonium salts as a group are absorbed slowly and to an incomplete extent. Further progress was not made until the advent of the "amine" ganglion blocking drugs, mecamylamine (Inversine) and pempidine, which are absorbed rapidly and almost completely after oral ingestion.

Following absorption there are important differences in behaviour between the quaternary ammonium and the amine ganglion blocking drugs. Hexamethonium is confined to the extracellular fluid compartment and does not penetrate the blood-brain barrier. It is excreted by glomerular filtration and not reabsorbed by the renal tubules. The restricted distribution, the absence of binding to tissue protein and the rapid excretion combine to produce rapid removal of the drug. For this reason the degree of ganglion blockade produced by hexamethonium fluctuates relatively rapidly.

The secondary amine mecamylamine is distributed throughout the body fluids. It is bound to the tissue proteins and tubular reabsorption in the kidney reduces the rate of excretion. Thus the degree of ganglion blockade produced by mecamylamine is more uniform than with hexamethonium. Mecamylamine penetrates the blood-brain barrier and some patients develop tremors.

The difference between hexamethonium and mecamylamine are due to the differences in the state of the nitrogen atoms in the two molecules. The heavily charged quaternary ammonium cation is not able to penetrate cell

membranes. The substituted amines are readily absorbed by cells as the free bases.

It is not possible to state which is the better of the two drugs mecamylamine and pempidine at present. A clinical trial of these two drugs is being conducted in the Royal Infirmary, Edinburgh, using a "double blind" technique.

The Cardiovascular Effects of Ganglion Blockade

Ganglion blockade produces only a slight fall in the supine blood pressure of the normal subject. The fall is greater, however, in the hypertensive patient. This is probably due to the fall in total peripheral resistance which results from the interruption of the sympathetic vasoconstrictor pathway. A much greater fall in both diastolic and systolic pressures is obtained when the patient stands erect. This is due to haemodynamic changes which can no longer be corrected.

With the assumption of the erect posture the hydrostatic pressure distending the veins of the abdomen and lower limbs is increased. In the absence of compensatory venoconstriction these veins dilate and accommodate a larger proportion of the total venous blood. The volume which remains in the great veins near the heart is therefore decreased. This is accompanied by a fall in venous filling pressure and in cardiac output. Reduced cardiac output and reduced peripheral resistance together produce a fall in arterial blood pressure. Normally this would evoke the compensatory reflex mechanisms described earlier, but ganglion blockade prevents this.

When the degree of ganglion blockade is excessive the pressure may fall from hypertensive to hypotensive levels. This is commonly associated with symptoms of cerebral ischaemia, dizziness, "light-headedness" and fainting. Many physicians encourage their patients to take enough drug to produce symptoms of postural hypotension once or twice during the day. They are also advised to take advantage of the postural effect by sleeping with the head of the bed raised.

The effects of ganglion blockade on peripheral blood flow vary from one tissue or organ to another:

1. Skin. The sympathetic adrenergic innervation of skin vessels is constrictor. Ganglion blockade is usually associated with an increase in blood flow to the foot and to the hand. This is due largely to increased skin flow.
2. Voluntary muscle. The sympathetic innervation of the arteries and arterioles of skeletal muscle is largely dilator. Forearm flow, which is chiefly muscle flow, is usually unchanged by ganglion blockade.
3. Brain. The blood flow to the brain is under autonomous control; it remains almost constant in spite of wide variations in arterial blood pressure. In the healthy young adult cerebral ischaemia is only produced by severe postural hypotension, but the aged hypertensive is quite different. Hypertensive arteriolar sclerosis offers a high, relatively fixed resistance to blood flow. Ganglion blockade reduces arterial pressure and predisposes to thrombosis, ischaemia and infarction.
4. Myocardium. Reduction in the aortic diastolic pressure has a two-fold effect. The coronary blood flow may be reduced but so also is the work demanded from the myocardium. The effect on coronary ischaemia depends on which predominates.
5. Kidney. The renal blood flow is never increased by ganglion

blockade. There is evidence that the reduction in renal blood flow produced by the fall in arterial pressure is temporary; adaptation may restore normal blood flow after a few hours.

Carefully controlled treatment by ganglion blockade with regular attendance at hypertensive clinics can be very successful. Some patients enjoy adequate control with the minimum of side effects. Others experience all the side effects at dose levels which are not adequate to control hypertension. The majority have one or two side effects.

It may require a great deal of encouragement to convince a patient with severe hypertension but minimal symptoms that the treatment is worthwhile; he feels better without treatment.

Almost all patients receiving ganglion blocking drugs are constipated, but most procure regular motions with Senokot or Petrolagar. A few develop an "all-or-none" bowel action. Without laxatives they are completely constipated yet the smallest effective dose of a mild purgative produces diarrhoea. Apart from the inconvenience involved, this hampers treatment; when constipated, more of the hypotensive drug is absorbed; when loose, part is lost in the motions. Smooth control of the arterial pressure becomes very difficult.

Urine retention is an important side action in older men with benign prostatic hypertrophy. Secondary hypertensive disease in brain, myocardium or kidney may prevent surgical relief of the obstruction, whilst the danger of acute retention prevents treatment by ganglion blockade.

Ganglion blockade may retard the progression of hypertensive renal disease but renal function is seldom improved. The reduction of renal blood flow has an adverse effect on impaired renal function. Further nitrogen retention may occur and renal failure can develop. Patients with a blood urea nitrogen level over 60 mg. per 100 ml. usually deteriorate on ganglion blocking drugs.

Other common side effects of ganglion blockade are blurred vision, dry mouth, reduced appetite and impotence. They seldom prevent continued therapy. The majority of the side effects are due to the interruption of transmission through parasympathetic ganglia. This prevents the normal functioning of the ciliary body, the salivary glands, the peristaltic reflex, the gastric and intestinal mucosae, the innervation of the bladder and the reflexes involved in erection and ejaculation.

Attempts to produce specific sympathetic ganglion block have not been successful in spite of the anatomical and physiological differences between sympathetic and parasympathetic ganglia. There are, however, drugs which act specifically on post-ganglionic sympathetic nerves.

4. Drugs which act on Sympathetic Post-Ganglionic Nerves

(*a*) RESERPINE.

Plants of the genus Rauwolfia have been used for centuries in Africa and India chiefly in the treatment of insanity. Only in this century, however, have the Rauwolfia alkaloids become recognised as hypotensive agents.

Three preparations from Rauwolfia are available; Raudixin is a powdered preparation of the whole root; Rauwiloid is a partially purified mixture of alkaloids; and reserpine is a pure crystalline alkaloid, the most important of the Rauwolfia group.

Reserpine produces changes in behaviour; a treated animal lies quietly in its cage showing the minimum of spontaneous activity. It is inattentive and lacks concentration. Left alone it merely sleeps. Comparable doses

produce a similar effect in man. This sedation is different from that produced by the barbiturates.

The cardiovascular effects of reserpine are bradycardia and a fall in arterial blood pressure. Other effects are increased gastro-intestinal motility, constriction of the pupil, relaxation of the nictitating membrane and loss of the pilo-erection response to cold. These effects develop very slowly, even after intravenous injection of the drug. Careful observation of animals soon after injection has revealed transient hyperglycaemia, pilo-erection, elevation of the arterial blood pressure and contraction of the denervated nictitating membrane.

The mode of action of reserpine has been elucidated recently. In 1955 Brodie and his co-workers showed that reserpine liberates 5-OH tryptamine from brain and other tissues. Other pharmacologically active amines occur in brain, notably noradrenaline and adrenaline. Methods for their extraction, purification and assay have been developed by M. Vogt. They have a very similar distribution to 5-OH tryptamine, being found in the hypothalamus, mid-brain and medulla. Recently it has been shown that these compounds are also liberated by reserpine.

Sympathomimetic amines are also stored in adrenergic nerves and in the adrenal medulla. Following reserpine the concentration of these compounds is reduced. In the cat, for example, reserpine reduces the noradrenaline in the superior cervical ganglion from about 4.5 microgrammes per gramme to 1.5 or less. When the concentration falls below 1.0 microgramme per gramme, peripheral transmission fails. Impulses pass through the ganglion but they fail to excite the effector structure. Apparently the quantity of noradrenaline released from the nerve terminals is reduced to an ineffective level.

Reserpine appears to allow the sympathomimetic amines to leak out from cells into the plasma. A transient rise in the plasma adrenaline concentration after reserpine has been demonstrated in rabbits. This probably accounts for the transient hyperglycaemia, hypertension, pilo-erection and contraction of the denervated nictitating membrane.

The repeated administration of therapeutic doses of reserpine to man is probably adequate to deplete the noradrenaline and adrenaline content of the sympathetic tissues; this has not yet been proved, however. Probably the hypotensive effect of reserpine is due to this.

Reserpine is widely used in the treatment of hypertension. Some cases respond well to reserpine alone. The hypotensive action is moderate and they do not develop postural hypotension. Reserpine potentiates the blood pressure lowering effects of the ganglion blocking drugs without enhancing the undesirable side effects.

The therapeutic ratio for reserpine is very much higher than for the veratrum alkaloids; nevertheless it has several side actions. Nasal congestion, diarrhoea and dreams are the most common. The sedative effects are advantageous in over-active hypertensive patients. Some, however, experience severe depression. This is the most serious disadvantage of reserpine and often limits the use of the drug. A derivative with hypotensive effects but no central depression would be valuable.

(*b*) BRETYLIUM TOSYLATE (DARENTHIN).

In 1957 Exley described a choline xylyl ether called T.M.10; this compound is parasympathomimetic but has highly characteristic effects in addition. When a dose of 5-15 milligrammes per kilo is given intravenously to a cat peripheral sympathetic transmission is prevented. Impulses pass through the sympathetic ganglion and along the post-ganglionic sympathetic

nerve but the innervated organ is not excited. For example, stimulation of the cervical sympathetic chain no longer elicits a contraction of the nictitating membrane. Stimulation of the sympathetic nerves to the heart does not increase the heart rate, nor does stimulation of the sympathetic nerves to the salivary glands produce salivation. Each of these structures responds normally to adrenaline and noradrenaline however. The block in transmission appears to be at the adrenergic nerve ending.

The properties of T.M.10 excited great interest and many structural analogues were prepared. The aim was to obtain a compound with the sympathetic blocking properties of T.M.10 but without the parasympathomimetic effects. This aim has been realised in bretylium.

Bretylium tosylate (Darenthin) is a simpler molecule than T.M.10. The anion is p-toluene sulphonate but this is not necessary for pharmacological activity.

Bretylium produces a specific sympathetic blockade; it lacks the parasympathomimetic effects of T.M.10. Low doses which prevent the effects of sympathetic nerve stimulation do not prevent conduction along the nerve. They appear to stop the release of noradrenaline from the nerve ending. Large doses given over a long period do not deplete the noradrenaline stores, so that a reserpine-like action seems unlikely.

Bretylium does not antagonise adrenaline or noradrenaline. On the contrary the treated animal becomes more sensitive to the sympathomimetic amines. The drug does not prevent the release of adrenaline from the adrenal medulla. It seems likely therefore that the influence of the adrenal on arterial blood pressure will be increased in patients treated with Bretylium.

Bretylium is a quaternary ammonium ion and is not well absorbed from the alimentary tract. This is a disadvantage but it does not prevent oral administration. Following absorption the drug is selectively accumulated by adrenergic nerves. Carbon 14 labelled bretylium is found at these sites but not in the central nervous system. Urinary excretion is rapid and none of the drug can be detected in the urine after 24 hours.

The cardiovascular effects of bretylium are similar to those of ganglion blockade. In healthy young adults there is little change in supine blood pressure but the erect blood pressure is reduced. In hypertensive patients the supine pressures are lowered to a moderate extent but a much larger drop occurs when the patients stand erect. Postural hypotension occurs with large doses, especially after a heavy meal. Following oral ingestion the effects appear in about an hour. The maximum effect is seen after about three hours.

Bretylium is undergoing clinical trial in many parts of the country. Suitable patients are those who have severe hypertension and would otherwise be subjected to ganglion blockade. Tolerance develops to bretylium as it does to the ganglion blocking drugs but the undesirable side effects of the latter are not produced. Patients on bretylium do not complain of constipation, dry mouth, blurred vision and loss of appetite. Early experience suggests that bretylium will have the same effects as ganglion blocking drugs on impaired renal function.

The development of a specific sympathetic blocking agent represents a major advance in the drug treatment of severe hypertension. Bretylium also provides the experimental pharmacologist with an exciting new tool.

5. Drugs which act on Adrenergic Receptors

Several peripheral antagonists of adrenaline and noradrenaline are known. They prevent access to adrenergic receptors. Some of them, like the ergot

alkaloids and tolazoline have additional actions which make them unsuitable for clinical use. Others, for example phentolamine (Rogitine), have an established place in the diagnosis of phaeochromocytoma. All the specific adrenaline antagonists are much more effective against adrenaline or noradrenaline circulating in the blood than against noradrenaline released at nerve endings. They are ineffective in the treatment of essential hypertension.

6. Other Drugs

In addition to the hypotensive agents described above, there are others which do not fit into the classification used. Hydralazine (Apresoline) is occasionally used in the treatment of patients with hypertension and impaired renal function. This drug is unique amongst the hypertensives in that it increases renal blood flow. However, the serious toxic effects of the drug restrict its use.

Chlorothiazide (Saluric) is a potent oral diuretic. Where hypertension is associated with fluid retention as in pre-eclampsia, patients often respond to this drug with a copious diuresis and a fall in arterial blood pressure. Chlorothiazide has also been shown to potentiate the effects of the hypotensive drugs. The dose of a ganglion blocking drug required for a given depression of the arterial blood pressure may be reduced by half. The mode of potentiation is not clear.

The peripheral vasodilator drugs, for example glycerol trinitrate and amyl nitrite, reduce peripheral resistance and lower blood pressure. The effect is variable and transient however, and a reflex tachycardia is produced. They are not suitable for the sustained lowering of blood pressure in hypertensive patients.

Summary

1. The arterial blood pressure in the patient with early essential hypertension is regulated by the carotid sinus reflexes. Many of the drugs which lower arterial blood pressure interfere with the reflex mechanism.
2. Several drugs which lower arterial pressure by actions on the sensory and central parts of the reflex pathway are described. The cardiovascular effects of ganglion blocking agents are outlined; attention is drawn to the desirability of specific sympathetic blockade.
3. Recent work on reserpine is described and the need for a similar drug without depressive effects is emphasised. The recently introduced specific sympathetic blocking agents are of great theoretical and practical interest. Several other hypotensive agents are given brief mention.

FURTHER READING

The following list is intended as a guide to review articles and publications of a similar nature. These contain full references to original literature:—

Hypotensive Drugs

Robson, J. M. and Keele, C. A. 1956. *Recent Advances in Pharmacology*, second edition, 61. J. & A. Churchill, London.

Veratrum Alkaloids

Krayer, O. and Acheson, G. H. 1946. *Physiol. Rev.*, 26, 383.

Ganglion Blockade

Paton, W. D. M. and Zaimis, E. 1949. *Brit. J. Pharmacol*, 4, 381. "The pharmacological actions of the polymethylene bis-trimethylammonium salts."

Moe, G. K. and Freyburger, W. A. 1950. *Pharm. Rev.* 2, 61. "Ganglionic Blocking Agents."

Paton, W. D. M. 1954. *Pharm. Rev.*, 6, 59. "Transmission and block in autonomic ganglia."

Perry, W L. M. 1957. *Brit. Med. Bull.* 13, No. 3, 220. "Transmission in autonomic ganglia."

Milne, M. D. 1959. *Practitioner*, 182, 367. "Pempidine and other drugs in the treatment of high blood pressure."

Reserpine

Vogt, M. 1957. *Brit. Med. Bull*,, 13, No. 3, 166. "Sympathomimetic amines in the central nervous system."

Bretylium tosylate

Exley, K. A. 1957. *Brit. J. Pharmacol.*, 12, 297. "The blocking action of choline 2:6 xylyl ether bromide on adrenergic nerves."

Boura and others. 1959. *Lancet*, ii, 17. "Darenthin—Hypotensive agent of a new type."

Adrenergic blocking agents

Nickerson, M. 1949. *Pharm. Rev.*, 1, 84.

Robson, J. M. and Keele, C. A. 1956. *Recent Advances in Pharmacology*, second edition. 33. J. & A. Churchill, London.

AN OCULIST LOOKS AT ENDOCRINE EXOPHTHALMOS

By C. R. S. JACKSON
M.A., M.D., D.O.M.S., F.R.C.S.E.

Based on a talk delivered before the Royal Medical Society on Friday, 12th December 1958.

When it was suggested to me that I should talk around some subject that held interest beyond the strictly ophthalmological one I saw a chance to present the ophthalmologist as someone other than a man confined within the bony boundaries of his orbit, often fighting stern actions to defeat the invasive tactics of his neighbours, the neurosurgeons and the nose and throat doctors. Here was an opportunity to demonstrate the many connections of our subject and the many other branches of medical practice with which we are at times associated, ranging from neurology and rheumatology, through paediatrics, midwifery, and dermatology, to metabolic disease and endocrinology—to mention but a few of the pies in which an ophthalmological finger may be found.

For the purpose of instructing the student and to enable him to compile lists of the 'signs of this' or the 'complications of that' it is necessary to present facts as being either black or white, with little of the many confusing shades of grey which actually lie between. Not only do our classes present this misleading picture but so of course do the books we use.

In the past few years the conception of endocrine influence upon the orbital contents has changed. In the textbook which I used before qualification I find the bare information that the eyes become prominent in Graves' disease and that various clinical signs mainly related to movements of the lids have been described by the gentlemen whose names are perpetuated in this way.

Since that time the emphasis has changed and there are recognised at least two varieties of exophthalmos of an endocrine nature. The first is the classical exophthalmos of Graves' disease, with the staring eyes, tremor, loss of weight and irritability; and the second a far less well-defined condition which may or may not have been preceded by a thyroid upset. This second variety is called exophthalmic ophthalmoplegia and its very name reminds us that one of its features is interference with ocular motility. It is uncertain just how exophthalmic ophthalmoplegia fits into the scheme of things and, in any given case, we may see exophthalmos without much paralysis, gross limitation of movement without exophthalmos, or both together. And again we may see patients showing obvious palsy of ocular muscles and the other features of exophthalmic ophthalmoplegia, together with such thyrotoxic manifestations as lid retraction.

Table 1 represents the general view of the differentiation between what we call 'thyrotoxic' and 'pituitary' exophthalmos. The pituitary appears here as there is little doubt that it has a part to play, and perhaps the major part, in the production of exophthalmos.

If we leave the underlying cause of exophthalmos for the present we can look at the possible forces which might lead to an increased protusion of the eye.

In some animals the globe is surrounded by a sheet of smooth muscle, which could act as a propulsor of the globe, but no such force is available in the human orbit. I am only speaking now of actual exophthalmos, for no

EXOPHTHALMOS

THYROTOXIC		PITUITARY
Female : Male :: 9:1	SEX	Female : Male
Early adult	AGE	Middle life or later
No	OEDEMA	Yes
Present	LID RETRACTION	Absent
None	DIPLOPIA	Often
Often improves	THYROIDECTOMY	May be disastrous

TABLE 1

	"THYROID"	PITUITARY	"MIXED"	TOTAL
MALE	3	2	3	8
FEMALE	14	11	6	31
TOTAL	17	13	9	39

TABLE 2

doubt lid retraction, as seen in thyrotoxicosis, occurs as a result of over-activity of the smooth muscle in the upper lid, either in response to thyroxine itself or some related substance.

Vascular congestion has to be ruled out as there is no muscle in the human orbit which might constrict the venous return.

Muscular weakness is another doubtful possibility as the development of generalised muscular weakness in thyroid disease does occur.

The final factor that I want to consider is an increase in the bulk of orbital contents, and this is a factor of recognised importance. It has been shown without doubt that the degree of exophthalmos is quantitively related to the increased bulk of the orbital contents, and a similar increase in bulk has been demonstrated in experimental exophthalmos.

But what is the ultimate cause of the protrusion?

There is no need for me to remind you that we should regard endocrine disorders as perversions of normal physiology rather than as true diseases,

and it is clear that each of the ductless glands may influence others either by the direct stimulating action of its hormone, or by the way in which variations in the concentration of one circulating hormone influence the production of another. We know that the anterior pituitary, by its thyroid stimulating hormone, controls thyroid activity. The amount of thyroxine produced, in its turn, alters the output of pituitary thyrotrophic hormone.

Thyroxine itself does not cause exophthalmos; though it (or one of its allies) has a sympathetic-like effect on the smooth muscle of the orbit, leading to lid retraction. That this sign is not due to actual sympathetic overactivity is proved by the occurrence of lid retraction in cases where the cervical sympathetic is paralysed.

That some substance other than thyroxine causes protrusion of the eyes is brought home to us most dramatically in those cases in which exophthalmos develops or increases after reduction of thyroid secretion, either surgically or otherwise.

It is more than twenty years since experimental evidence was produced to show that the pituitary could lead to proptosis in rabbits and that this proptosis occurred more readily after thyroidectomy. Soon afterwards, the injection of anterior pituitary extracts was shown to induce proptosis of the eyes in minnows.

In man, however, the circulating levels of pituitary thyroid stimulating hormone have not been linked with the degree of exophthalmos; and the injection of serum from certain exophthalmic patients has been shown to give rise to ocular protrusion in a certain species of goldfish, while serum from other patients produced no such effect.

It is in fact uncertain that there is a single pituitary hormone involved. Methods of assay are so difficult technically and so uncertain in their interpretation that it cannot be said that the exophthalmos producing factor and the thyroid stimulating hormone are one and the same thing.

This brings one to wonder whether there are not perhaps two variables interacting with one another; the first a hormonal stimulus whose nature is certainly linked in some way with the pituitary, and the second the orbital contents acting as the target organ, whose response to the stimulus is so uncertain. That some variation in organ response occurs is indicated by the not infrequent occurrence of unilateral proptosis, or proptosis which is so asymmetrical as to remain unilateral for some time and to lead to the suspicion of the presence of a local orbital lesion.

We cannot leave the question of the causation of exophthalmos without wondering if other endocrines are in some way involved. A suggestion linking the adrenals with Graves' disease was originally based on the occurrence of skin pigmentation in thyrotoxicosis. With the introduction of cortisone and corticotrophin into clinical practice, it was not unexpected that the effect of these substances on exophthalmos should be investigated. In fact the Medical Research Council sponsored two investigations into the problem and the net result was to the effect that no significant benefit occurred after the use of cortisone and ACTH in exophthalmic ophthalmoplegia.

While the use of steroids therapeutically has not found support, we are now seeing some evidence of the influence of cortisone on the development of exophthalmos. In this case experimental exophthalmos induced by cortisone is prevented by removal of the pituitary and lessened by the production of thyrotoxicosis by thyroxine. A similar result has been obtained in rats rendered exophthalmic by thiouracil due to uninhibited activity of the pituitary. The exophthalmos was markedly increased by cortisone. There seems no doubt that cortisone was acting through the pituitary and not by a direct action on the contents of the orbit.

I think we can accept the pituitary as being the prime mover (literally)

in the production of exophthalmos though the mechanism is not clear. Whether this result is simply a secondary effect of uninhibited thyroid stimulating hormone or a specific function of some other fraction of the pituitary secretion is unknown. It seems hardly possible, as someone has previously remarked, that the small amount of fat found in the normal orbit has a function so important that a pituitary hormone is detailed to control its amount.

Whatever may be the actual cause of exophthalmos I think that we would now agree that the two types are not separate entities, but merely represent, as it were, a change of emphasis; an alteration in balance; an infinite gradation of features, from the condition seen in simple toxic goitre where lid retraction predominates, to the grossly oedematous state of the orbit, with diplopia, ocular palsies, and, often, real risk of the loss of an eye.

It is not my intention to discuss differential diagnosis or treatment. This avoidance is not to be taken as indicating any lack of importance, for the choice of appropriate treatment and the time at which to apply it may stretch the combined judgment of the physician, ophthalmologist, neurosurgeon and radiotherapist. Battles may easily rage among the rival claimants of radiotherapy, orbital decompression, tarsorrhaphy, and endocrine replacement therapy, as being the treatment of choice in any given case. It is simply that I regard these problems as too technical to be usefully discussed at this time.

I have said that we speak about two types of exophthalmos; the thyrotoxic variety associated with lid retraction, and generally accepted as being much commoner in women; and the pituitary type, characterised by oedema of the orbital tissues, palsy of ocular muscles and risk of damage to the eye through exposure. In this type the sexes are equally represented and the disease tends to occur at a later age than does the first variety.

We must remember that, working in a specialised field, each of us may be seeing a series of cases not at all representative of the overall picture. This snag is illustrated by my examination of the records of the cases of exophthalmos appearing in the index of the Eye Department for the years 1955, 1956, and 1957. There are thirty-nine cases, which must indicate that only certain cases come into our hands, as exophthalmos must surely be commoner than this.

It has not been possible for me to divide these cases strictly into the 'toxic' and 'pituitary' groups, for there are a number of cases showing features of both kinds, and these we must call the 'mixed' group. (Table 2.)

There are appreciably more women than men, but there is no evidence in these figures that would say that toxic signs are more likely in the early age groups or that exophthalmic ophthalmoplegia is really a disease of later life. In this series I have a girl of seventeen and an old lady of seventy-three, both apparently suffering from thyrotoxicosis; while there are also three women in the middle thirties showing well-marked paralytic signs. Even if you take the average ages you are not getting much help, for the average ages of the women with toxic eye signs is fifty and of those with pituitary eye signs forty-five years; though you do not need me to remind you of the dangers attached to the taking of averages when there are only small numbers involved.

In the past there has been more than one suggestion that these cases of exophthalmos sometimes get worse if the balance between their various glands is interfered with, by a surgical or medical attack on their thyroid activity.

I think we have all seen this happen; though a reported series of 533 operations of thyroidectomy performed elsewhere apparently only produced three such events. I find it difficult to be so sanguine. Of the thirteen cases

I have designated purely 'pituitary' in this small series, nine had had previous treatment directed at reducing thyroid activity. This had taken the form of antithyroid drugs in five cases, surgery in three and radioactive iodine in only one. The other four cases of exophthalmic ophthalmoplegia apparently arose ab initio with no previous thyroid disturbance.

There are these various ways, therefore, in which our rather specialised experience in an eye-department seems to show us a different side of the picture from that seen elsewhere.

For my part, I find difficulty in understanding why exophthalmic ophthalmoplegia may arise sometimes several years after the original disturbance of endocrine balance and why this condition so often subsides again, apparently spontaneously, if allowed time to do so. Time is the important factor here. If we can ensure the integrity of the eye and watch the progress of the various orbital changes day by day or month by month, a condition of stability seems often to be restored, and we may find that all is well.

Another feature that is hard to explain is the occurrence of ocular palsy without exophthalmos. It is easy to understand limitation of ocular movement in the grossly oedematous orbit of the severe case, where the whole orbital circulation seems almost strangulated; but why should an isolated ocular palsy occur in the absence of a local lesion to account for it?

There is a great deal more that could be said about exophthalmos; about its treatment; about its effect on the function of the optic nerve with consequent field changes; about corneal ulceration and perforation; and about the severe burden that the condition imposes on its sufferers, for it may be unsightly in the extreme.

Nobody knows the answer to it all, and perhaps some of you may, in the future, be granted the ability to put another brick or two in place and so help to build up the whole.

RES MEDICA

NOVEMBER 1959

Research: From Genesis to Revelation

The Inaugural Address of the 223rd Session of the Society was given by PROFESSOR JOHN MCMICHAEL of the Hammersmith Postgraduate Medical School. Before a large audience he spoke of the conditions under which research is initiated and finally brought to fruition. The general climate of opinion is important and he instanced Padua at the time of the Renaissance. Here Harvey was launched on his career in a University which housed Galileo, Vesalius and Fabricius. By contrast in our own time, Hitler had destroyed more thoroughly than he knew the scientific spirit in Germany. America in medicine and Russia in the physical sciences were today taking the lead because of abundant support from national funds.

The inspiration of the investigator was often a matter of chance or accident. Sometimes it was a quick flash of insight, but in others like Harvey and Darwin the ideas took a decade or two to mature. The source of the idea might be odd or disreputable. Digitalis was found by Withering in the hotch-potch remedy of an old woman in Shropshire; the idea of immunisation against smallpox came from primitive African and Arabian medicine, while Jenner's method started in the farmyard.

Sometimes discoveries were made and lost through lack of interest or comprehension. Satisfactory means of cure of scurvy were known to Jacques Cartier (1536). Insulin had been made and lost before Banting, who only succeeded because the technique of blood sugar estimation had been elaborated. The effect of X-rays had been noted before Roentgen. Tyndall (1875) had observed the anti-bacterial properties of the mould penicillin, while Fleming scored a near miss twelve years before Florey succeeded. Sometimes the right discovery was made when following the wrong lines. The discovery of adrenaline was made when trying to disprove a claim that an extract of the suprarenal glands was inactive when taken by mouth. Whipple's liver extract was thought to accelerate recovery from post-haemorrhagic anaemia. The patients with pernicious anaemia to whom it was given were controls! It was they who responded so dramatically and unexpectedly.

Discoveries, the Professor pointed out, might be made and lost and made again and the invention of a catchword was often an important influence, "vitamins" being an example. The word was coined centuries after clinicians had realised the existence of some curative properties of an obscure character in the diet. The recognition of the bacterial cause of disease was a slow process extending from John Hunter to Robert Koch.

Observations of precision and accuracy might antedate the knowledge necessary to account for them. The Rev. Stephen Hales made precise measurements of expired air but as he was working half a century before the discovery of Oxygen and Carbon Dioxide he was at a loss to account for his observations.

In concluding, Professor McMichael referred to the opposition invariably encountered by new ideas. Uselessness of an observation should never destroy interest. Medicine requires maximum effort and thought, and speculation must always be subjected to the final test of experiment.

* * *

It is only possible to give here an outline of the wide range of ideas and thoughts about research which Professor McMichael elaborated in his address. In fact, it is reasonable to say that this must be one of the most comprehensive dissections ever carried out into the mechanisms of medical discovery.

Even if he wished to, no editor would be entitled to criticise an address of such outstanding scope and quality. Comment, however, is a different thing and we would like to draw attention briefly to one of several thoughts with which Professor McMichael has left us. These are the days of the biochemist and the biophysicist, of grants and scholarships, of elaborate and glamorous laboratories, and of keen competition among the drug firms, the medical schools, and the medical research centres of every sort with which the country is generously populated. Medical scientists in America are supported, as we have been told in the address, by abundant national funds.

How many of us, however, are capable of carrying out pure research on this scale? The scarcity of first-class brains with the enthusiasm and aptitude to make full use of the laboratory means that only a small proportion of medical graduates are capable of conducting full-time research. And it is by his references to Harvey, Withering, Jenner and Koch that Professor McMichael does one of his finest services in reminding us that there always has been, and there always must be, a place for the teacher, the general doctor and even the astute medical man in the street in the progress of discovery and research.

Medical Education—for the Public

In his article on the Treatment of Cancer in this issue, JOHN MCKENDRICK expresses himself forcibly in opposition to the further unrestricted dissemination of medical knowledge to the layman. While he speaks primarily about cancer, the same arguments may be applied to other medical fields, and the conclusion that over-concern with matters of health "is more likely to breed neuroticism than complacency," will find an echo in the minds of many.

There is, however, a reverse to this, as to every question, Besides the need for control of aetiologically significant factors, for which purpose an active and informed public opinion is essential, the need for earlier diagnosis, especially of malignancy, is continually being emphasised. Indeed it may well be that the most important advances of the immediate future in this field will be diagnostic rather than therapeutic.

Until such advances are made, early diagnosis must rest upon the speedy reporting of the significant symptom, and while not all those with recurrent dyspepsia can be given a Barium meal, nor all those with chronic coughs a chest X-ray, amplified investigation of those within the cancer age group with a symptom arising "de novo" might enable us to use what weapons

we have to better effect. If this is indeed so, the potential patient must at least know what the significant symptom is likely to be, and must receive every encouragement to consult medical advice with as little delay as possible.

Would this not lead to a nation which takes its temperature when it cleans its teeth, weighs itself when it washes, and castigates the waitress for bringing a portion over-rich in Cholesterol esters? The risk is there, but the public is neither so foolish nor so ignorant as some seem to believe. Already no small amount of medical information finds its way to the general public by way of the women's weeklies and the *Readers' Digest* and the results do not seem to be unduly demoralising.

Indeed, it would seem likely that most of those afflicted by uncertainty and fear by reason of medical knowledge would be such people as have a predisposition to hypochondriasis. At worst, such people might be converted to worrying about what might conceivably happen, instead of about what most decidedly will not.

Rationalising the Irrational

Visionaries are no longer in vogue. Their decline in social importance has probably been brought about by the advent of a common belief in the superiority of scientific reasoning. In so far as visions are a natural phenomenon they come within the concern of the scientist and are no longer immune to rational investigation. It is now possible to induce states of altered consciousness under controlled conditions by employing various chemical or physical methods, the classical example being the use of the drug Mescalim. The mere taking of a pill does not transform the scientist into a William Blake but it does give him some insight into the otherness of a prophet's world and the uncharted areas of his own mind.

In a fascinating account of his experience with this drug, ALDOUS HUXLEY has described the curious purposeless intensity encountered by the Mescalin taker. He supports the view that the brain is normally only concerned with what is biologically useful and that it is actively engaged in eliminating the majority of irrelevant sensations which it receives from the world at large. The drug reduces the efficiency of this mechanism and a curious state of heightened consciousness is produced. Whatever may be thought of the validity of such an explanation, the essay itself is one of great importance as a description of the impressions of a man blessed with such lucidity of expression that we are enabled, through him, to share some part of his experiences.

Of even greater significance than the scientist's subjective understanding of this detached state of mind is the objective study it enables him to make of the chemical processes which go on within the mind at such a time. The observed structural similarity between adrenaline and Mescalin set off a train of investigations which have already contributed to an understanding of the chemical basis of the mind. The immediate medical importance of this research is in developing our understanding of the schizophrenic disorders which bear some resemblance to these induced states.

As was stressed by LORD ADRIAN in his address to the B.M.A. conference in Edinburgh this year, the chief problem facing workers in this field is that of relating physiology to psychology. Whether such an understanding will ever be attained is indeed debatable. Such a discovery would be of unparalleled significance both from a practical and a philosophical point of view. It is a solemn and awe-inspiring concept that the heart would have no reasons which reason did not know.

Res Medica

In June our first editor and the members of his pioneer committee disposed of the ultimate obstacle and joined the enviable ranks of the wage-earners. The Journal was conceived, produced and weaned by their enthusiasm and indulgence: it has matured strong in its adherence to their ideas and ideals. They will find the pattern of this issue almost entirely their own, little altered by subsequent tampering.

We have, however, disposed of one original institution. The introductory editorial has been replaced by a series of leaders. This is in fact the only major structural alteration the Journal has undergone since it first appeared, and we hope that it will prove acceptable. The presentation of a few items of topical comment in this way can only serve to add colour and character, qualities which are liable to disappear when a single editorial (usually reading well but saying little) consistently introduces the efforts of the contributors. The Journal of the Royal Medical Society must cling to character, beware of stereotype.

For this reason, we are confident of the support in this new move of JAMES GRAY, and also of FORRESTER COCKBURN, A. W. DELLIPIANI and C. V. RUCKLEY. It is also our hope that it will increase the value of *Res Medica*, the success of which is so exclusively their own, and which each, in reviewing his undergraduate career, must regard as an individual triumph.

THE TREATMENT OF CANCER

By JOHN McKENDRICK

Based on a Dissertation read before the Royal Medical Society on Friday, 16th January 1959.

AN overall view of the adequacy of the treatment of cancer at the moment presents a very dismal picture. To be satisfactory this treatment must mean cure, but until the cause or causes of cancer are known this will seldom be achieved.

The possible means of treatment available are:—Surgery, Radiotherapy, Chemotherapy, Serotherapy and Psychobiological methods. Prophylactic measures designed to prevent a person from getting cancer are, of course, of great importance also.

Let us first consider Surgery. The human race has been faced with the problem of cancer for thousands of years. Carcinoma of the breast was described by the Egyptian surgeon Imhotep in the year 3000 B.C. It is mentioned in the papyrus Ebers of the 16th century B.C. and in the remnants of the literature of India and Persia. In those ancient times the mainstay of treatment was excision and caustics and in A.D. 180 Leonides of Alexandria was dissecting out breast cancers extensively, cutting through healthy tissue with knife and cutlery essentially the same technique as is used to-day. In no other branch of Therapeutics has so little advance been made against a disease known for so long. It is a measure of our ability to conquer the neoplastic process that such a crude and primitive procedure as surgical excision should be the main, and in some cases the only, radical weapon at our disposal.

Surgery is successful in curing cancer in so far as it can get right down to the "roots" and remove the growth, plus the immediately surrounding tissues, where there will be a small number of outlying cancer cells. It is thus effective in removing a superficial tumour where no metastases have occurred, such as one of the skin, uterine cervix, bladder, rectum and a few cases of cancer of the thyroid and parotid glands. In other cases a significant remission may be obtained. A surgical procedure may also be effective in relieving obstruction or pressure, controlling infection or stopping persistent bleeding. But, on the whole, Surgery is not a satisfactory method of treatment, and its possible advantages must be weighed against its many shortcomings, which include: mutilation, inadequate removal of cancer cells, further spread of cancer cells, disturbance of the normal physiological mechanisms of the body and possibly death.

There is now an increasing pressure on the surgeon to "do something about cancer." Articles in lay magazines, the "education" spread forth by the satanic T.V. set, reports of ultraradical operations and the patient's natural desire for cure make it difficult to tell those with certain types of cancer that they cannot be helped by operation. Consideration must be given to the fact that the "something" may do more harm than good. The persistent failure of ultraradical surgery to arrest cancers of high malignancy and the devastating side-effects of these operations make it obvious that it is time to give first thought to the patient as a whole, and to develop operations which control the malignant process as well as possible, but with the minimum

deformity and impairment of function. There is some place for radical operations, especially in treatment of cancer of the head and neck, rectum, colon and cervix, but the initial wave of enthusiasm is now being replaced with more caution. Definite rules must be followed in their procedure: they should only be done by specialists, there must be proper selection of patients, at no time should cancer tissue be cut across and the possibility of seeding into the wound allowed to occur, routes of spread must be sealed off as early as possible, the wound should be washed before closure, possibly using cytotoxins and in the future there may be a possibility of administering cytotoxins parenterally before, during and after the operation.

Surgery by itself, however, has probably reached the stage at which no great advance in method can be expected, but there is a field for its possible use in conjunction with other methods.

X-rays were discovered by Roentgen in 1895 and have been used in therapy ever since. The gamma rays emitted by Radium are most commonly used since they have much the greatest penetrating power. Many advances have been made recently in this form of therapy, and its main advantage is that it does not involve the possibility of cutting into malignant tissue. Critical assessment of the results obtained, however, indicates that there is little justification for complacency. There may result increased comfort and palliation, but the long-term or "cure" rates have shown little improvement.

Radiotherapy is especially effective against actively dividing cells, but normal cells are also damaged to a greater or less extent and not all cancers are affected by it.

In general the conservative optimal dosage to all organs is 6000r delivered over a period of time depending on several clinical factors, but most tumours have a wide range of lethal dose. Surface applicators containing the Radium can be moulded to a part of the body and applicators can be placed in hollow organs such as the uterus. Interstitial irradiation is obtained by means of Radium or radioactive Cobalt needles, Radon seeds or radioactive Tantalum wire coated with Platinum to absorb the Beta rays. Such methods are effective against superficial or localised growths. For deeper growths the teleradium or radium beam treatment can be used, but this is usually less successful since the risk to surrounding normal tissue is much increased. The best effects are obtained with carcinoma of the cervix and some lympho-sarcomas.

For many years Radiotherapy has been used only for palliation, but it can be curative when properly applied to certain types of cancer. It is now used in the treatment of seminoma of the testis, dysgerminoma of the ovary, medulloblastomas and lymphoepitheliomas of the throat. The results are not good, but are better than those obtained by methods previously used in these cases.

There is a growing necessity for teamwork between surgeons and radiotherapists to ensure maximum chance of cure with the best functional results. Some tumours are now amenable to treatment using either or both surgery and radiotherapy, and radiotherapy is an alternative to surgery in treating carcinomas of the skin, mouth and lip, cervix and bladder.

Sources of super-voltage therapy are now available, including the super-voltage X-ray machine, betatron, thoratron, the linear accelerator and high specific intensity radioactive sources of Cobalt 60 and Caesium 130, by which means sources of radiation are provided which allow a homogeneous dose to be delivered at a definite volume. Radiation can now be produced with a shorter wave-length and higher energy which penetrates more deeply into the tissues, with less damage to the intervening normal tissues and portals can be shaped to shield the normal tissue and allow accurate high dosage to small volumes.

The emphasis in Radiotherapy is tending to shift to the radiobiological aspects of the tumour and attempts are being made to render malignant tissues more susceptible to irradiation without increasing the vulnerability of the normal tissues. Biochemical methods involving thyroid hormone, adrenocorticoids, oestrogens, androgens and oxygen alter the intracellular homeostasis and so enhance the effects of irradiation. Radiotherapy has also been used along with other drugs, such as Synkavit, nitrogen mustards and Actinomycin D.

Artificial radioactive isotopes were first used therapeutically in 1936 and since then a wide variety of applications have been developed. They have not proved so beneficial as was initially expected, though they can be effective in certain forms of malignancy. Radioactive Phosphorus was the first to be used—this localises in body tissues which have a high exchangeable phosphorus content (especially bone), a high metabolic rate and a rapid rate of cellular reproduction. It is still used in the treatment of polycythaemia vera and chronic lymphatic leukaemia. Strontium 90 applicators can be used to irradiate superficial tumours of the eyelids, conjunctivae and cornea. Colloidal chromic phosphate, radioyttrium and radiogold are now widely used for the control of malignant effusions and are being administered interstitially in cases of carcinoma of the prostate after surgical removal of as much of the tumour as possible. Good results have been reported following intracavitary or interstitial application of Cobalt 60 in a variety of tumours, such as carcinoma of the bladder and uterus, but its use as a gamma source of teletherapeutic units of deep penetration is currently of most interest. Recent studies of autoimmunisation indicate that it may be possible to deliver a radiation dose to tumours using radioactive antibodies. Neutron fission therapy in glioblastoma multiforme is another interesting approach. Boron 10 is administered and the patient is subjected to slow neutrons which cause the Boron to disintegrate into Lithium and alpha particles within the tumour. But it is too early to predict the place of this work in cancer therapy. Radioactive isotopes have still only a very limited use, but they constitute a fruitful field for research.

Chemotherapy, as a rational means of treating cancer, has only recently been developed, but various diverse agents have been used at different times in the past, including belladonna, aconite, mercury, antimony, arsenic and potions of animal, vegetable and other ingredients brewed under the charm of magical incantations. A popular application in this country during the 15th century was a powder made by burning together sulphur, lead and "arnement" (a black powder used for making ink) which was applied to the ulcerated surface after it had first been washed with the urine of a male child. In the 18th century live toads were bound over the diseased part and left there for 24 hours. Live kittens, puppies and fowls, pigeons split lengthwise, minced lizards and pounded crabs have all had their vogue. In 1802 a remedy was published which was to dry the corns and pairings from the feet of an uncastrated horse, beat this to a powder and take as much as would lie on a sixpence in a glass of white wine night and morning. Medicine, greatly helped by Science, has made significant advances since then—or so we would hope.

In the past few years many new chemicals have been developed for use in the treatment of cancer, but in actual practice the therapeutic gains have been very little. No chemotherapeutic agent has been shown to cure a patient of cancer, though in some cases drugs may relieve symptoms, reduce time spent in hospital, prolong life and increase the possibility of eventual cure by other means.

As with other methods of treatment, the efficacy of Chemotherapy depends on the differential sensitivity of tumourous as against normal tissue, and

there is often a slight margin of safety between the effective dosage and that which will cause degeneration of the haemopoietic system and the development of an aplastic bone-marrow.

The chemicals which are available can be divided broadly into three groups: the alkylating agents, the antimetabolites and a small miscellaneous group mainly of vegetable origin.

The alkylating agents comprise a vast number of drugs, including "TEM," "Myleran," "Tretamine," 'Chlorambucil" and the nitrogen mustards. Studies on similar substances have proved that they are effective on certain malignant tumours of mice, human carcinoma of the breast and some C.N.S. tumours. However, nitrogen mustards and other alkylating agents are used mainly in the treatment of the chronic leukaemias and widely disseminated Hodgkin's disease, and may produce remissions of several months or even a year. Direct instillation of nitrogen mustards may decrease or eliminate reaccumulation of malignant effusions and they are of some benefit in the terminal stages of bronchogenic carcinoma, especially of the small cell type. The indications for using nitrogen mustards include: radioresistance, severe radiation sickness, exhaustion of the skin portals, intractable systemic symptoms, acute mediastinal compression, advanced disease and metastatic lesions not amenable to X-ray therapy.

Antimetabolites such as "Aminopterine," "6-Mercaptopurine," 'Pyrimethamine" and "Urethane" are used mainly in the management of acute leukaemia. However, the length of remission obtained is very variable, and these drugs are liable to have serious toxic effects, such as damage to the bone-marrow and alimentary epithelium, and the neoplastic cells are able to develop resistance to them.

The miscellaneous group have two things in common—none of them is of great value and most of them are still undergoing trial. "Colcemid" may have some success against chronic myeloid leukaemia. Actinomycin D is effective to some extent in the treatment of soft tissue sarcomas and some epithelial tumours. Actinomycin C gets a response in a few cases of Hodgkin's disease. Cyanocobalamine has been recommended for disseminated neuroblastoma, particularly in infants.

It has been suspected since about 1925 that Insulin may cause some inhibition in the growth of malignant tissue. Glucagon also has this action and the two combined give an even greater carcinostatic effect. Experiments have been done on rats, and the greatest limitation seems to be that the retardation of tumour growth persists only during the period of administration. These investigations must be carried much further before they can have any application to treatment in humans.

A new method of using drug treatment is now being tried. In the case of certain tumours the blood supply to the tumour-bearing area is isolated, and by using a pump oxygenator system the viability of the limb or organ can be maintained while at the same time it can be perfused with high concentrations of chemotherapeutic agents sufficient to destroy the cancer cells but unable to destroy the normal host tissue cells. The temporary isolation of the blood supply prevents the passage of the agent into the bloodstream and thus prevents bone-marrow depression.

Better results may be obtained using a combination of drugs, or of drugs with radiotherapy. The normal physiological activity of the cancer cell is disturbed either by direct alkylation of cell constituents, blocking essential metabolic pathways, interfering with the normal enzymatic reactions, altering the hormal milieu of the cell or by the effect on the mitotic activity and chromosomal structure produced by ionising radiation. Thus different

methods of treatment may have a synergistic effect when applied in combination.

The use of specific hormones is another aspect of Chemotherapy, and combined with endocrine ablation therapy has proved of value in the palliative treatment of breast and prostatic carcinomas. Oestrogens may favourably affect the primary growth on the soft tissue metastases and also relieve the pain of bony metastases. They should be reserved for inoperable breast cancers in women who are at least 5 years past the menopause, and for prostatic cancers when the testes are known to be producing androgens. Androgens are of little use and may in fact exacerbate tumour growth, probably due to conversion of oestrogens. About 50% of mammary carcinomas are oestrogen dependent and will respond favourably to removal of endogenous sources of oestrogens, such as the ovaries, adrenals and hypophysis.

Serotherapy has yet to become a practical procedure and may not do do so until the cause or causes of cancer have been better elucidated. There is now much research into the theory involving a transmissable viral-like particle found in the cell cytoplasm. A serum specific to the virus of avian myeloblastic leukosis has been developed and this is able to neutralise the infectivity of the virus. Research into the application of this theory to treatment has, as yet, produced equivocal results.

Psychobiology is another way of regarding the chemical, nervous, hormonal or electromagnetic environment of the cancer cell. Since both the host and a cancer draw on a common nutritional substrate and share a common vascular supply, it seems desirable that attention should be given to the metabolic equilibrium and growth partition which exists between them. This contest can be turned in favour of the host cells by spontaneous activity of the body itself without any apparent assistance, but the phenomenon of spontaneous regression is still a complete mystery. Perhaps some people are able to develop antibodies against a possible cancer virus or have hormonal changes which lead to death of the malignant cells. Such possibilities are all remote, but the fact that the body sometimes knows how to kill cancer may some day show the way to a method by which all cancers can be killed.

In general, treatment should be directed at the patient-tumour system and not at the tumour in imaginary isolation. The difiicult question of the relationship between stress and host resistance has been slightly clarified recently and it appears that an unavoidable accompaniment of the disturbed physiology of the stressed organism is diminished resistance to disease, including cancer. A definite inverse correlation between psychotic withdrawal from reality and the incidence and progression of malignant tumours has been noted; in withdrawn patients' response to therapy, if any is required at all, is usually excellent and they can expect much longer remissions than their anxiety-ridden fellow sufferers. This is added proof that cancer is not a predictable, irreversible process and that every effort should be made to improve the patients' emotional state. Confidence in the healing ability of something or someone has proved curative in many organic lesions, including cancer.

Of supreme importance in the treatment of cancer is the physician who meets the patient as an individual with a problem, whether he be suffering from cancer or cancerophobia. This latter is a powerful new disease, insidious, contagious and crippling and its increasing incidence is greatly contributed to by the medical propagandists who have in the past consistently used the weapon of fear in their relations with the public. The question arises whether or not to educate people about cancer, and since "scare them

out of their wits" is nearer what actually happens, it is certainly undesirable. Instilling knowledge into people about cancer will probably have the opposite effect to that desired, will do no good to their mental health and may cause great suffering. Stimulated by fear we may find Man reverting to the time of the ancient Egyptians and diverting all his efforts to the building of tombs.

Some education about cancer is necessary—that regarding avoidance of those factors which are known to be liable to initiate a cancerous growth. Some of these are occupational hazards such as tar and aniline dyes and assorted factors such as X-radiation, cigarettes, clay-pipes and atomic bombs.

Gallstones and chronic gastritis should be promptly treated, as should lesions with a definite malignant potentiality such as some bone growths, papillomatous growths (especially of the large bowel), some glandular hyperplasias and hydatidiform moles. But there is a danger in the so-called "prophylactic operation" which may, in fact, over a large number of cases cause more deaths than would have resulted had the operations not been done.

An important new development in prophylactic treatment is the routine examination of cervical smears when women over about 30 are under examination for some other gynaecological complaint. Many "carcinoma in situ" may be detected by this means, and it is reckoned that 50% of these will eventually progress if not treated at this stage, though actual symptoms may not be experienced for about ten years and the diagnosis not made for a further five years. Also in the case of a persistent pneumonia, especially in a middle-aged male, it is advisable to do chest X-rays, bronchoscopy and examination of the sputum for malignant cells. These, at the moment, are the only two routine procedures which can be recommended, since the technique is simple, the patient need not be unduly disturbed and the number of cases in which a diagnosis of malignancy is made will be relatively high. Routine medical check-ups on healthy individuals involving thorough physical examination, X-rays of the whole body, bronchoscopy, gastroscopy, cystoscopy, proctoscopy, colposcopy, etc., etc., etc., as are often recommended, should in fact be discouraged since the procedure is more likely to breed neuroticism than complacency.

At the moment surgeons and radiotherapists are well aware of the many defects in their particular forms of treatment and, along with the other members of the team, these and many other difficulties are being attacked with optimism and enthusiasm, and so: "O Tempus Futurum, te magna spe expectamus!"

DOCTORS AND ARTISTS

By PROFESSOR W. I. C. MORRIS
F.R.C.S.E.
Professor of Obstetrics and Gynaecology,
University of Manchester

In "The Doctor's Dilemma," Bernard Shaw suggests that there is more antagonism than attraction between the doctor-scientist and the painter. The average doctor may, however, make some claim to be an artist. In his professional work, art plays some role, even if it is restricted to that much-maligned professional accessory the bedside manner. Doctors in their hobbies sometimes display a wider taste in art—for instance as painters or collectors.

It is, however, my desire in this article to deal less with the links between doctors and art than with those between certain doctors and their artists. From the introduction of printing these links have been very close. The medical text-book has always required skilled illustration to make intelligible a letterpress which has not always been artistic. Many works of great medical importance owe their lasting fame as much to the perspicacity and skill of the illustrator as to any other inherent merit.

My own interest in this particular subject arises from my browsings in the historical literature of obstetrics and gynaecology. In the various incunabula there appear a number of woodcuts. Engravers of modest skill have chiselled out the grooves to hold the printer's ink, and have printed, from these, illustrations which appear to us now to be quaint rather than instructive. Indeed it is not until the eighteenth century that really accurate pictures begin to appear, and the starting point for my consideration is actually in 1774, when the historic Atlas of the Anatomy of the Human Gravid Uterus was published by Dr William Hunter. It is doubtful whether William Hunter was a particularly skilful obstetrician, though he must have been one of the most successful. There is no doubt, however, of his massive contribution to the knowledge of the anatomy of his subject.

Copies of William Hunter's Atlas are found in many libraries, and probably in some private collections. The library of the Manchester Medical Society is fortunate in possessing a copy in very good condition. It is a large volume of the type referred to as an elephant folio. The title page, like the rest of the work, is in duplicate sections, one in Latin, the other in English. It sets out the qualifications of the author, which included the posts of Physician Extraordinary to Queen Charlotte (consort of George III), Professor of Anatomy in the Royal Academy, Fellow of the Royal Society and Fellow of the Antiquarian Society. The work is set in beautiful type and is printed by Baskerville in Birmingham. The subsequent pages show magnificent life-size illustrations, interleaved with parallel columns of prose in Latin and in English, which provide a most lucid description of the picture displayed. Incomparably the best of such pictures is one which shows the full-term child in the presentation position and attitude frequently adopted by the unborn infant. For precision and accuracy this picture is still quite unrivalled by any modern techniques of illustration.

William Hunter was singularly fortunate in having available an artist

whose greatness was fit to be measured with his own. Comparatively little is known about this particular artist. His name was Jan van Rymsdyk, and it seems pretty certain that he came to London from Holland and may well have been introduced to London teachers of midwifery by Peter Camper, who was eventually Professor of Anatomy and Midwifery at the University of Leyden.

Van Rymsdyk's name appears on each of the plates in Hunter's Atlas. His original drawings were executed in red chalk, and are preserved in the Hunterian Museum of the University of Glasgow. Undoubtedly, William Hunter must have thought highly of him, but the terms in which he acknowledges assistance received in the preparation of his Atlas make no reference to van Rymsdyk by name:

> " If it be allowed that the author has spared neither labour, nor time, nor expense in improving an important part of anatomy, this is all the merit that he can claim. In most of the dissections he was assisted by his brother, MR JOHN HUNTER, whose accuracy in anatomical researches is so well-known, that to omit this opportunity of thanking him for that assistance, would be in some measure to disregard the future reputation of the work itself. He owes likewise much to the ingenious artists who made the drawings and engravings; and particularly to MR STRANGE, not only for having by his hand secured a sort of immortality to two of the plates, but for having given his advice and assistance in every part with a steady and disinterested friendship."

It is not part of my present plan to discourse on the personal relations between William Hunter and his brother John. Suffice it to say that the paragraph quoted was in later years deemed by John Hunter to be an insufficient acknowledgement, while the entire lack of reference to van Rymsdyk certainly wounded that sensitive soul. On the other hand, the flowery expression of thanks to Mr Robert Strange, upon whom van Rymsdyk almost certainly looked as a mere engraver, may, in its way, have given equal offence.

Here we come up against one of the main differences between the delineating artist and the engraving artisan who prepares and transmutes the artist's work into graven lines suitable to receive the printer's ink. In general, the original artist is a creator, the engraver is a copyist. Ruskin says, " Engraving . . . is in brief terms the art of scratch." There seems no doubt, however, that William Hunter regarded his engraver as more worthy of specific thanks than he who originally drew the pictures.

Of the eighteenth century engravers, Robert Strange was probably the best known and the most successful, but William Sharp and William Woollett are still famous, while Hogarth himself first made a living as an artist by engraving family silver, door plates, seals and other commonplace articles. It is probable that many other famous artists of the brush or pencil passed through this particular apprenticeship.

Robert Strange was born in Orkney. His family came from the Kingdom of Fife. He was born in the year 1721 and after a classical education in Kirkwall he made his way to Edinburgh, where he was eventually apprenticed as a Writer to the Signet, to his stepbrother, who was already established in legal practice in that city.

There was a wide disparity in their years, but it is clear that the older man treated young Strange with quite exceptional kindness, tact and consideration. Strange has left a vivid account of the circumstances in which he idly occupied his time, drawing in pen and ink, " sometimes from my own fancy, others from the ornaments and title pages of books, etc." These

drawings he concealed from a certain sense of guilt, but the brother accidentally discovered them, and, recognising real talent, took steps to obtain the criticism of one better versed in artistic matters, as a result of which Robert Strange, with his brother's approval, discontinued his legal studies and became apprenticed to Richard Cooper, an engraver of some distinction.

Cooper was a Londoner. He maintained quite a large training establishment in Edinburgh. Cooper's son eventually became drawing master at Eton, but Strange himself seemed very likely to become the successor to his master in the expanding world of medical illustration in Edinburgh. He became acquainted with Alexander Monro, First, and engraved a number of plates for him. He tells that he became some sort of favourite of this great anatomical teacher, and it is probable that his first commission was to illustrate an anatomical specimen of unusual cranial ossification. The illustration is still extant, although it bears the name of Richard Cooper, not Robert Strange.

Whatever might have been the destiny of Strange, it was completely altered in the year 1745. At this time, Strange, already having certain Jacobite sympathies, was enamoured of a Miss Isabella Lumisden, whose Jacobitism was fervent and uncritical. It is said that she informed Strange that his advances would meet with no favour unless he joined the forces of the Young Pretender, which Strange did, becoming a member of the Prince's Life Guards, a rather curious cavalry formation commanded by Lord Elcho. Strange took part in the campaigns of 1745 and 1746. In addition to combat, his activities included the execution of a portrait of Prince Charles Edward Stuart, a portrait which was far from flattering but may be for all that a truer likeness of the so-called " Bonny Prince " than those which are now in circulation. Strange could not resist showing his latinity in the quotation from Virgil in which he described the Prince as sent to set right the times that are out of joint.

Another engraving which Strange executed at this time was a copper plate designed for the printing of bank notes. This was completed just before the battle of Culloden. The notes were never printed and the copper plate was lost in the rout, and remained lost until 1835 when it was accidentally discovered in Loch Laggan. Prints were recently made from this plate by the late Sir D. Y. Cameron. They are difficult to read and confused, but this is hardly surprising after 89 years exposure to the elements. From different sections of the plate a composite picture has been prepared, showing the Prince's cipher under a coronet decked with the three feathers of the Prince of Wales, with an entwining thistle for Scotland and a multitude of martial background subjects.

Little is known of how Strange escaped from the battlefield. It appears, however, that he made his way to Edinburgh where he was sheltered by Miss Lumisden, to whom he was married in 1747. There is a highly romantic story of how she sheltered him from searching soldiers under the wide hoops of her skirt, the while she sang loudly the Jacobite songs which she thought appropriate for the occasion. The authority for this story is Richard Cooper younger, the drawing master at Eton. It is, however, almost too good to be true.

When Strange was studying in Edinburgh before the rebellion, there dwelt only a few hundred yards from Richard Cooper's atelier, an eccentric wigmaker named Allan Ramsay. This man was well known as a bon-viveur, and had an easy taste for song-writing, and even for some major works, such as his pastoral drama " The Gentle Shepherd." He had a son, also named Allan Ramsay, some eight years older than Robert Strange. It is doubtful if they ever met in Edinburgh, but by no means impossible. They were certainly well acquainted in later life, for Allan Ramsay Junior, after studying in

London and in Rome became established as a fashionable portrait painter, and indeed in the 1750's he became THE fashionable portrait painter of London, proceeding in 1767 to become personal portrait painter to His Majesty King George III. The King was notoriously apt to present portraits of himself to his various friends, and Ramsay was rarely short of commissions. Before his royal appointment he had in fact amassed a considerable fortune, and through his charm and address became a person of no small influence. Even Dr Johnson, whom Lord James has described post-prandially as " that bellicose old boor," said of Allan Ramsay Jr., " You will not find a man in whose conversation there is more instruction, more information and more elegance than in Ramsay's."

About the year 1759 Allan Ramsay painted full-length portraits respectively of George III, then Prince of Wales, and the third Earl of Bute, later George III's very unsuccessful Prime Minister. Strange was approached by Allan Ramsay to engrave copies of these portraits for general sale and distribution, under the patronage of the Prince of Wales. Strange refused. The request was repeated directly by the Prince of Wales himself. Strange again refused.

The reason for Strange's refusals cannot now be exactly determined. The remuneration offered for the work (£100) was regarded as ridiculously low by 18th century standards, and the fee eventually paid to the engraver who did undertake the work was very much more. It seems quite certain, however, that Strange's reluctance to undertake this commission was attributed, if not attributable, to his distaste for the House of Hanover. At all events, the immediate consequences to Strange were very serious. In the great days of aristocratic patronage, royal disfavour was a serious professional handicap. Strange found it necessary to withdraw from London and spent the next five years in Italy. There he engaged in making chalk copies of works of the Italian masters, from which he subsequently prepared engravings, prints of which he published on his return to London about 1765. There seems no doubt that this was Strange's most useful service to art appreciation in Britain. The engravings were published with Strange's critical comments, and, while they could not in any way emulate the glorious originals, it has been said that " in several of the higher qualities of his art he is unsurpassed. His tender, flowing line gives a peculiar delicacy and transparency to his flesh, and his works are excellent in power, drawing and character."

Despite this distinction, grave disappointment awaited Strange. When the Royal Academy was founded in 1768, engravers were specifically excluded from its membership. Strange felt obliged to protest about this in print. In 1775, that is in the year after the publication of William Hunter's Atlas, Strange published an attack on the Royal Academy, prefaced by a letter of reproach to Lord Bute, now Prime Minister. This produced no favourable response, and Strange removed with his family to Paris, whence he did not return until 1780. We shall quite shortly note events following this, but for the moment I propose to call your attention to yet another artist, one Benjamin West. So far as I know, he had no close link with medicine, except through his friendship with Robert Strange.

Benjamin West was born in Springfield, Pennsylvania, in 1738. He was therefore 17 years younger than Robert Strange. West had a backwoods education. He is said to have had his first instruction in art from a Cherokee Indian. Nevertheless, he received early notice in the admirably liberal society of 18th century Philadelphia, and by the age of 18 he had set himself up as a portrait painter in that city. In 1760 when he was some 22 years old he went to Rome to study. He received much attention as a handsome young American, with a supposedly savage background. As his stay there corres-

ponded with one of Strange's Italian periods, it is more than likely that they met and established then their friendship.

In 1763, West came from Rome to England. His Philadelphia patrons introduced him to their friends—including Dr Johnson, Edmund Burke and Joshua Reynolds. Despite the alleged deficiences in his education, he endeared himself to all. His particular forte was the imaginative production of historical pictures. His most famous include the Death of Wolfe, William Penn's Treaty with the Indians, and the Battle of the Boyne.

In 1772, Benjamin West was appointed historical painter to the king. His mural decorations to St. George's Hall, Windsor, are still in existence. In 1792, he was elected President of the Royal Academy, an office which he held, except for one year, until his death at the age of 82 in 1820. His private life was irreproachable. He was kind to young artists, free from jealousy, and generous beyond his means. He was offered a knighthood, but declined. So far as I know he is the only American to have held the office of President of the Royal Academy.

It was to Benjamin West that Strange applied for help on his return from France in 1780. Strange had conceived a wish to engrave two of the Van Dyck portraits of Charles I and Queen Henrietta Maria with her family. These portraits were in Windsor Castle, and, through West's intercession, Strange was allowed to copy them there.

Although Strange's wife never lost her strong Jacobite affiliations, it seems likely that Strange was no longer rabid. George III, now aged 42, was probably less irascible than when Strange incurred his emnity in 1759. At all events, Strange was courteously received by George and by his family, who used frequently to visit him as he undertook the meticulous chalk copies of the famous paintings.

It was 1784 before the plates were ready. The prints proved an enormous success, and Strange, in gratitude, copied and engraved the picture which Benjamin West had painted to commemorate the lamentable death of two of the King's progeny, the Princes Octavius and Alfred. Known as the "Apotheosis of the Royal Children" this is no doubt a little sickly to modern taste, but it is possible that Strange admired it, and it is certain that the King was fond of it. From the Gentleman's Magazine of January, 1787, the following is extracted:

"January 5th. Friday.

> Mr Strange had the honour of presenting to Their Majesties at the Queen's Palace, some fine impressions of the Apotheosis of the Princes Octavius and Alfred, which he has lately engraved from a picture painted by Mr West, in the royal collection. Their Majesties were graciously pleased to express the highest approbation of this last work of Mr Strange; and in consequence thereof, he was afterwards introduced at the levée at St. James, when His Majesty was pleased to confer on him the honour of knighthood."

There is a rather charming account of the manner in which the King informed Strange of his desire to confer a knighthood on him. "It is my desire, Mr Strange, to confer an honour upon you, that is, of course, provided you have no objection to receiving a knighthood at the hands of the Elector of Hanover." The wheel of fortune had come full circle. He who in youth rode in the bodyguard of the Young Pretender, now was admitted to the chivalry of George III.

There is an interesting little echo of the knighthood. The only portrait of Robert Strange which I can trace is an engraving in the National Portrait Gallery. It bears the legend: "J. B. Greuse, delineavit. R. Strange, eques, sculpsit"—Drawn by Greuze, engraved by R. Strange, knight. This dates

the engraving as 1787 or later. The date of execution of the original I do not know. Nor do I know where the original is housed. According to Charles Trotter, writing in the Dictionary of National Biography, Strange had the honour, during his Italian visit of 1760-64, of having his portrait painted on the ceiling of the print room in the Vatican. Perhaps this painting may still be in existence, and may be the original from which Strange prepared his copper plates. Certainly the portrait is more like that of a man of forty odd than one of 66, as Strange was at the time he received his knighthood. Strange died aged 71 in 1792. His gallant consort, still hoping for a restoration of the Stuarts, survived until 1806.

I have enjoyed my enquiries in this colourful chapter. I still think Strange, van Rymsdyk and William Hunter made a fine artistic team. I would not have you think, however, that it is my opinion that medical art died with them. Far from it. With new graphic techniques, with the development of photography, and with the close collaboration between the delineating artist and the blockmaker, medical illustration still improves.

SOME ASPECTS OF RHEUMATIC FEVER

By DAVID J. CLARK

Based on a Dissertation read before the Royal Medical Society on Friday, 27th February 1959.

Hippocrates described "severe pain in the joints, which fixes itself presently in one joint, presently in another, of short duration, acute, non-fatal, and more inclined to attack the young than the old." Bouilland called attention to the all-important carditis in 1840, and the modern study of rheumatic fever began at the turn of the present century when Newsholme investigated its epidemiology.

Many rheumatic fever patients have experienced a "sore throat" in the fortnight before their illness, and all show a significantly raised level of antibodies against *Beta* haemolytic streptococci of Lancefield's Group A. Quite a large proportion are unaware of their infection because of its sub-clinical nature.

In relating the acute rheumatic illness to the cardiac damage, a general tendency for a severe acute indisposition to be followed by serious cardiac deformity may be distinguished, and children who go into cardiac failure have a particularly poor life expectancy. Nevertheless it is unwise to make prophesies for the individual patient. A mild attack of rheumatic fever may be followed by crippling endocardial disorganisation, while a healthy middle-aged individual will cheerfully announce that during childhood he was extremely ill with acute rheumatism. The rheumatic patient may therefore first present with tonsillitis, with rheumatic fever itself, in cardiac failure later on in life, or with the sequelae of cardiac disease (notably bronchitis, pneumonia and subacute bacterial endocarditis).

This absence of quantitative relationship between infection, fever, and chronic heart disease has made the statistical study of rheumatic fever very difficult. The following statistics may perhaps interest the reader, but their accuracy is impossible to guarantee.

The annual disability in terms of days per thousand of population was in 1955 equal to that for tuberculosis.

Ten years ago there were two new cases per thousand school children per year. Today the figures are probably only a tenth of that number.

Approximately 20,000 people die each year in Great Britain from rheumatic heart disease.

Findlay (1937) reported that of 700 rheumatic patients, one third died before middle age, one third reached it with clinically detectable rheumatic heart disease and one third appeared to be unscathed. Hill agrees with these figures.

Rheumatic fever is commonest in February and March and least common in July. The affliction is rarer in hot dry climates than in cold damp ones, and it prefers to attack the poor and the overcrowded. These tendencies can all be assigned to the epidemiology of streptococcal infections. The

strong familial tendency that is sometimes found, and the slight preponderance of female children, are more difficult to explain, and though the familial tendency may, to some extent, reflect a liability to infection, it is likely that both of these factors reflect a property of the rheumatic process *per se*.

But what is the rheumatic process *per se*? It has been shown that the streptococcus is not itself present in the lesions. It has been proved that no particular one of Griffith's types is involved, and some workers have suggested on the basis of animal experiments that a series of Griffith's types may be needed like the ingredients in a cocktail. This suggestion has received little support. For the moment the "allergic" explanation seems to be preferred, but what this adds to our knowledge of the fundamental processes is very hard to say. It was found by autopsy at the Post Graduate Medical School in London that of those who died between the ages of 40 and 60, 6% showed gross evidence of rheumatic heart disease, and 90% showed microscopic evidence. One wonders whether streptococcal infection is always followed by some degree of cardiac damage which reaches serious proportions in those who are called "allergic."

The importance of rheumatic fever stems largely from its tendency to damage the cardiac valves and the first aim of treatment is to minimise this effect. The available methods are to some extent symptomatic but they do tend to reduce the damage

Hilton's classic work "Rest and Pain" was followed by the introduction of bed rest in rheumatic fever therapy. The obvious importance of this measure has prevented any modern scientifically inclined physician from running a clinical trial with a non-resting control series. In 1941, however, a resting "obedient" group of patients were compared with a "disobedient" group and Taussig and Goldberg were convinced that improved results were obtained by virtue of bed-rest. Moreover, it has been claimed since that time that there is a relationship between cardiac output and cardiac damage. When one crosses the gulf between theory and practice, however, a different problem arises. It is difficult for a child to remain as inactive as science demands. One has seen children, in the earliest stages of convalescence having pillow fights, playing football, wrestling, sprinting up and down the ward and jumping in and out of bed, doing, one assumes, grave damage to their hearts. Several such episodes were followed in a few hours by relapse. There seemed little sense in feeding these children from drinking cups and giving them bed baths in the morning (sister being on duty), when, unsupervised, they were creating riots in the evening. The ideal is that little boys and girls should lie as still as possible for many weeks, and Bywaters is investigating the use of sedatives to help make this ideal attainable.

In 1874 MacLagan introduced salicylates for acute rheumatism, and though some workers regard them as exclusively symptomatic, others believe that they reduce the cardiac involvement as well. Their antipyretic action must lessen the demands on the cardiac output, and they certainly reduce the ESR, which is the best index of the patient's progress during the acute phase. Reduction of the salicylate dosage is sometimes followed by relapse, which is again controlled by increasing the amount. This should be enough to control the ESR and joint pains and yet not enough to produce severe toxic symptoms. When these aims cannot be achieved steroids may be of dramatic assistance. There are at least six main theories for the method of action of the salicylates, but these need not be thrust upon the reader.

The supporters of the focal infection theory were proved wrong when penicillin failed to prevent cardiac damage in the established case of rheumatic fever, and one wonders whether the reputation of penicillin is still

suffering from this blow. Penicillin should be used in large dosage as soon as the diagnosis is made, not in the hope of reducing the cardiac damage but rather to eradicate any residual streptococcal infection. Before the discovery of penicillin it was not uncommon for an unhappy surgeon to be forced to perform an emergency tonsillectomy on a critically ill child.

The high recurrence rate of rheumatic fever can be completely abolished by faithful dosage with penicillin or sulphonamides. The prognosis is worse after two attacks than it is after one, and since two patients out of three do sufler from more than one attack if untreated, this prophylactic measure is of the greatest importance. Its value goes yet deeper than this. Comparison of a treated group with a non-treated group who had not suffered a second clinical attack indicated a better cardiac state among the treated than the untreated patients. From this it would seem that periodic subclinical infection may have caused additional though unsuspected damage, and in this discovery may lie part of the answer to the question "Why is a mild attack sometimes followed by severe cardiac disability in middle age?" Prophylactic antibacterial therapy should prevent any such infection. Once again, however, there is a great difference between theory and practice. "It is surprising that routine protection of rheumatic children in this country should lag behind that in the United States, where, during the last twenty years, it has been universally accepted. In this country it has been practised in only a few centres. There are only a few consultants and practitioners who at this moment employ what is now a proven method of prevention," says Bywaters in an illuminating article in the *Practitioner*. Rheumatic fever is the result of an abnormal relationship between the body and certain streptococci. By using drugs to maintain a constant antibacterial level in the blood we can prevent the presence of those streptococci and so make it impossible for the abnormal relationship to occur. Either the doctor is not giving the patient his drugs or the patient is not taking them regularly. Both of these faults occur fairly commonly in this country.

Work on tuberculosis has shown that the public are often very careless when they are entrusted with their own care, and it is extremely difficult to ensure that children will swallow their sulphonamides or penicillin in the proper amounts and at the proper times. As in diabetes, the more intelligent patients might derive great benefit from education in this matter. In others the long-acting penicillins could be injected regularly by a district nurse. It is obviously difficult for a busy doctor to give such patients adequate care. There can be no doubt that much better and more effective treatment could be given to the vast majority of rheumatic children.

The common objections to the prophylactic therapy are that the treatment is expensive, that allergic reactions might be evolved, and the presence of resistant stages of bacteria encouraged, according to Professor Bywaters. None of these arguments is valid. The cost of prophylactic antibacterial drugs is about 2d. per patient per day. By saving recurrences and by limiting cardiac damage, the country will be spared heavy expense. In the course of five years treatment of 500 patients at Taplow there was one serious case of allergy to the prophylactic penicillin, and one case of agranulocytosis, recovering after treatment among the sulphonamide-takers. Of the third argument Bywaters says: "Streptococcal resistance to penicillin does not occur, and only under epidemic conditions has sulphonamide resistance appeared. Staphylococcal resistance to penicillin may be a nuisance but is unlikely to cause trouble in home conditions. We have no trouble on this score." No doubt every regime has its disadvantages, but in this case these are so heavily outweighed by the advantages of prophylaxis that they can

be dismissed. Prophylactic treatment has been advised for the following groups:—

(*a*) For patients who have had one attack—treatment is advised until they are 25 years old.

(*b*) For children of susceptible families.

(*c*) For National Service recruits.

Another field of preventive treatment arises in tonsillitis. Until the fifth day of a streptococcal throat infection vigorous penicillin treatment can save the patient from rheumatic fever. Every rheumatic fever patient should be told to report to his doctor whenever he gets a sore throat. If prophylactic therapy is not being given, or if the patient becomes careless, this can very easily occur.

In 1953 cortisone appeared, and it was hoped that rheumatic carditis could be suppressed if the anti-inflammatory action prevented vascularisation and fibrosis of the valves. A clinical trial was held in twelve centres in Britain, America and Canada, and after a year the results for cortisone and corticotrophin were no better than those obtained with the humble aspirin. The pendulum of opinion seemed now to swing away from cortisone, and it seemed that no progress had been made by introducing the drug. Illingworth *et al*, however, tried the effect of combining cortisone and aspirin, and they claimed better results for the combination than for either drug separately. Later, it was decided to hold a second international clinical trial, this one to last for three years and to use a wider range of cortisone dosage. This trial is still in progress.

In the meantime Hill comforts us with the news that, in some cases, steroids are remarkably effective. Unfortunately, there seems no way of telling which cases these are except by trial and error. Some of the drug houses think that steroids should be used in preference to the nasty-tasting salicyclates, but no independent body has yet lent support to this view.

In this short article no mention has been made of surgical treatment, since it belongs not in the preventive category but rather to that of undoing damage which has already occurred.

ABDOMINAL PAIN

By GEOFFREY T. MILLAR
M.B., Ch.B.

Based on a Dissertation read before the Royal Medical Society on Friday, 30th January 1959.

" Every pain has its distinct and frequent signification if we will but carefully search for it; pain the monitor is a starting point for contemplation which should ever be present to the mind of the surgeon in his reference to treatment."

With these words, John Hilton advises us to regard the symptom of pain with suspicion. Many causes of pain are of organic origin, but pain of psychological origin also betokens an alteration in the state of health of the patient.

Pain is the only visceral sensation which man can appreciate. William Harvey remarked on the insensitivity of viscera in these words—" I carried the young man to the king that His Majesty might with his own hand behold this wonderful case—that in a man alive and well, he might, without detriment to the individual, observe the movement of the heart, and with his proper hand even touch the ventricles as they contracted. And His Most Excellent Majesty, as well as myself, acknowledged that the heart was without sense of touch, for the youth never knew when we touched his heart." This remarkable experiment has been repeated on other viscera in operations under local anaesthetic and in cases of external fistulae. It raises the question of the mechanism of the production of pain. Perhaps it is fortunate that space does not permit a discussion of this searching question.

There is a wide variation in man's response to the stimulus of pain. Age may play a part in this, for infants, adolescents and adults sometimes appear to vary in their susceptibility to pain; we seem to harden ourselves to it with the addition of years. Again, individuals obviously vary in their tolerance of pain. We read of the disarticulation of the foot of a wounded Cossack (and of three fingers and their metacarpals of his comrade) without any anaesthetic. The surgeon tells us that the Cossacks were less perturbed by the operation than he was himself. The Indian fakirs on their beds of nails and those unusual cases of people refusing operative anaesthesia for moral and other reasons, recall the phenomenal demonstrations of hypnotism in a class of psychiatry or in the music-hall. Even to look at a picture depicting an early operation makes one shudder. However, with the advance of civilisation and the advent of pain-relieving drugs, we have perhaps become more pain-sensitive. Well indeed might the purist, replying to the question " Where do you feel the pain? ", reply " In the sensorium."

The understanding of abdominal pain requires its subdivision into visceral (or splanchnic) and parietal components. Each component depends on an effective stimulus if pain is to be felt. We cannot be sure of the precise nature of the effective stimulus, but evidence suggests the compression of a sufficient number of nerve elements, and this is enhanced by the accumulation of tissue metabolites in a relatively ischaemic field.

Visceral pain is the pain of colic, of muscular spasm in a hollow viscus. This is the type of pain felt in acute intestinal obstruction, when its coming and going is associated with a wave of peristalsis passing along the gut. The patient is often more aware of its coming than of its going. It is also the pain of labour as the contractions pass through the myometrium. In the form of biliary and renal colic it is cited as one of the most severe pains

known. The biliary passages and the ureter are both small-bore tubes and the colic is usually due to the pressure of a relatively solid object. Sir David Wilkie, who suffered both, considered renal colic to be the more severe. As a symptom, colicky abdominal pain is extremely important, for it may be an early symptom of a serious condition and therefore of great diagnostic value. A residual soreness or tenderness (after the acute attack has receded) appears in many instances.

The region of the abdomen in which visceral pain is felt is dependent on the embryonic formation of the gut, with its bilateral innervation. It has been stated that pain produced in the appendix, stomach, or the rest of the gut is invariably situated centrally in a definite and constant site for the simple reason that the related innervation was acquired, and the reference map in the cerebrum completed, while the gut was a short midline tube. Future migration of certain parts of the later elongated and tortuous intestine alters neither the reference map nor the local sign. The registered address remains constant. The embryological divisions of foregut, midgut and hindgut can conveniently be transferred to the anterior abdominal wall, where they are represented, roughly speaking, by the epigastric, hypogastric and umbilical regions. It is deep to these regions that splanchnic pain originating in the appropriate viscus is felt. It is there that the initial pain of visceral disorder is located by the patient, and, by taking careful note of what he says and where he points, the surgeon can learn much that will help him to make the diagnosis.

There is in the reference map a tendency for a constant error of draughtsmanship in one direction. The map always indicates that the pain is felt higher in the abdomen than the anatomical site of the viscus in which it originates. This rule of superior localisation has been explained by the adoption of the upright posture, all the abdominal contents shifting caudally under the influence of gravity. It appears that the quadripeds used for experiments in this field keep their viscera relatively nearer the cranium than we do.

Some extra-abdominal lesions cause pain to be felt in the abdomen, and some intra-abdominal pathology brings about pain in other sites. In the first category, a neglected source may be the fashionable prolapsed intervertebral disc lesion although there are many others more common. Surgeons have operated on cases of what they thought to be intra-abdominal disease when a spinal tumour turned out to be the underlying pathology. This might be even more uncommon than it is if careful history-taking and a full examination of the patient in pain were to take place instead of the spot diagnosis based on faulty intuition. The often-cited example of irritation of the diaphragm (in the course of a disease process or else experimentally) causing what is called " shoulder-tip " pain, complies with the statement quoted above in relation to the acquisition of nerve supply at an early embryonic stage. The diaphragm has its embryological origins in the tissues of what is later to become the neck, and in its migration to the anatomical site which it eventually occupies, it does not acquire an additional nerve supply. Although the precise region is of little importance clinically, it should be pointed out that the shoulder-tip may extend in the mind of the subject from the root of the neck to the greater tuberosity of the humerus. The pain is not so variable as the term " shoulder-tip." In patients undergoing phrenic nerve crush operations for pulmonary tuberculosis under local anaesthesia, it was found that the pain was always felt, at the moment of crushing, two inches above the mid-point of the clavicle. The term " referred pain " is applied to this phenomenon.

Irritation of the parietal layer of the peritoneum by chemical or infective agents causes continuous abdominal pain which is not relieved except by removal of the cause by surgical intervention, or by one of the natural pro-

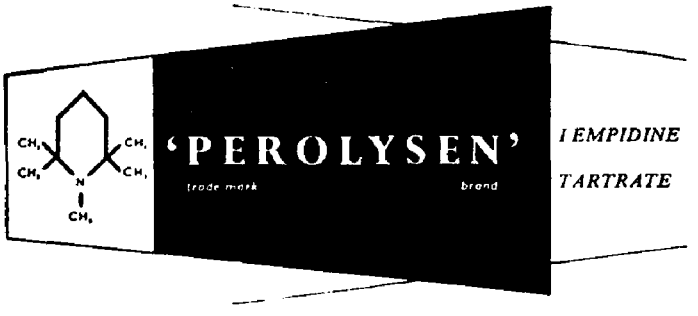
for the control of hypertension

'Perolysen', the newest ganglion blocking agent synthesised in the M&B research laboratories, has an autonomic ganglion blocking action resembling that of mecamylamine, but of shorter duration. It is devoid of other pharmacological actions in the dosages used clinically.

The moderate duration of action ensures that any necessary dosage modifications are rapidly effective.

'Perolysen' is presented as tablets of 1 mg., 5 mg. and 10 mg.

Detailed information is available on request



An **M&B** *brand Medical Product*

MANUFACTURED BY
MAY & BAKER LTD

DISTRIBUTORS PHARMACEUTICAL SPECIALITIES (MAY & BAKER) LTD · DAGENHAM

Glasgow Office: 19 Newton Place, Glasgow, C.3. Tel: Douglas 3507

MA5920

cesses—localisation; abscess formation and discharge; or absorption. Peritoneum is extremely thin tissue, and it appears that, while it is not itself sensitive, the sub-serous layers are extremely sensitive, and an inflamed organ lying in contact with the parietal layer can induce reaction and oedema in the sub-serous layers in a very short time. The pain is then felt in the abdominal wall where the process is acting. The character of this pain is quite different from that of visceral pain, being continuous and of a burning, stabbing or tearing nature. It is this sort of condition involving the diaphragmatic peritoneum which causes the supraclavicular pain mentioned above. Parietal pain does not appear if the parietal peritoneum is not involved in the pathological process as, for example, in certain cases of appendicitis and in some perforated peptic ulcers. It should not be confused with tenderness.

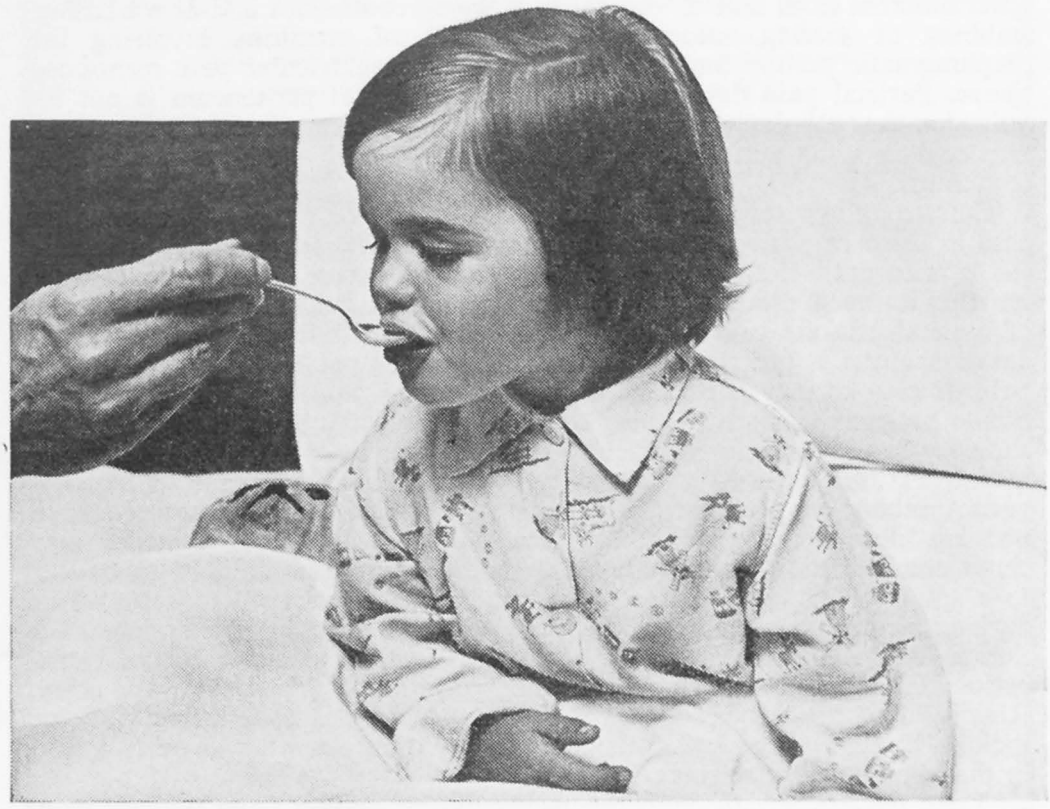
Cutaneous hyperalgesia has been estimated to be present in about one case in three of parietal peritoneal involvement. The best method of testing for it is to draw the sharp point of a long pin across the abdominal wall, exerting an even pressure throughout. The factors determining the presence of hyperalgesia are two in number—emotion and local tissue reaction. The emotional one is described as a tuning-up of the nervous system in severe pain. It may or may not be manifest as a state of apprehension on the part of the patient. It can be likened to a simple stimulus such as a tap on the shoulder in the company of friends—perhaps after a good dinner—when the response is like that of the normal subject on testing for cutaneous hyperalgesia: nothing happens. If pain is present, the picture is like that of a man walking alone down a quiet dark road, when a tap on the shoulder may cause considerable alarm. Abdominal rigidity is generally agreed to be due to a spinal reflex. The afferent limb may be either or both the visceral or parietal nerves. It seems that the parietal nerves usually predominate, for the rigidity may follow injury to the abdominal muscles or an intra-abdominal accident, and be more pronounced on one side than on the other. Rigidity due to biliary colic can be abolished by splanchnic nerve block or induced by distension of the biliary tract—for example, when there is a tube in the bile duct post operatively.

Deep tenderness can be distinguished by the sufferer from parietal pain, and is found on palpation over the affected site. The pain is described as being felt deep to the area of palpation rather than in the superficial layers. This has been called the " borrowed local sign." The impulses must originate in the viscera themselves for deep tenderness is found early in appendicitis before the inflammation has spread to the outer layers, and therefore before the parietes can be involved. It is also found in peptic ulcer where there can be demonstrably no contact between the affected part and the parietal wall. In cases of pelvic appendicitis, palpation through the rectal wall may be the only time when the patient complains of tenderness.

The borrowed local sign is explained as a single sensation caused by the correlation of deep tenderness with skin sensibility to the examining hand. As viscera have a bilateral innervation there does not appear to be any other explanation. Normally no sensation arises from viscera, but when pain deep to the abdominal wall and touch and pressure from the abdominal wall arise simultaneously, they can easily become inextricably linked in the patient's mind. It can be roughly compared to Aristotle's experiment of crossing two adjacent fingers and feeling an object placed between the two in the groove they thus form. Because we do not usually feel one single object with these two surfaces at the same time, we find it hard to believe that we are not feeling two separate objects.

Many questions are left unanswered, many topics remain untouched. As our knowledge advances and our experience widens, we may be able to find the key which will open the door and even to answer the age-old question " What is pain? "

Nicer than injection—
just as effective!



Readily accepted by children, Icipen V Suspension, given three times a day, provides penicillin blood levels comparable with those obtained by injection, and adequate to deal effectively with all infections due to penicillin-sensitive organisms.

'Icipen' V Suspension is pleasantly flavoured–children take it readily. Each teaspoonful (3.5 ml.) of prepared suspension contains 150 mg. penicillin V, as calcium salt. Available in bottles of 1 and 2 fl. oz. Basic N.H.S. cost 1/6d. per day's treatment for an infant, and 3/- for a child.

'Icipen' V Tablets. Each contains 300 mg. penicillin V as potassium salt. In packs of 12, 100 and 500. Average basic N.H.S. cost for a day's treatment (3 tablets) is 2/9d.

Icipen V Suspension TRADE MARK

Penicillin without tears

IMPERIAL CHEMICAL INDUSTRIES LIMITED PHARMACEUTICALS DIVISION Wilmslow Cheshire

Ph. 954

TWO HUNDRED YEARS AGO

By JAMES A. GRAY
M.B., Ch.B.

An extract from the Senior President's Valedictory Address delivered before the Society on Friday, 6th March 1959.

The setting is Edinburgh in the second half of the eighteenth century, the era of the post-chaise, the phaeton and the sedan-chair, when the North Bridge had just been opened to traffic and Princes Street was scarcely built. The hero is a typical Edinburgh medical student, Sylas Neville by name. This young man combined few virtues with not a few of the vices of his age. He was neither rich nor brilliant but might be classed as comfortably average at most accomplishments. Indeed the only work he left was his Diary, which is of great value to posterity in that part of it comprises a frank and detailed account of his five years in Edinburgh as a medical student. His story is of particular interest to us because, in 1775, rather by accident than design, Sylas Neville became a President of this Society—yet to become the Royal Medical Society.

Sylas Neville's background is involved and not clearly understood. He was born in London in 1741 and may have been descended from the great Neville family. He died, a penniless bachelor, in 1840 in his ninety-ninth year. His father had died when he was young and apparently left Sylas with a considerable amount of money, most of which he squandered by living a gay life in London as a frequenter of race-course and theatre—" a devotee of music and the arts, an antiquary, a sightseer, a lover of natural beauty, a believer in fresh air and exercise, an outspoken censor of morals and often very indulgent in dangerous gallantries. Always ailing, or fancying he was, like the creaking gate, he hung long." By 1768 London was too expensive for him and so he decided to go in for " house-keeping." With this end in view he toured the West Country and South Coast and at Eastbourne engaged as house-keeper a girl (already with a child) Sarah Bradford—whom he later calls Sally Russell. This woman, who shortly became his mistress, dogged his footsteps wherever he went, first to Yarmouth where he was for a while a minor squire and thence to Edinburgh where he was to study Physic.

When Sylas Neville began his studies, Edinburgh University was in a state of rapid growth. At the beginning of the eighteenth century there were only eight Professors and 300 students in the University. By 1800 there were 21 Professors and over 1,500 students, 660 of whom were medical, the rest being arts and divinity. In 1726, Edinburgh could only claim to have conferred 21 medical degrees, but by the close of the century, on an average, 47 took the degree each year.

There was little corporate life for the students when Neville arrived in Edinburgh. Up till 1733 there had been accommodation for a few within the College precincts, but the rooms fell into disrepair and were let to miscellaneous members of the population. The advantage of this accommodation seemed to be only in as much as the Professors could keep a watchful eye on their charges, and this would doubtless have proved irksome to our friend

had these regulations still been enforced in his time. Neither, by this time, had the University authorities any moral or religious hold over the undergraduates.

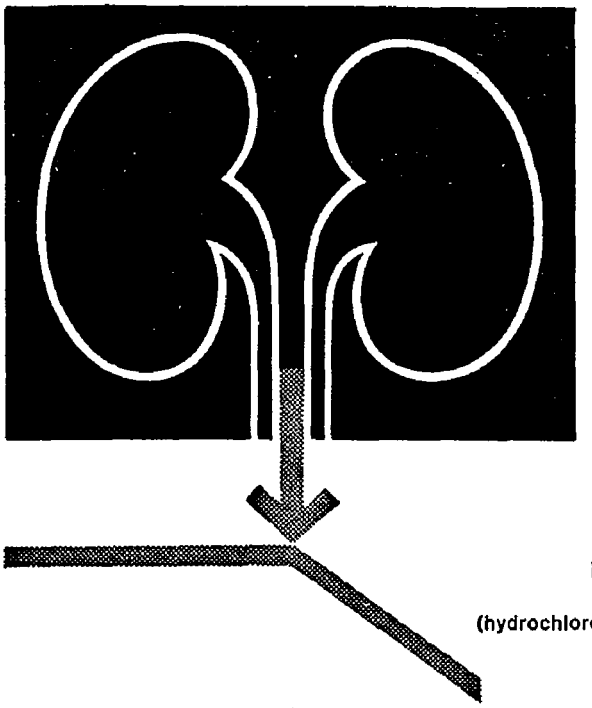
On the advice of Dr Monro (Secundus), and Dr Joseph Black, Neville first took up Anatomy and Chemistry since neither of these subjects required any previous knowledge. Soon he was hard at work and complains in his Diary: " Did not get to bed till half past twelve o'clock. Extending my notes taken at the Chemistry and Anatomical Lectures employs my whole time and prevents my doing anything else. Tired, weary and low- spirited." He studied too under the excellent John Innes who was the dissector under Monro Secundus. By the next year, 1772, he was attending: " Dr Cullen's lectures upon the Institution of Medicine and those of Dr Duncan upon Therapeutics. The last is not a Professor in the University but a private lecturer and thought clever." This was a just reflection on Dr Duncan who was then an extramural lecturer prior to his becoming Professor in 1790 upon the death of James Gregory.

By 1774, Neville's time-table read as follows: " Institution of Medicine by Dr Duncan (for Dr Drummond) at 8 a.m., Practice of Medicine by Dr Cullen at 9 a.m., Chemistry by Dr Black at 10 a.m., and Anatomy by Dr Monro at 1 p.m. I have an immense deal to do this winter. May God enable me to go through with it."

Neville took medicine very seriously and it might be of interest to us now if we followed him through the various stages of his degree examinations. Although he had a high opinion of his own capabilities, he was certainly well thought of by his Professors and particularly by the great Dr Cullen who remained his influential ally.

On completion of four years of study, Neville approached Dr Monro telling him of his intention of taking the degree. Dr Monro encouraged him in this and two days later he took his certificates of lectures he had attended to Dr Home, Dean of the College of Physicians, rather in the same way in which students of to-day present their ' D.P.' certificates. The following Friday, Dr Home examined him: " on the circulation and the diseases of the skin . . . Old Cullen took me next upon the insensible excretion or halitus from the lungs, catarrh, measles and the peripneumony, which is often the companion of that disease. He began by telling me that he was so well satisfied with the answers he had heard from me that he did not think it necessary to ask me further, but as it was the custom etc.—Dr Black, who, with Dr Monro, came in after the examination was begun, asked me the definition and symptoms of Diabetes. Dr Monro asked me some questions concerning the cure of the same disease. Dr Home then desired me to retire a little, and in about half a minute, being called in again, Dr Home told me after the specimen I had given of my erudition and knowledge in Medicine, the Faculty very willingly admitted me among the number of candidates. Thus the first step in this important business which has given me so much uneasiness, is over with credit, thanks be to God, who I hope will enable me to bring it to a happy conclusion . . . I drank a few glasses of port before going which was of great service to me, as I found myself more at ease after the hour came than I had done all day. The whole examination was in Latin, and I find that if the questions do not need very long answers, I can speak that language with tolerable fluency and correctness."

Only nine days after his decision to take the degree, he went to Cullen to ask his device upon a thesis and was encouraged to confine his remarks to the subject of ' Prognostic in Fever.' The Professor warned him that he had left himself far too little time in which to do it justice because the theses were to be handed in a fortnight later. However, Neville's was in very late. Cullen perused it and he was " pleased to say that he found no grammatical



The advantages of

Esidrex

(hydrochlorothiazide, a product of CIBA research)

For oedema and hypertension

Highest potency—low dosage.

Fully active orally—often effective where mercurials have failed.

Less risk of potassium depletion.

Almost a pure sali-diuretic. No significant effect on urinary pH.

Low cost of treatment—averages 4d. to 1/- daily.

The dosage range is usually 25 to 100 mg. daily, taken in two doses, after breakfast and after lunch.

Tablets of 25 mg. and 50 mg.* hydrochlorothiazide in 25's, 100's and 500's.

C I B A

Esidrex is a registered trade mark. Reg. user

CIBA Laboratories Limited, Horsham, Sussex.

1/-

Materia Medica Riker

DEANER *

'Deaner' is the para-acetamidobenzoic acid salt of 2-dimethylaminoethanol indicated for the treatment of debility and mild endogenous depression. Good reports have also been received on the use of 'Deaner' in chronic and migraine headache.

DUROPHET

'Durophet' contains a new formulation of *dextro* and *laevo* amphetamine, in the ratio of 3 to 1, bonded to an ion-exchange resin to give prolonged action. It assists appetite control in the treatment of obesity without producing overstimulation and the effect lasts 12 to 14 hours. It is available in capsules containing 7½ mg., 12½ mg. and 20 mg., to meet the requirements of individual patients and the dose is one capsule a day at breakfast time.

FERROIDS *

A new iron compound containing iron aminoates in which the iron is partly chelated with a mixture of amino acids. The compound provides an exceptionally high degree of utilisation of iron with negligible side effects. Daily rises in hæmoglobin of up to 2% a day have been reported.

INTRALGIN *

A percutaneous analgesic for the treatment of acute trauma, sprains, strains and all forms of non-articular rheumatism. 'Intralgin' is not a rubefacient but is absorbed through the skin into the affected muscles. 'Intralgin' liquid is available for application as a wet dressing. 'Intralgin' Gel is intended for gentle massage in less severe cases.

* *Regd. Trade Mark of* RIKER

THE MEDIHALER *

The first product to apply the principle of the pressurised aerosol to inhalation therapy. In each 'Medihaler' the drug is suspended in an inert propellent under pressure in a stainless steel vial. The drug is micronised to optimum particle size to ensure effective deposition in the lower respiratory tract.

The following 'Medihaler' products are available for use in the *symptomatic relief* of bronchial asthma.

'Medihaler Epi' *

Each unit contains 7 mg/ml of Adrenaline Bitartrate B.P. and a dose equivalent to 0.15 mg. of adrenaline base is delivered at each operation.

'Medihaler' Iso' *

Each unit contains 2mg/ml of Isoprenaline Sulphate B.P. and a dose of 0.075 mg. of the drug is delivered at each operation.

For prophylactic treatment in bronchial asthma the following is recommended:—

'Medihaler' * Cort.

Each unit contains 30 mg/ml of Hydrocortisone Acetate B.P. and each single operation delivers 1.5 mg. of the drug.

Each 'Medihaler' vial contains approximately 200 doses.

PENTOXYLON *

A more complete treatment for angina pectoris, combining the bradycardic and tranquillising effects of Rauwiloid with the prolonged vasodilating action of pentaerythrityltetranitrate.

RAUWILOID *

A standardised Rauwolfia product containing all the desirable alkaloids of the crude drug in purified form.

RAUWILOID + VERILOID *

A balanced combination of 'Rauwiloid' and 'Veriloid' enabling higher doses of the latter to be administered with no undesirable side effects.

RIKER LABORATORIES LTD. LOUGHBOROUGH LEICESTERSHIRE

errors and that I was so good a linguist he would rather ask my judgement in that matter . . ." A month after the entry date the rough copy was complete even though Dr Cullen was " fretful of the delay." With the help of a transcriber, Neville had a clean copy made and handed in three days later. Some nights he was up till three in the morning: " when my eyes hurt so much I could not see any longer."

With the thesis out of the way he was now ready to pass on to the second part of the examination. On August 7th, 1775, he was examined by Dr Hope (Professor of Botany and, incidentally, Founder of the Royal Botanical Gardens) and then by Dr Cullen on erysipelas. After a commentary on the second Aphorism of Hippocrates, he was then given two cases to write upon as a third and last exercise. Monro examined him on these cases and also upon " digestion." He handed them in on September 1st after they had been perused by his student friends and three days later was again examined on them by the Faculty of Medicine.

Next, with true 18th century politic, he went to call on Dr Hope on September 11th for the following reason: "As Dr Hope is appointed to examine me upon my thesis at the Graduation tomorrow, I thought it right to pay him the compliment of calling upon him today, and telling him that I was glad I had fallen into such good hands. He received me very politely, said that he was preparing to attack me, but found me so well guarded that he could hardly find anything to object to—that he had very little to say to me."

So, by September 12th, 1775, over two months after his decision to take the degree, Neville graduated with compliments from Dr Home that his dissertation was " bene eleganter et erudite scripta." Eleven others graduated with him but at the end, after shaking hands with the Principal and the Professors, Dr Cullen singled out our friend and said " with usual affability, ' I must not forget you, Mr Neville '."

So much for the academic life—but what of extra-mural activities? When he was not hard at work, Neville enjoyed games of billiards, the races at Leith and the theatre. With his student friends, the licentious Dennison and the earnest but misguided John Brown, he partook of lengthy discussions on the subjects dear to all students' hearts—metaphysics, vice and virtue, religion and the bible. Dennison, too, encouraged him in less erudite pursuits like visiting the city's brothels and in heavy drinking. Apparently Neville was not an alcoholic and after each carousal he would have sad misgivings about his own conduct. On one occasion, a few days after Graduation, he remarked: " Dined at the Fox and Goose, Musselburgh, with Gerard and Shiel who have lodgings in that town. Lucky I did not go yesterday as a company of only 8 or 10, chiefly Shiel's friends, drank 27 bottles of claret and 12 of port besides Punch, and were all beastly drunk . . ."

These are but a few of the many accounts of life as an 18th century medical student to be gleaned from the pages of Sylas Neville's Diary. There are doubtless also great tracts of his journal, which, had they been printed, would have been of tremendous interest to the medical historian and to those of us who are fascinated by the early, formative years of the Royal Medical Society.

Macdonald Printers (Edinburgh) Limited, 18 West Nicolson Street, Edinburgh 8