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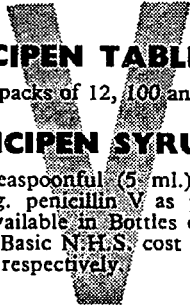
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PERFUSION

By W. ARTHUR MACKEY

St. Mungo Professor of Surgery, Royal Infirmary and The University,
Glasgow.

Part of an Address delivered to the Royal
Medical Society on Friday, 10th March, 1961.

The value of perfusion is reasonably well established yet the field is still developing and the ultimate applications and potentialities of perfusion techniques are as yet undefined. It is a subject on which, as I am sharply aware, my knowledge is very incomplete, and I will discuss, in the main, work being carried out in my department in Glasgow Royal Infirmary and the University of Glasgow.

Perfusion means, as you know, literally " through pouring "—a pouring through a part or all of the body by artificial means, of blood or an equivalent fluid capable of sustaining at least for a time some or all of the vital functions of the parts concerned. It is a technique which has, of course, long been familiar to physiologists, and much of our knowledge of the function of individual organs and their components has been built up by its use in recent years. The scope and complexity of the techniques available has been greatly increased, and if to-day one uses the word without qualification the concept implied is whole-body perfusion with blood, by-passing the heart and lungs. At the present time there exists in surgery, that is to say clinical surgery and related laboratory work, five main practical applications of the technique of perfusion.

1. Exclusion of the heart and usually the lungs from the blood circuit (which is meantime maintained by artificial means) in order to permit operation in a precise and orderly fashion on the heart.
2. The extension of this technique to include profound hypothermia, the circulation being maintained artificially until the temperature of the body is reduced to levels much below those at which efficient cardiac action is possible, after which it may be allowed to stop for quite long periods.
3. Maintenance or support of the circulation which is being acutely impeded either by recoverable cardiac embarrassment or modifiable obstruction to the vascular channels, usually in the lungs.
4. The introduction of powerful chemotherapeutic agents into an isolated sector of the vascular bed in concentrations that would be intolerable or even lethal if generally distributed.
5. The perfusion of organs such as the heart, the adrenal gland, the mammary gland, the kidney and so forth in order to study problems in their physiology and in particular their response to hormones.

Imaginative experimentalists of every age since the circulation and functions of the blood were first determined must have dreamed of the possibilities that would be opened up if one could substitute a machine, a pump, for the heart. The present-day reasonably satisfactory solution of the problems involved is based upon many years of dedicated work on animals by John Gibbon of Philadelphia, a surgeon and physiologist. The clinical develop-

ment was probably due in the main to De Wall, Lillehei and Varco in
Minneapolis, Kirklin in the Mayo Clinic, Clowes in Cleveland and after
them a great host of others. The requirements for an efficient whole-body
perfusion are :

> a pump
> an oxygenator
> an abundant supply of heparinised blood
> and efficient connections to the patient.

The pump needless to say replaces the heart. Initially there was an im-
pression that possibly there was some inherent merit in a pulsatile circulation
and some pumps, especially the earliest of those designed by Denis Melrose
in this country, were designed to provide an intermittent systolic ejection. It
soon became apparent, however, that the technical requirements were simply
adequate output and minimal trauma to the blood. In normothermic or
near-normothermic conditions the output of the pump should come fairly
close to that of the heart under basal conditions. It is found that this relates
in a more linear fashion to the surface area of the subject than to his weight
—about 2.4 litres per square metre of surface area per minute. It is easier
to maintain this rate of pumping in children than in adults for whom a
pump output of 5 litres per minute may be required. To circulate rapidly this
amount of blood through tubes of modest calibre demands forces which,
applied even by the most efficient sort of pump, tend to be rather violent
and to inflict physical damage on the blood, especially on fibrinogen and
platelets but to some extent on all the cellular components and on the plasma
proteins. Many kinds of pump are available, all reasonably satisfactory. The
most widely used is a roller pump running over a loop of elastic plastic
tubing which refills by gravity and by recoil. This sort of pump gives a
fairly continuous non-pulsatile output.

The oxygenator represents the lung of the apparatus. Its function is to
expose blood to an atmosphere consisting largely of oxygen over as wide a
surface as possible. This surface may be provided by bubbling oxygen through
blood, filming blood in oxygen or exposing it to oxygen across a fine
membrane ; but at their best and most ambitious oxygenators can provide
only a fraction of the area for gaseous interchange represented by the avcolar
surface of the lungs and in practice the factor which limits the output of the
heart-lung machine is the capacity of the oxygenator to maintain adequate
oxygenation and removal of carbon dioxide for the volume of blood passing
through. If the speed of the blood flow is increased beyond a certain point,
oxygenation falls off rather steeply. The massive oxygenator of the Melrose
machine has a filming area of 1.3 square metres. This has been somewhat
increased in the most recent modification by Gerbode. The total area of the
pulmonary alveoli in a human adult is about 90 square metres !

To carry out efficiently a total body perfusion a large volume of blood is
required and this must be by all known tests identical in group with that of
the recipient. The blood must be as nearly freshly drawn as possible, prefer-
ably within a few hours of perfusion and its clotting mechanism must be
held in suspense by the use of heparin. The amount of blood required is
often large and a perfusion of an adult may require 10 litres. If many per-
fusions are being carried out, it is difficult repeatedly to obtain so much
accurately cross-matched blood and this problem is obviously likely to increase
rather than diminish. At the present time I have to give 3 weeks' notice in
order that arrangements can be made for the supply of blood for a perfusion.
Attempts are being made to ease some of the difficulties involved and in
particular to make blood more swiftly available for perfusion, and to permit

of the use for other purposes of blood drawn primarily for perfusion. For example blood preserved in " ACD mixture " or " Edglugate Mg." is found to store fairly well, and if it is to be used for perfusion it may be heparinised and recalcified just before use. Finally some evidence is accumulating that blood cells may be preserved deep-frozen in a water-glycerol mixture, and that after very long periods they may be thawed, washed and re-suspended in plasma and used as if they were fresh. This rather elaborate technique could make possible the establishment of a true blood bank containing blood of all conceivable groups in a quickly-available state.

At the end of the operation, the clotting mechanism of the blood must be restored as fully as possible by the administration of an appropriate dose of an antagonist to heparin. The substance originally used in this way was protamine sulphate. This is reasonably effective, but has certain disadvantages such as a troublesome hypotensive action, and Polybrene (hexadimethrene bromide) is probably superior. After a prolonged perfusion the blood remaining in the patient will be found to be significantly deficient in fibrinogen and this also may require to be added. Sometimes—fortunately rarely—the terrifying complication of fibrinolysis may follow any major bodily trauma, especially if associated with hypotension or haemolysis. It is due to activation of the plasmin mechanism in the blood, and it is liable to result in a progressive and hardly controllable haemorrhagic state. The platelet count also is markedly reduced to about 25 per cent of its original value. This appears not to be a desperately serious matter and at most the infusion, at the end of the operation, of a modest amount of fresh carefully-drawn citrated blood, will restore adequate platelet action.

TABLE 1.

Indications for Whole Body Perfusion	
Clear :	
V.S.D.	Foramen primum type of A.S.D.
Fallot's Tetralogy	Other severe developmental lesions
Conditional :	
Aortic stenosis	Myocardial infarct and aneurysm
Complicated mitral disease ...	Coronary artery disease
Borderline :	
A.S.D.	Pulmonic valvular stenosis

The heart-lung machine is coupled to the patient's circulation on the venous and on the arterial side. The venous connections usually consist of two plastic cannulae introduced into the cavae via the right atrium. In some techniques the atrium itself is cannulated and sometimes, as in Drew's double perfusion technique both atria are cannulated. The blood may be re-introduced on the arterial side at almost any convenient point, usually in the femoral or the external iliac artery, or occasionally the aorta itself. The blood moves freely and swiftly throughout the arterial tree and it is best simply to introduce a cannula of as wide a bore as possible into the most accessible capacious artery available.

INDICATIONS FOR WHOLE-BODY PERFUSION (Table 1).

At the present moment the primary indication and probably the only one is the intention to carry out upon the heart major operations demanding more than a few minutes of interruption of the circulation (in conditions of

moderate hypothermia—between 28°C. and 30°C.—the circulation of the blood may be stopped by caval compression for as long as 8 minutes without irreparable damage to the brain). The clearest indications are ventricular septal defect, Fallot's tetralogy and the most complicated types of atrial septal defect—persistent foramen primum and persistent atrioventricular canal. Conditional indications for by-pass are aortic stenosis, complicated cases of mitral valve disease, myocardial infarct or aneurysm and coronary arterial disease. If facilities for efficient by-pass are freely available, some surgeons would use by-pass for such easily treated lesions as foramen secundum type of A.S.D. and pulmonic valvular stenosis, which the majority would still treat by inflow occlusion under hypothermia.

CARDIOPLEGIA

The continuous activity of the heart makes it difficult to stitch and patch moving parts with accuracy and the field tends to be obscured by ejected blood, coming ultimately in the main from coronary return and bronchial return, the latter being very large in many cases of cyanotic heart disease. The principal danger is injury to important vital structures and in particular to the atrio-ventricular bundle which in all cases of ventricular septal defect, whether simple or associated with other lesions, runs very close to the posterior and inferior margins of the septal opening. It lies in the main to the left side of the septum, and careful stitching may avoid it but damage to the bundle leads to heart block and if this persists it is usually fatal after a time. Cardioplegia is, however, a two-edged weapon. On the one hand it facilitates operation and therefore renders the bundle of His less liable to casual injury, on the other the effect of encroachment on the bundle is not so immediately perceptible as it is when the heart is beating. The heart may be arrested by a variety of methods. Possibly the most physiological is to use parasympatheticomimetic substances such as acetylcholine or acetycholine and prostigmine. Introduced into the coronary circulation these will exercise an intense vagal action and stop the heart. On the other hand the heart may be stopped chemically. Cardiac action is depressed and conduction slowed by potassium ions while conduction is supported and accelerated by calcium ions. Infusion of potassium citrate has a double effect of adding potassium ions to the extracellular fluid and diminishing the ionisation of calcium by virtue of the citrate content. A third chemical which has been used either alone or in combination with others is adenosine triphosphate.

In Scandinavia anoxic arrest is widely used by cross-clamping the aorta and so cutting off the coronary circulation. After a time the heart slows and finally it stops with or without passing through a phase of ventricular fibrillation. When the coronary circulation is restored by removal of the aortic clamp, the heart re-starts, commonly with ventricular fibrillation, but this arrhythmia is easily converted electrically.

The newest method of producing cardiac arrest is by local hypothermia, perfusing the coronary vessels with ice-cold oxygenated blood. This is probably the best method of all because it is reliable, it produces no chemical disturbance and it permits the heart to be arrested with safety for quite long periods—probably 30 minutes to an hour—and it is immediately reversible without impairment of the efficiency of muscular contraction by re-infusion of warm blood from the general by-pass circulation.

COMPLICATIONS OF BY-PASS

The general complications of by-pass surgery are as for any major surgery The special ones are myocardial insufficiency, infection, bleeding and

pneumonitis.

Myocardial insufficiency may be temporary or permanent, temporary related, for example, to chemical upset, electrolyte imbalance, too slow recovery from a period of asphyxia or the traumatic injury inevitable in a cardiotomy and suture. The insufficiency may be more permanent and irrecoverable if, for example, the bundle of His has been interrupted or if the heart has been so deformed pre-operatively that its chambers are incapable of doing the work demanded of them following anatomical " cure " of the defect.

Infection is particularly dangerous, of course, in that it may settle upon the operation area in the heart and be very difficult to eradicate. Particularly troublesome organisms have been the now ubiquitous and unregenerate Staphylococcus aureus and Pseudomonas pyocyanea.

Possibly the most characteristic complication of by-pass is bleeding related to thrombocytopenia, fibrinogenopenia and sometimes fibrinolysis. It is insured against by meticulous haemostasis before closing, restoration of normothermic conditions (hypothermia slows the clotting mechanism), the administration of fresh blood or fibrinogen solutions.

Finally, a characteristic type of complication is the post-perfusion pneumonitis, a rather diffuse process involving both the vascular tree and alveoli of the lungs. Its aetiology is obscure. It is not known whether it is in part embolic due to emboli of, for example, fibrin, minute globules of antifoam, or fat or what you will. The aveolar pathology may be related to the rather long period of hypoventilation.

RESULTS

With a well-trained and practised team a very low mortality and a high success rate is nowadays attainable with correctable lesions. It must be remembered that some lesions are anatomically incorrigible. For example, there may be no pulmonary artery. An only slightly less daunting problem is offered by cases of complete transposition of the great vessels with wide septal defects. These represent a technical challenge which is unlikely ever to be immediately met and even following a successful operation there must inevitably be a very long period of re-education of the heart, for redeployment and development of myocardial forces to cope with a circulation that has been abruptly brought up to the normal post-natal pattern with a high-pressure and a low-pressure circuit.

RELIEF OF CONGESTIVE FAILURE

Some ten years ago I talked with Professor Ian Aird at the Postgraduate Medical School in London, where he had recently gone from Edinburgh. He told me of work being done by Denis Melrose to develop a heart-lung machine. Asked how he would propose to use it, he said with one of his highly characteristic sharply perceptive flashes of inspiration : " I should like to try it first of all on cases of congestive cardiac failure to take blood from the overloaded venous side, oxygenate it and inject it on the arterial side."

It is surprising that the perfusion technique has not been used more extensively in this frequently-met problem. There may be many instances in which a temporary but potentially lethal cardiac embarrassment could be relieved by the use of a machine which would supplement the propulsive power of the heart and the oxygenating power of the lungs over a period of one or two hours and permit them to resume their task refreshed. Never-

theless I believe that heart-lung by-pass has been little used clinically in
this field.

However, in my laboratory, William Bain has been working over the past
year on the relief of acute pulmonary hypertension by heart-lung by-pass.
The pulmonary hypertension is produced by the injection of a suspension
of small glass beads into the pulmonary artery of animals. In appropriate
doses this leads to a sharp rise in pulmonary vascular resistance, severe over-
loading and overstrain of the right heart and cardiac failure culminating in
death. If, however, the blood in the right atrium is allowed to flow out, is
oxygenated and pumped back on the arterial side, the congestion is relieved
and normal blood pressure and haemodynamics can be restored.

There are surely many cases in clinical medicine in which patients suffering
from congestive failure or cor *pulmonale* could be markedly helped by a period
on by-pass if the latter could be instituted without too great inconvenience
and at a very low risk. A benefit comparable to those conferred by haemo-
dialysis in acute renal failure, or assisted respiration and oxygenation in
respiratory failure with carbon-dioxide narcosis, should be within reach .

HYPOTHERMIA WITH CARDIAC BY-PASS ·

As indicated above it is possible by lowering the general temperature of
the body to prolong the period during which the circulation even to the
brain may safely be arrested, up to as long as eight minutes. This process
cannot be extended indefinitely downwards, however, because at about 28°C.
the myocardium of the ventricles becomes irritable, ventricular fibrillation
occurs and effective cardiac action therefore ceases. Ventricular fibrillation
cannot be reversed easily at these low temperatures. Consequently it has
become customary to use some technique of by-pass or perfusion if it is
desired to take the temperature down below 28°C. The circulation of the
blood is maintained independently of the cardiac action and when the tem-
perature is sufficiently low the pumping is stopped, the circulation of the
blood ceases and the necessary operative procedure, usually on the heart but
occasionally on the brain, may proceed in a virtually bloodless field under
greatly simplified operating conditions.

When the operation is finished the pump is started once more and the
blood is now re-heated relatively quickly, with fluid in the jacket of the heat-
exchanger at about 45°C. As the temperature of the heart rises its electrical
action is resumed, usually in ventricular fibrillation, but this is easily reversed
with a single electric shock when the temperature reaches about 30°C.

One of the most important steps forward in this field was made by Drew
of the Westminster Hospital in London using a double by-pass technique,
one circuit containing the heat-exchanger by-passing the left heart and the
other the right, the blood being pumped through the patient's own lungs
for its oxygenation. The lungs are, of course, more efficient than any con-
ceivable artificial oxygenator and the blood is less traumatized. However, it
is not always convenient to cannulate the patient's pulmonary artery and
most surgeons prefer to use a heat-exchanger in association with a heart-lung
machine providing total body by-pass.

Murray Harper in my department is studying the effect on general and
cerebral metabolism of profound hypothermia and circulatory arrest. He has
found, as have others, that the oxygen consumption falls as the temperature
falls and that, for example, at a muscle temperature of 30°C. the oxygen
consumption is about 58 per cent. of the original value. At 15°C. it has

fallen to only 12 per cent. Thereafter the saving in oxygen consumption appears to diminish. In fact there is not a great deal to be gained by reducing the temperature below about 10°C.

During the subsequent phase of re-heating and restoration of the circulation there is a considerable release of lactic acid, presumably formed by anaerobic glycolysis during the phase of circulatory arrest. This produces a metabolic acidosis which, however, can readily be relieved by the administration of sodium bicarbonate and the whole complex process seems to be reasonably well tolerated. The main technical difficulty which may arise in association with this method is sludging of the blood, which may occur in small vessels at low temperatures. In the clinical field Drew has used the method with notable success, producing cardiac arrest of up to 45 minutes at temperatures below 15°C. This time is certainly adequate for most intra-cardiac surgical procedures. The technical limits of the technique have not yet, however, been fully determined.

This consideration applies in some degree to all methods of perfusion—of the whole body, with or without hypothermia, of regions, with cancer-icidal drugs or of organs, with active drugs or hormones. These afford an unusually good opportunity of seeing and learning more about human physiology.

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ABDOMINAL CRISES
I.

By I. S. R. SINCLAIR, F.R.C.S.

The first of three articles written by the Author for Res Medica.

PROBLEMS IN DIAGNOSIS

Despite the mechanical contrivances which clutter our modern world solutions to the crises which constantly beset us in every sphere still depend upon the wisdom of individuals. This is nowhere more true than in the management of abdominal crises which at some stage falls to the lot of every medical man. If disaster is to be averted, a correct diagnosis has to be made and a correct line of action determined within a space of time so short that the opportunity to call upon other opinions or to invoke the corroborative aid of laboratory tests may be severely curtailed. For the vast majority of doctors who are not practising surgeons the overriding responsibility is to decide whether an abdominal crisis is such that operative treatment may be needed. If the medical student, nurtured in the hospital environment, gains the impression that this decision is one of no great difficulty he is forgetting that the wheat has already been separated from the chaff before the patient ever reaches hospital. It is a tribute to the general practitioners that so few patients are needlessly referred to hospital and that even fewer are referred with serious complications already established.

THE HISTORY

The key witness in the doctor's efforts to reconstruct the pattern of events is, of course, the patient himself. The general practitioner has usually a considerable advantage over his hospital colleagues through personal knowledge of the patient which helps him to assess the reliability of the witness, but on occasions this knowledge may be dangerous and the memory that a particular patient or his relatives have often "called wolf" in the past must not be allowed to prejudice the family doctor in his assessment of each new episode. Even the most reliable patient may be reduced to incoherence by the distraction of pain or the exhaustion of vomiting while the senile, the psychotic, the unconscious and the very young by their inability to communicate deprive the doctor of his first vital diagnostic weapon.

The Interpretation of Pain

Except in the case of internal haemorrhage by far the most important single symptom of intra-abdominal pathology is pain. The threshold for and reaction to pain undoubtedly vary greatly from one individual to another. The new-born

infant is virtually insensitive to pain : the thick-set labourer accustomed to blows and tolerant of the pangs from a mouthful of carious teeth may conceal a gangrenous appendix without admitting to more than minimal abdominal discomfort. Again, pain appreciation may be disturbed under certain abnormal conditions, most notoriously after some major operation or injury. Under these circumstances the pain of the primary condition and the effects of analgesic drugs may obscure the true diagnosis. Quite as important under these circumstances is the inability of the attending doctors to maintain their alertness. Patients are as likely to develop abdominal crises in hospital as elsewhere yet once a patient has come under our care with an established diagnosis it goes against our nature to think that some other catastrophe may befall him and against our training to explain a fresh symptom on the basis of some new and unrelated condition. There is some truth in the charge that there is no more dangerous place in which to develop an abdominal crisis than a surgical ward.

Pain sensation may be impaired or absent in certain disease processes affecting the conducting tracts such as tabes dorsalis or syringomyelia, or following mechanical division of the tracts. A young soldier was admitted to hospital with a complete paraplegia due to a bullet wound of the upper dorsal spine. He deteriorated suddenly the following day with vomiting and a silent distended abdomen. At laparotomy there was a perforation of the jejunum with gross generalised peritonitis. Similar silent perforations have been reported in patients who have had a bilateral splanchnicectomy to control malignant hypertension or to relieve the pain of chronic relapsing pancreatitis. The splanchnic nerves carry only those afferent fibres whose peripheral endings lie in the visceral walls and the visceral peritoneum. The sensory supply of the parietal peritoneum passes along the segmental somatic nerves so that after splanchnicectomy only true " visceral " pain is abolished and pain will be felt as soon as the parietal peritoneum becomes involved. Thus the early central abdominal pain of acute appendicitis will be absent but local pain and tenderness in the right iliac fossa will appear as usual.

Suppression of the inflammatory reaction by gluco-corticoids provides another mechanism whereby the pain response may be modified and silent gastro-intestinal perforations have occurred in patients under treatment with these drugs.

Because of the median origin and scanty cortical representation of the intestinal tract the truly visceral component of abdominal pain is felt in or near the midline and is poorly localised. It shows some degree of segmental distribution but the limits of segmental innervation vary from patient to patient. Moreover, with the continuance of pain central summation results in a diffusion of the ascending impulses over an increasing number of segments. In other words the pain will become more diffuse even in the absence of a spreading pathological process within the abdomen. This explains the great importance of ascertaining the location of pain at the onset of the illness. At this time visceral pain from " foregut " organs—stomach, proximal duodenum, biliary tree and pancreas—will be located in the epigastrium ; from the " midgut " organs—small intestine, appendix, ascending and trans-verse colon—in the umbilical region ; from the hind gut, in the hypogastrium.

BACK PAIN is a frequent feature in disease of certain abdominal organs. Where the disease process involves the posterior parietes, as in pancreatitis or extensive carcinoma, this is deep somatic pain. Sometimes, however, back pain is present without any such involvement of the parietes due partly to misinterpretation by the sensory cortex of the origin of the painful stimuli ; partly to spread of subthreshold visceral impulses on the posterior column

synaptic areas to nearby neurones carrying stimuli from the body surface ; and partly to the anatomical limitation of the number of ascending fibres available, so that the same central fibre may perforce be used to convey messages brought to the cord by both visceral and somatic peripheral fibres. The posterior body wall is less liberally endowed with sensory fibres than the anterior wall and this may explain why a patient will rarely complain primarily of back pain but will often admit to its presence on being questioned. When, however, some disease is present in the components of the posterior body wall, for example osteoarthritis of the spine, the summation of subthreshold stimuli from the viscera with similar mild stimuli from the deep somatic nerve endings of the vertebral column may together produce back pain as a primary complaint. Although visceral pain may be misinterpreted as coming from both the posterior and anterior areas of the body surface it is remarkable that it is never described by the patient as following the distribution of the intercostal nerves : girdle pain does not arise from the hollow viscera. In most cases this so-called referred pain is experienced in areas which correspond fairly closely to the site of the viscus concerned and so blends with the true visceral pain but sometimes, through a developmental rearrangement of segments, referred pain may be felt in remote areas, for example the shoulder-tip pain of diaphragmatic irritation.

The most potent stimuli of visceral sensory endings are crushing, stretching and ischaemia. In contrast to the hollow viscera, solid organs are rarely subject to distension or strangulation and rarely give rise to acute pain. Renal pain arises from the renal pelvis and not from the parenchyma : the pain of splenic infarction is accurately localised somatic pain due to irritation of the parietal peritoneum. However the peritoneal capsule of a solid organ like the liver is sensitive to the tension produced by vascular engorgement so that acute congestive heart failure may mimic an upper abdominal crisis.

THE MODE OF ONSET of abdominal pain is a valuable diagnostic pointer. Catastrophic abdominal pain of sudden onset is always of peritoneal origin and is due either to perforation of a hollow viscus or to torsion or strangulation. Inflammation, on the other hand, gives rise to an aching pain of gradually increasing intensity without the throbbing so common in inflammatory lesions of parietal structures. This pain is due to stretching of the visceral peritoneum over the swollen part and is similar to the pain of an engorged liver or of a tense pancreatic cyst. The same aching pain is felt in obstruction of a hollow viscus but in this case the spasmodic pain of excessive smooth muscle contraction is superimposed. Such " tension pain " is immediately relieved when the distension passes off. Thus relief may follow the drainage of a pancreatic cyst, the release of an obstructed loop of bowel or the removal of an obstructed appendix but it may equally well follow the rupture of the cyst or bowel or appendix into the peritoneal cavity. Sudden spontaneous relief of abdominal pain which has been constantly present for some hours must be viewed with the utmost suspicion. In the same way the sudden disappearance of pain from an active peptic ulcer is more likely to be due to the sudden decompression of the hyperaemic tissues by haemorrhage than to any medicaments and calls for a very close watch for signs of internal haemorrhage. In the absence of haematemesis or melaena the earliest indication of bleeding in the recumbent patient is very often the appearance of beads of sweat on the forehead. I have noticed this on a number of occasions some time before there was any rise in pulse rate.

Rarely, a patient will describe abdominal pain as cutting or stabbing in character. This type of pain is found where inflamed serous surfaces rub

together and so may be located in the upper abdomen in diaphragmatic pleurisy or the left hypochondrium and flank in perisplenitis. In the absence of such pathology this type of pain is suggestive of functional illness or of the rare but never to be forgotten tabetic crisis.

Vomiting and Bowel Dysfunction

When vomiting is present information as to its nature is second in importance only to analysis of the pain picture, although because of the great variety of diseases which may provoke vomiting, especially in children, the presence of vomiting per se is not of great help as a localising sympton. As with pain, the longer vomiting lasts the more likely is there to be a serious cause. The stage of reflex disturbance in acute appendicitis or in perforation of a peptic ulcer is short, and it is unusual for vomiting to be repeated more than once or twice. Torsion or internal strangulation on the other hand is productive of early and repeated reflex vomiting, the vomitus remaining small in quantity and watery or bilious in appearance.

In one typical case of " acute appendicitis " vomiting had occurred no less than seven times : the operative finding was torsion of a long Meckel's diverticulum. On another occasion repeated retching in a supposed case of perforated duodenal ulcer was due to torsion of a pedunculated mass of fat on the lesser omentum.

Obstructive vomiting classically progresses from clear gastric juice to green bile, then straw-coloured jejunal contents and finally to " faecal " fluid. But this progress is not always seen, being possible only in low intestinal obstructions. Besides, to await faecal vomiting before diagnosing obstruction is no less heinous than to await clinical metastases before diagnosing cancer.

The presence of constipation is of relatively little diagnostic value in the acute abdominal crisis and conversely the occurrence of a bowel movement shortly after the onset of symptoms does not exclude intestinal obstruction. However, the absence of a bowel movement for even one day after vague abdominal pains have developed remains one of the greatest hazards to the patient in his own home, and especially to children for the administration of a purgative remains common practice in cases of abdominal pain. In the presence of an obstructive lesion the augmented intestinal activity produced by purgation greatly increases the risk of perforation of the obstructed part. Should the clinical picture suggest to the doctor that his patient might have appendicitis, a history of recent purgation is a positive indication for hospitalisation.

Diarrhoea is often present in cases of food poisoning and is helpful in the differentiation of gastro-enteritis from appendicitis but it is otherwise rare in temperate climates.

THE EXAMINATION

Inspection of the abdomen, so often neglected, is directed first to observe movements—respiratory, pulsatile or peristaltic ; secondly to observe the presence of abnormal fullness due to distension or masses ; thirdly to look for less common findings such as the urticarial rash of food poisoning, the vesicular segmental rash of herpes, the " caput medusae " of engorged periumbilical veins of portal hypertension or hepatic metastases or signs of bruising in cases of injury.

PALPATION is always performed—after a fashion. Sir James Mackenzie wrote " There is not to be found yet any person who can intelligently palpate an

abdomen." The secret lies in the warm hand, the gentle pressure with the pads of the fingers and the recognition that just as one equation with two unknowns is insoluble, so it is pointless to expect results if the examining hand moves about while the patient is asked to breathe deeply ! In particular, palpation should at first be light and cover all quadrants of the abdomen. Only in this way will relaxation be achieved enabling the presence of local rigidity to be detected. Deep palpation follows and will elicit tenderness of the parietal peritoneum, and the presence and characteristics of masses. There is no doubt that inflamed viscera are themselves tender to deep palpation. Thus the inflamed gall bladder, duodenum or appendix is acutely sensitive even when the anterior parietal peritoneum is not involved. Palpation must always include the external hernial orifices : in the obese patient the fold of the groin can easily hide the small bulk of a strangulated femoral hernia. When a peritoneal surface is inflamed any sudden change in position or tension gives rise to pain. Because of the unpleasant sensation produced by sudden pressure on the abdominal viscera, the sudden application of pressure is unhelpful in recognising peritoneal pathology but the sudden withdrawal of the palpating hand will produce pain only if the peritoneal surface is unduly sensitive. This phenomenon of " rebound tenderness " is quite non-specific but I believe it to be a useful index of some degree of peritoneal irritation and hence of primary intra-abdominal pathology. Certain more subtle tests such as the presence of hyperalgesia of the abdominal skin due to viscero-cutaneous segmental summation are used by some surgeons but have proved of little practical value in my hands.

Just as the sudden relief of pain may give rise to a false sense of security so the absence of acute signs in abdominal examination is liable to misinterpretation. The lack of signs of intraperitoneal pathology in the heavily muscled male has already been mentioned and the same is true in the obese and the debilitated. In the patient severely ill with typhoid fever or ulcerative colitis the only sign that perforation of the bowel has occurred may be the sudden onset of peripheral circulatory failure. The absence of pain in the early stage of peritonitis in the patient on cortisone, with a spinal cord lesion, or after splanchnicectomy is paralleled by an equivalent lack of physical signs. But the commonest pitfall occurs in the patient with an acutely inflamed pelvic appendix. In the early stages such a patient may show no abnormality whatever on careful abdominal examination, though rectal examination will disclose acute tenderness in the pelvic peritoneal pouch. When tenderness does spread into the abdomen it may first appear in the left iliac fossa to which the inflammatory exudate is diverted by the pelvic meso-colon. The inflamed retrocaecal or retro-ileal appendix may likewise produce only minimal signs of peritonitis, and the same is true of acute pancreatitis and of perforation of a gastric ulcer into the lesser peritoneal sac, in all of which circumstances the anterior parietal peritoneum is protected from the pathological process.

ABDOMINAL PERCUSSION is of limited value except in the detection of and distinction between a pelvic mass, such as a distended bladder or ovarian cyst, and gross ascites. Attempts to elicit shifting dullness are seldom justified in acutely ill patients while the reduction in liver dullness in cases of perforation of a hollow viscus is so inconstant as to be of little diagnostic value.

AUSCULTATION is directed principally to the detection of an increase or decrease in peristaltic activity, or more rarely to the elicitation of a friction rub as in splenic infarction or of a systolic arterial murmur in arterial aneurysm. It is often forgotten that the normal abdomen may remain silent for periods

of over one minute. To be of value, therefore, auscultation must be prolonged. Furthermore, active peristalsis may continue in the presence of localised intra-peritoneal pathology while it will cease altogether in severe shock due to extra-abdominal injury.

ANCILLARY DIAGNOSTIC AIDS

Despite what has been said about the need to establish a diagnosis quickly in the absence of ancillary techniques the value of laboratory and radiological techniques must never be forgotten. The leucocyte count, microscopic examination of the urine and determinations of serum amylase and blood urea are all extremely useful tests in the abdominal crisis. The value of the plain abdominal X-ray has long been recognised, especially to demonstrate the presence of free peritoneal gas (indicative of perforation of bowel) or of gas and fluid levels in the small intestine (indicative of intestinal obstruction). More recently the emergency use of contrast films has become established. With water soluble opaque media, for example, the presence of gastro-duodenal or bladder perforations can be safely and reliably confirmed.

EXTRA-ABDOMINAL CAUSES OF ACUTE ABDOMINAL SYMPTOMS

Acute infections

Apart from the pancreatitis of mumps it is not uncommon for acute infections in children to give rise to abdominal manifestations. Thus an acute pharyngitis is often associated with abdominal pain and vomiting, due perhaps to a reactive mesenteric adenitis. In such cases the history of a sore throat, the faucial congestion, the flushed face with circum-oral pallor, the localisation of abdominal tenderness along the line of the mesenteric attachment above the usual location of the appendix and the absence of signs of progressive peritonitis may enable a confident diagnosis to be made and expectant treatment adopted.

Thoracic disease

In older patients confusion between CORONARY THROMBOSIS and an upper abdominal emergency may lead to serious errors in management. When pain of thoracic origin is referred to the abdomen the muscles may exhibit reflex spasm which closely mimics rigidity, but tenderness is absent under the rigid muscles and the muscle spasm often relaxes during inspiration, a phenomenon never seen in rigidity due to intra-abdominal pathology. The presence of pleural or pericardial friction rubs and of other cardiac or respiratory symptoms and signs will usually resolve the dilemma. If not, the electro-cardiogram has reached a remarkable degree of accuracy in the detection of either myocardial infarcts or major pulmonary emboli and in the distinction between these, while estimation of the serum transaminase reveals an elevation in most cases of myocardial infarction within twelve hours. However the transaminase may also be elevated in liver disease or acute pancreatitis.

DISSECTING ANEURYSM of the aorta may occasionally present as an abdominal crisis but as the dissection almost always starts in the ascending aorta the history is of pain starting in the neck, chest and back and travelling downwards through the abdomen to the legs. This history associated with diminution of pulses in some or all of the major branches of the aorta is virtually pathognomonic. The basis of contemporary treatment is the attempt to ensure by surgery what nature rarely achieves unaided—the re-entry of the dissecting current of blood in the lumen of the aorta.

Spontaneous rupture of the oesophagus characteristically occurs during a bout of post-prandial vomiting. The sudden retrosternal pain is more likely to be mistaken for a coronary thrombosis than a perforated peptic ulcer in the absence of a dyspeptic history. The tear, always at the left side of the lower thoracic oesophagus, ruptures early into the left pleural space where air and fluid containing food or gastric juice accumulate and upward extension of air

through the mediastinum may produce surgical emphysema in the root of the neck. The only chance of survival lies in immediate suture of the rent.

Spinal disease

OSTEOMYELITIS of the vertebral bodies is an uncommon cause of abdominal crisis. To add to the diagnostic difficulty this condition sometimes arises in the wake of an acute abdominal upset, perhaps due to direct spread of infection by way of the vertebral veins or the lymphatic trunks which course close to the vertebral bodies. Clinical examination always reveals localised tenderness over the spine of the involved vertebra while in some cases a tender, boggy mass is palpable per rectum, not anteriorly, as in a pelvic abscess, but posteriorly between rectum and sacrum. As with early osteomyelitis in other sites X-ray examination is negative but direct aspiration culture of the vertebral body may prove the diagnosis. The greatest hazard of a delay in effective treatment is thrombosis of the spinal arteries. If this occurs there will be a sudden onset of irreversible paraplegia due to infarction of the cord.

TABES DORSALIS is now rare but by no means extinct. Although tabetic crises usually involve the lower limbs most acutely, paroxysms of stabbing pain in the abdomen with severe vomiting constitute the well-known gastric crises while in yet other cases the clinical picture resembles acute intestinal obstruction. Interrogation generally reveals that leg pains are present and these are always of a stabbing or " transverse " character quite unlike the shooting pains of sciatica or dissecting aneurysm. The combination of such pains with " pins and needles " in the limbs is almost pathognomonic of tabes but even in their absence the routine of examining papillary and tendon reflexes in every abdominal case will avoid needless surgery.

In HERPES ZOSTER the development of cutaneous erythema and vesiculation is often delayed for 3 or 4 days after the onset of posterior root irritation. Vesicles may develop on the visceral surfaces as well as on the skin so that haematemesis or haematuria may increase the resemblance to an intra-abdominal crisis. But the visceral vesicles will be accompanied by the typical cutaneous vesicles which, like the preceding pain, are strictly unilateral and of girdle distribution. In practice herpes more usually mimics thoracic than abdominal disease.

In the preparalytic phase of ACUTE ANTERIOR POLIOMYELITIS abdominal pain and tenderness may accompany the more usual limb pain. A physiotherapist in the Middle East developed a headache and vomited. When I saw her she was acutely ill with pain and tenderness over the right iliac fossa. Fortunately her headache continued and as this is extremely unusual in my experience in appendicitis I decided to defer operation. Twenty-four hours later leg pains appeared and on the fourth day she developed paralysis of the lower limbs and of the lower abdominal muscles on the right side.

Another classical impersonator of intra-abdominal crisis is CHRONIC LEAD POISONING. The onset of symptoms is acute with colicky pains and sometimes with reflex vomiting. Although uncommon, we have encountered two cases in the Surgical Out-Patient Department of the Royal Infirmary during the past year. Neither showed the tell-tale dropped wrist (" The Dangles ") but both had the black lead-line on the teeth.

Intra-cranial disease

Acute abdominal crises may follow a variety of intra-cranial lesions. Many of these have involved the hypothalamus but severe gastric disturbances have been reported after operative procedures confined to the frontal lobes. Haematemesis, increased intestinal secretion and disordered peristalsis are a frequent complication of head injuries and often constitute a major problem in supportive therapy.

Among the PSYCHIATRIC CAUSES of abdominal crisis the bizarre symptom patterns of the psychoneurotic, embellished with a wealth of minute detail are usually self-evident but it has to be remembered that such patients may have gleaned some medical knowledge and present quite a plausible story. Acute symptoms due to the gastro-intestinal hyperactivity of an anxiety state are usually equally obvious. Psychotic patients, on the other hand, are particularly liable to certain types of abdominal disaster such as perforation of stomach or bowel by foreign bodies or intestinal obstruction due to the swallowing of un-

chewed material and their mental attitude may greatly complicate the diagnosis. Undoubtedly the most intriguing of the psychiatric pattern: is that which is responsible for the so-called " Munchausen syndrome." There are a number of individuals wandering round the country from hospital to hospital, always gaining emergency admission with an apparently authentic picture of head injury, haematuria, perforation or some other such crisis. The symptoms settle immediately and after 24 hours or so they become difficult and take their own discharge only to repeat the performance elsewhere.

ENDOCRINE AND METABOLIC DISEASE

The endocrinopathies provide many pitfalls in the diagnosis of abdominal crises. By far the most important are those associated with diabetes. Apart from the additional hazards of any acute illness in a diabetic patient (and it must never be forgotten that 15 per cent of all the surgical diabetics registered in the Royal Infirmary are first diagnosed after admission to hospital for some unrelated illness) the occurrence of abdominal pain in diabetic ketosis represents the commonest problem. More rarely acute urinary infections, so common in diabetic patients may cause abdominal pain which suggests the possibility of an intra-abdominal crisis. The syndrome of the " diabetic abdomen " is never seen in stable diabetics. The pain is of gradual onset and is often preceded by vomiting associated with the ketosis. The pain and tenderness are usually diffuse and the abdomen moves freely on respiration. A marked polymorphonuclear leucocytosis may be present even in the absence of any infective process. The air-hunger of acidosis with the aroma of acetone in a dehydrated drowsy patient should lead to a suspicion of the diagnosis, but the final exclusion of primary intra-abdominal disease depends upon the resolution of the abdominal symptoms following energetic treatment of the diabetic state.

Acute adrenal failure is usually characterised by a shock-like state without pain but it is occasionally marked by the sudden onset of abdominal pain, vomiting and diarrhoea. The abdominal muscles are flaccid, like those of the limbs but there may be vagus tenderness, sometimes most marked near the adrenal glands in cases of infarction. The presence of generalised extreme asthenia coupled with pigmentation should not escape the alert doctor.

Whereas diarrhoea is common in thyrotoxicosis the muscular hypotonicity of myxoedema results in constipation which in severe cases is so complete as to produce the picture of intestinal obstruction. Indeed death from ileus used to be a common outcome in untreated myxoedema. The other features of the disease and the fact that peristalsis is diminished rather than increased should avoid diagnostic errors.

Hypercalcaemic crisis in patients with hyperparathyroidism is a somewhat exotic cause of acute abdominal symptoms. A high proportion of patients with this disease suffer from dyspeptic symptoms and constipation due to intestinal atony but if the serum calcium rises suddenly to levels above 15 or 16 mg%, severe vomiting with vague upper abdominal pain may develop. These patients may be drowsy or comatose, and death is imminent unless immediate operation is undertaken to remove the parathyroid tumour. Like urea and sugar, excess calcium in the urine acts as a diuretic and a history of polyuria and nocturia in the drowsy, vomiting patient who is not a diabetic should rouse interest in the serum calcium level. Two such patients have been admitted to the Royal Infirmary in recent years; both died—one undiagnosed until

autopsy revealed a parathyroid carcinoma with pulmonary metastases and the other despite emergency parathyroidectomy.

The vomiting and intestinal distension of uraemia may mislead the unwary and I am aware of at least two laparotomies on uraemic patients with an ill-founded diagnosis of intestinal obstruction. In the confused elderly man with hiccup and a dry tongue an emergency blood urea estimation is well worth while.

Over the past few years a number of patients, like those just mentioned, have been operated upon in the Royal Infirmary because of a clinical picture which resembled organic intestinal obstruction. I have called this condition " intestinal pseudo-obstruction." In some of these patients the abdominal disorder was secondary to disease elsewhere, as in the uraemic patients or those with intra-cranial disorders, but the most interesting group were patients who had suffered from haemorrhage. Three of these patients had bled severely over more than a week from a peptic ulcer ; the fourth was an old woman who had cut her scalp in a fall and, living alone, had sustained considerable blood loss before help arrived.

In each the features of intestinal obstruction developed without any demonstrable organic cause. We know that intestinal contractions cease in profound hypotension and that the local hypoxia produced by distension may result in lack of contraction. Experimentally, hypoxia in animals can cause incoordinate contraction of both small and large bowel. In man the motor innervation of the blood vessels is upset by minor degrees of hypoxia and it is my belief that the motor activity of the gut may also suffer under similar circumstances.

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FIBRINOLYSIS
AND
OCCLUSIVE VASCULAR DISEASE

By JOHN D. CASH, B.Sc., M.B.. Ch.B.

The magnitude of the problem of occlusive vascular disease needs no introduction ; we should therefore be acquaint with any new therapeutic developments, particularly if these have reached the stage of clinical trials. I apologise for any bias and simplification in this article. The purpose of the original Dissertation was to arouse curiosity ; this article attempts to do no more.

The System

The end-product of the complicated clotting mechanism is a fibrin clot. Fibrinolysis appears to be an equally complicated mechanism, the end-product of which is an enzyme, Plasmin, which can lyse the fibrin clot. Less detail is known of the various stages in Fibrinolysis than is known of the clotting mechanism. Astrup (1956), however, has produced a rough scheme which represents current thought fairly well. His scheme (Fig. 1) is based on the work of Christiensen & McLeod (1945).

Space does not permit discussion of known details in the fibrinolytic process. Suffice to say that circulating in the blood of all mammals so far studied is the precursor of the enzyme, Plasminogen. In the presence of an activator, which in turn is the end-product of a complicated process, Plasminogen is converted to Plasmin, the active fibrinolytic enzyme.

Inhibition of this mechanism appears to occur. So far the inhibitors appear to attack specifically at two sites. There are specific inhibitors of Plasmin and of Plasmin activators. One circulating Plasmin inhibitor is known to be an a-globulin. Synthetic inhibitors have been produced, the most recent being D-amino caproic acid.

Physiology

Fearnley (1953, 1955), pioneered the concept of a basal level of spontaneous fibrinolysis in normal people. He was able to show a diurnal variation, and a measurably higher level of activity in venous blood, particularly in that from the muscles. Buckell and Elliot (1959) using different assay methods have confirmed this, and agree with Mullerzt (1956) that the cause of the raised activity in venous blood was a raised level of activator. Sherry (1960) has also confirmed a raised level of activator following periods of fear, parenteral adrenaline, anoxia and after intravenous acetyl choline.

The mechanisms behind the release of Plasminogen activator are still for the most part obscure. Two significant observations, however, deserve mention. Albrechtsen (1957) has shown that certain organs store a high concentration

of activator ; the uterus, prostate, adrenal gland, thyroid, lungs and ovaries are such organs. The kidneys, all muscle, testes and spleen have very little, while the liver has none. It is possible that those sources of activator listed above may be used to raise the level of circulating activator.

Many workers have found a high level of fibrinolytic activity in venous blood draining muscles, despite Albrechtsen's finding of a low yield of activator from muscle tissue. Kwaan & McFadyean (1957, 1958) in some brilliant experiments on this problem concluded that there exists in the walls of arteries, veins and of some capillaries, cholinergic effector mechanisms which can react locally and reflexly to release Plasminogen activator. They have very tentatively suggested that constriction of the vasa vasorum producing relative ischaemia may trigger off this mechanism. Confirmation of these observations is urgently required.

PROACTIVATORS

LYSOKINASES ⟶ ACTIVATOR ⟶ PLASMINOGEN

PLASMIN

FIBRIN ⟶ Split Products
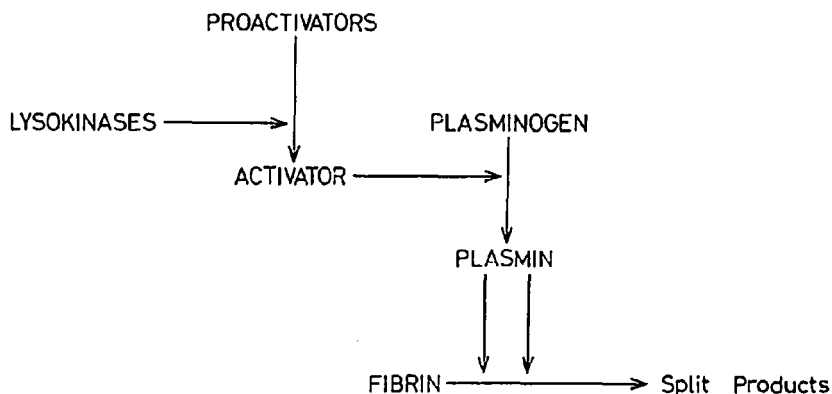
FIG. I.

Pathology

Thus we see so far that Fibrinolysis is a complicated yet delicately controlled mechanism. It is now necessary to look for any disturbance in the mechanism in association with occlusive vascular disease.

Over 100 years ago Rokitansky postulated that arteriosclerosis was the result of organisation of mural fibrin thrombi. Duguid (1946, 1948) has recently revived this hypothesis as giving a part explanation for the origin of arteriosclerosis. Duguid's work has been confirmed by many other workers, but he has shown great restraint in explaining why focal deposits of fibrin occur. Mole (1948) and Astrup (1956) have concluded that the cause is an upset in the fibrinolytic mechanism. Gillman (1958) believes that a decreased level of fibrinolysis plays at least some part in thrombosis.

Work has only just begun in measuring the fibrinolytic activity of circulating blood in patients with occlusive vascular disease. There is as yet no convincing evidence of reduced fibrinolysis after myocardial infarction, but Nestel (1959) has shown convincingly a 2/3 reduction in fibrinolytic activity in patients suffering from intermittent claudication.

The work of Kwaan & McFadyean (1957) and Buckell & Elliott (1959) has shown that fats, specifically saturated fatty acids, inhibit fibrinolysis. It is perhaps all to easy and fashionable to relate the association of fats with occlusive vascular disease through fibrinolysis. Measurements of the fibrinolytic

activity in diabetics on simple reducing diets are urgently required. In them,
Beckett & al. (1960) observed an incidence 20% higher than expected of
occlusive vascular catastrophes, and Southwood & al. (1959) had previously
shown a profound lipaemia at such times, and that the fats were saturated.

The evidence supporting the hypothesis that a disturbance of the fibrinolytic
system plays an important role in the pathology of occlusive vascular disease
is still fragmentary and controversial. Nevertheless, armed with this evidence,
American workers haxg proceeded into the exciting field of therapeutics.

Therapeutics

The possibility of unblocking blood vessels using fibrinolytic techniques is
an exciting one. It is perhaps necessary to set apart atherosclerosis in which
epithelization has taken place as compared with the more sudden process of
thrombosis or embolism. The evidence suggesting that fibrinolytic therapy is
useful in atherosclerosis is slight and the more interesting results have come
from treatment of thrombosis and embolism.

At the moment the only effective method involves the use of human Plasmin
intravenously. An American company now produces a preparation known as
"Thrombolysin." Local infusions are necessary to be really effective, as the
circulating Plasmin inhibitors soon nullify a raised systemic fibrinolysis.

Ruegesegger & al. (1960) have obtained some important results from radio-
graphic studies, in the dog, of occluded coronary vessels infused with
"Thrombolysin." Their work merits close study. Frieman & al. (1960) have
also given successful local infusions in dogs' peripheral vessels.

The amount of work performed on patients is still very limited. The problem
of assessing the results is particularly difficult in such fields as coronary
thrombosis and cerebral thrombosis. Nevertheless, Richter & al. (1960) and
Boucek & al. (1960) have both reported promising results. The latter have
successfully perfused the coronary vessels with "Thrombolysin."

The treatment of peripheral thromboembolic disease has involved more
straightforward techniques and the results therefore are of more definite
significance. Anylan & al. (1960) and in particular Clifton (1960) have pro-
duced some most encouraging results, from patients with femoral embolism
and femoral thrombosis.

The possibility of preventing occlusive vascular disease becomes very
real, particularly when a patient has been enabled to survive a first acute
attack. Since the limitations of long-term anticoagulant therapy are daily more
apparent, it must be considered whether a raised level of spontaneous fibrin-
olysis would not be a safer and more effective prophylaxis. Certainly, at least,
Frieman & al. (1960) were unable to produce artificial thrombi in their dogs,
once these had been thoroughly " thrombolysed."

Intravenous "Thrombolysin" for the rest of one's life is obviously incon-
ceivable but attempts have been made to find compounds which when taken
orally will produce a raised level of spontaneous fibrinolysis.

Finding a powerful hypolipaemic agent is an obvious start in the solving of
this problem. Constantintides & al. (1960) have reported that a sulphated
polymannuronide, " Paritol C " is a powerful hypolipaemic agent with no
side effects. One oral dose is effective for 24 hours. Fearnley (1960) and
Singh & al. (1960) have produced some remarkable improvements in patients
with intermittent claudication by giving them oral sulphonylureas, Tolbut-
amide and Chlorpropamide. Fearnley has demonstrated a raised level of
spontaneous fibrinolysis in patients taking these drugs.

These advances in the study of Fibrinolysis promise an important break-
through in the management of occlusive vascular disease. The foregoing

has been a brief, biased account ; lest we become wildly enthusiastic it should be pointed out that no " double blind " trials have yet been reported. There is a great need for more effective fibrinolytic agents and for careful, critically-reported trials. Despite the many problems, the clinical and anatomical restitution of occluded vessels and prophylactic measures against such catastrophes by medical means, is an exciting goal.

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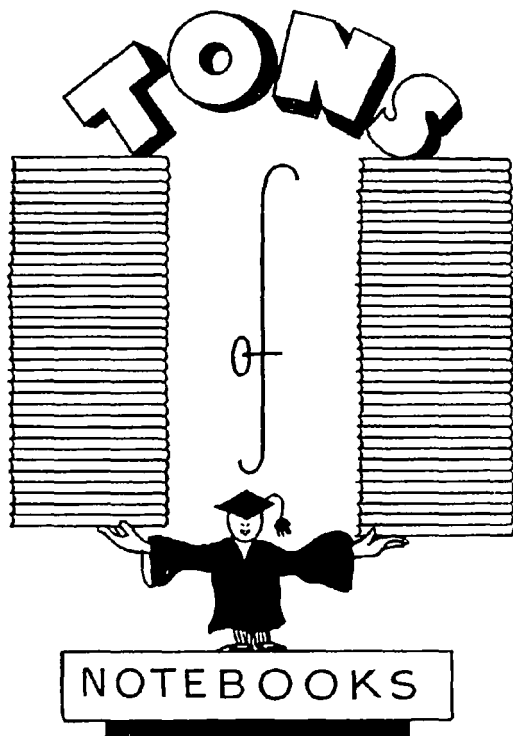
RES MEDICA

AUTUMN, 1961

VIRUSES AND CANCER

The discovery of many new tumour viruses has established beyond doubt that the virus is a common cause of neoplastic disease in plants, amphibians, birds and mammals. There is as yet no experimental proof available that any one type of human cancer is induced by a virus, although it would be strange if nature were to divide so sharply the origin of cancer in animals and man. Several reports strongly suggest the presence of tumour virus in human neoplasms. These include :—

(1) Electron-microscopic findings of virus-like particles in lymph nodes of patients with acute leukaemia.
(2) Isolation of nucleic acids with cytopathic properties from human tumours.
(3) Development of mammary tumours in mice injected at birth with extracts of a variety of human tumours ; the uninoculated controls showed an insignificant tumour incidence.

However, the problem of applying the important precedents established by animal experiments to man presents many difficulties.

It may be that the long association of tumour virus(es) with the human host make it difficult to reproduce the disease in other than a human milieu and it is probable that if cancer is to be proved viral in origin, the proof will have to be indirect based on :—

(1) Repeated isolation of the same virus from similar tumours.
(2) Supporting serological studies.
(3) Other techniques evolved from animal experiments.

The indirect evidence will be truly convincing if procedures based upon it are effective in the prevention or treatment of human cancer.

Tumour viruses may spread in the same way as any other virus, through contact between animals or by secretions and excreta. Experiments have also demonstrated that some tumour viruses may exist in animals in a latent form and may be transmitted from one generation to another. It may be that common viruses, following a sojourn in cancer cells can acquire, by the process of transformation, the ability to induce malignancy. Whatever implications concerning treatment may be implicit in these suggestions, it must be remembered that the cause of cancer is not a single problem ; it is many problems. It concerns the multitude of factors that enable cells to proliferate, it concerns the factors that enable some proliferating cells to invade and destroy the host. These factors whether they be particular viruses, radiations, chemicals, or

endogenous agents, may only be acting as stimuli that initiate proliferation, much in the way that the orderly sequence of events leading to the complete formation of an individual is initiated by the fertilization of the egg. However, these agents cannot cause cancer *without* the cell to play the major role and the ultimate cause of cancer must be sought *within* the cell. These cellular mechanisms are still unknown. When they have been elucidated, it may be simple to treat the disease. The value of studying aetiological factors is in the information that they can supply regarding the intracellular mechanisms of carcinogenesis.

PSYCHOSES AND THE NEUROHUMORAL AMINES

The role of serotonin and other neurohumoral amines in the above connection is currently being related, if ony tentatively, to the activities of the reticular formation.

The significance of this structure is much disputed, but it is usually described as a central network of grey matter, with pathways extending in both directions through the spinal cord as well as the bulbar, pontine and mid-brain levels. Impulses ascending the lemnisci to bring information of sensory stimulation excite also the mid-brain reticular formation which in turn arouses the cerebral cortex via the diffuse thalamic projection system. Activity in this system is characterised by the waking EEG pattern.

Serotonin, adrenaline and nor-adrenaline are three related substances which occur in many parts of the central nervous system in parallel concentrations. The highest concentrations occur in the hypothalamus, the mid-brain and the floor of the fourth ventricle.

Because of the considerable emphasis that has been placed on the role of serotonin and adrenaline in psychosis, the role of other neurohumoral amines has been relatively neglected. This is particularly true with regard to acetyl choline, which is localised in very much the same regions as the others mentioned. Cholinesterase inhibitors can produce both stimulatory and inhibitory effects at all levels of the nervous system, including severe psychotic episodes induced by extremely small doses.

These areas mentioned within the brain are associated functionally with the autonomic system and with the regulation of emotion, while the hypothalamus is closely connected also with the thalamo-cortical relay of the reticular activating system.

The interaction of the autonomic and central somatic nervous system may be illustrated by the actions of adrenaline. This compound is liberated into the blood-stream during emotional states, the stimulus being neural; the compound in its turn acts upon the C.N.S. The central effects comprise a direct action on central neurons, and secondary effects due to carotid sinus stimulation. The secondary effects are inhibitory upon both the spinal cord and the cerebral cortex, while the direct neural action of adrenaline is eventually to accelerate the activity of the cortex and to facilitate conduction within the spinal cord.

The excitatory actions of adrenaline are brought about simultaneously, it is said, by the reticulo-cortical and reticulo-spinal systems, and serve to heighten considerably the level of activity of the whole somatic system.

Recent studies of sensory physiology lend support to Huxley's view that the brain normally seeks to concern itself only with what is biologically useful and that it is actively engaged in suppressing from consciousness the majority

of irrelevant sensations which it receives. It may also be, as he believes, that hallucinogens can exert their effect by interfering with this mechanism.

Certainly, such drugs as mescalin and lysergic acid diethylamide (L.S.D.) do induce states reputed to be similar to those present in schizophrenic disorders, and L.S.D. is used to induce mental recall in abreaction.

Of greater interest now is the hypothesis that the tranquilising action of drugs such as reserpine is due to the release of serotonin from a bound form in the brain and other tissues. Conversely, the hallucinogens have supposedly been shown to act by antagonising the normal functions of serotonin.

Regardless of the eventual proof or disproof of this hypothesis, which seems entirely based upon circumstantial evidence, it has been established that certain types of psychotics are made more amenable to psychotherapy by administration of synthetic tranquilisers. Hence it remains possible that the hypothalamus and the thalamo-cortical projection may by a mechanism involving these neurohumoral amines be implicated in the development of psychotic states.

A TIME TO WEEP

" That was an affecting moment in the history of the Prince Regent, when the First Gentleman of Europe burst into tears at a sarcastic remark of Beau Brummell's on the cut of his coat."

It can be deduced from the affecting scene thus described that at one time it was not considered unmanly to cry. Since the Prince Regent's time, however, England has suffered under Dr. Arnold of Rugby, and the Stiff-Upper-Lip school of Philosophy—which has done much harm.

An illustration of this is the late 19th century corruption of the famous words of the dying Nelson. As every schoolboy knows, these were, " Kiss me, Hardy," and as every doctor should appreciate, they were not effeminate, but wholly natural in the mouth of an agonised and dying man. But our 19th century predecessors, suffering as we now can see from an overdose of suppressed effeminacy, shrank from the natural and came out with the unlikely suggestion that the words were in fact " Kismet, Hardy ! "

The purpose of this article is to voice a plea that weeping be once again considered normal. Tears have been shed in all great moments of history ; Caesar wept on hearing of the treacherous assassination of Pompey ; Napoleon wept at the destruction of the Imperial Guard at Waterloo ; and the characters in Dicken's novels weep nearly all the time. Let me end with these immortal words of the great Huxley :—

> *" Your maiden modesty would float face down,*
> *And men would weep upon your hinder parts."*

THE UNBORN CHILD

By C. SCOTT RUSSELL, M.D., F.R.C.S.[Edin.], F.R.C.O.G.

Professor of Obstetrics and Gynaecology, University of Sheffield.

Just as the clinical picture of any pregnancy changes from week to week so the picture of obstetric practice as a whole is changing. As childbearing and childbirth have become safer for the mother more and more attention has been directed to her unborn child. The foetus and its placenta, however, are remote when compared with the mother and therefore can often only be studied indirectly.

The Examination of the Foetus

The methods of examination of the foetus in late pregnancy are mentioned first. We can palpate it, estimate its size however roughly, recognise movements, look at its shadow on an X-ray film and over a period of time estimate its growth. Also we can listen to the foetal heart sounds, but listening is one thing and understanding what we hear is another. It is difficult to interpret foetal heart irregularities and observed changes may mean different things in different cases. The ordinary methods of listening to the foetal heart are good enough in most cases, but for some, rather more precise techniques should be employed. In cases of special difficulty the foetal heart can be monitored with a cardiophone. This apparatus is expensive but provides a clear and continuous record of the foetal heart rate, though the sounds differ from those heard with the ordinary stethoscope.

As a result of this monitoring of the foetal heart in special cases we have noted changes in the rate, not otherwise detectable, which we have interpreted as meaning that the child was in danger. Some of these changes have been translated into graphic records. Figure 1 demonstrates intermittent slowing of the foetal heart rate in a case of severe placental insufficiency. The routine interrupted listening had revealed no abnormality but continuous recording over many hours showed that from time to time the heart rate dropped alarmingly. After observation for 24 hours it was decided to deliver the baby by Caesarean Section despite its tiny size because it was thought that otherwise it would die in utero. This was done and as we suspected, the placenta was small and extensively infarcted. The child did not survive.

In another case, illustrated in Figure 2, a patient who had lost her previous child was admitted because she was a few days beyond the expected date of delivery. Induction of labour was decided on and an attempt was made to rupture the forewaters, but no liquor was obtained. The child was small and the foetal heart in this case was also monitored. For nearly an hour after the

attempted artificial rupture of the membranes there was no suggestion of foetal heart irregularity. Then quite suddenly and rather unexpectedly the rate became grossly irregular, occasionally falling to 80 and 90. Believing the foetus to be in danger, we performed Caesarean Section ; this child survived. A particular question which we were not able to answer was why the foetal heart should have shown this gross slowing and irregularity, and why in a case which was otherwise perfectly normal at 41 weeks was there no liquor in the uterus.

Attention to the foetus is very important and so is attention to the placenta but this remarkable structure is even more difficult to study ; as there is no direct method of examination, indirect methods have to be relied on.
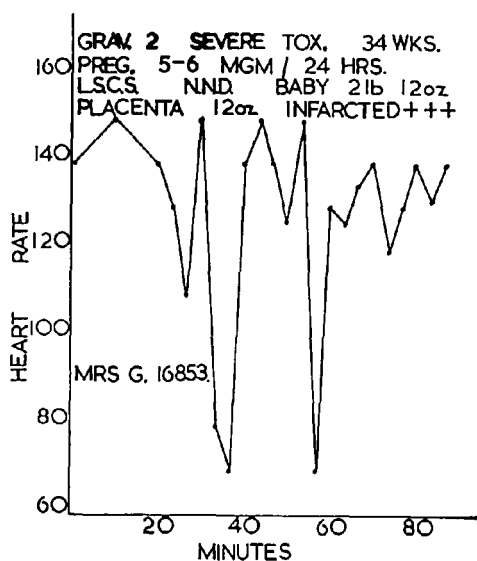
FIG. 1. Intermittent slowing of the foetal heart in a case of severe placental insufficiency.
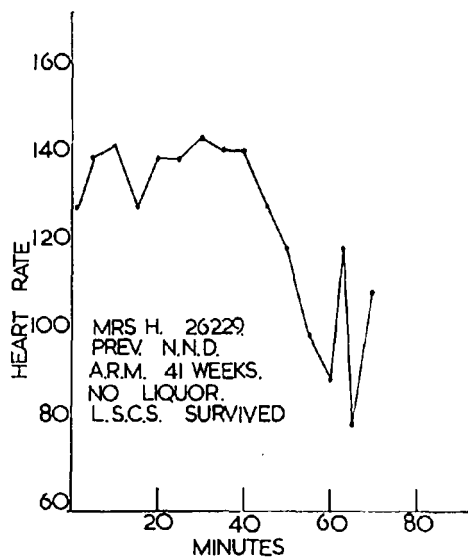
FIG. 2. Slowing of the foetal heart in a case with absent liquor.

Placental Reserve

The placenta normally has ample reserve for supplying the needs of the growing foetus. Sometimes, however, diminishing vascularity and increasing fibrosis can materially reduce this reserve until the amount of functioning tissue is barely sufficient or is insufficient for the foetal requirements ; interference with nutrition will then retard foetal growth and the child may just survive, or succumb during labour, or in cases of severe placental insufficiency, die in utero some time before term. Sometimes the placenta is too small to nourish a normal sized foetus and the placental reserve gets used up before term.

Placental Insufficiency

Placental insufficiency though as old as midwifery itself is rather a new expression and like other new expressions has different shades of meaning. The failure of function can occur quickly, e.g. in accidental haemorrhage or more slowly as in pregnancy toxaemia ; also the failure may occur at different stages of pregnancy. Placental insufficiency is most often seen in association with hypertension or toxaemia of pregnancy or both, but it is not an invariable complication of even the more severe examples of these diseases and it may

occur in the absence of these conditions. The problem is how to recognise in any particular case if there is sufficient placental damage to affect the foetus. In the Ante-natal period, the recognition of a small child which fails to grow shows that it is in danger, and the estimate of the degree to which its growth is affected is the first measure of how great this danger is.

Hormonal Excretion in Pregnancy

Additional information enabling a better estimate of placental function would be of undoubted benefit in such cases. To this end we have in Sheffield been studying the hormonal excretion in pregnancy, and particularly the excretion of pregnanediol, the principal excretion product of progesterone. During pregnancy there is a steady increase in the urinary output of pregnanediol until about the 35th or 36th week when the rising curve of excretion flattens off and falls slightly as term approaches (Fig. 3).

Our early work (Russell, Paine, Coyle and Dewhurst 1957) indicated that in cases in which there was placental damage, the levels of excretion were below normal and therefore that knowledge of the levels of excretion should prove helpful in practice.

More recently we reported (Russell, Dewhurst and Blakey 1960) a study of the pregnanediol excretion in a group of 58 patients in whom we had diagnosed on clinical evidence placental insufficiency or in whom there was the possibility that it might be present. Most of the patients either suffered from hypertension or pre-eclampsia or gave a history of a previous still-birth believed to be due to placental insufficiency ; a few patients had no such associated abnormalities.

We based our clinical diagnosis of placental insufficiency on the finding
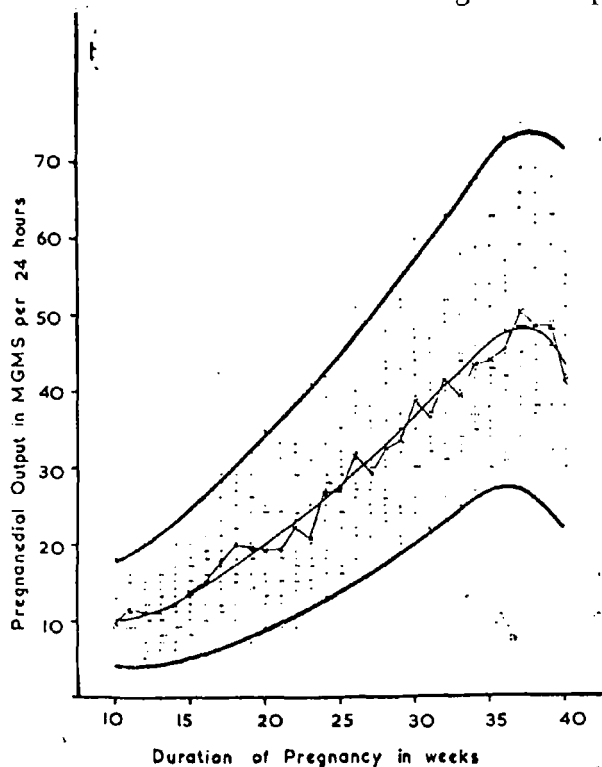
Fig. 3. Pregnanediol excretion in pregnancy : normal distribution.

By courtesy of *The Journal of Obstetrics and Gynaecology of the British Commonwealth.*

of a small child which did not grow normally ; on this basis we made a confident diagnosis of placental insufficiency in 16 cases (Group 1) ; in another 14 (Group 2) we considered placental damage was not significant ; and in the

remaining 28 cases (Group 3) we could not decide on clinical grounds alone whether there was placental insufficiency or not.

Pregnanediol studies were carried out in all cases. The method of assay was that described by Klopper (1955). In Group 1 low readings of pregnanediol confirmed our diagnosis of placental insufficiency in 14 of the 16 cases ; in the remaining 2 cases normal readings indicating good placental function led to a revised diagnosis (Fig. 4). In Group 2, normal readings were obtained in
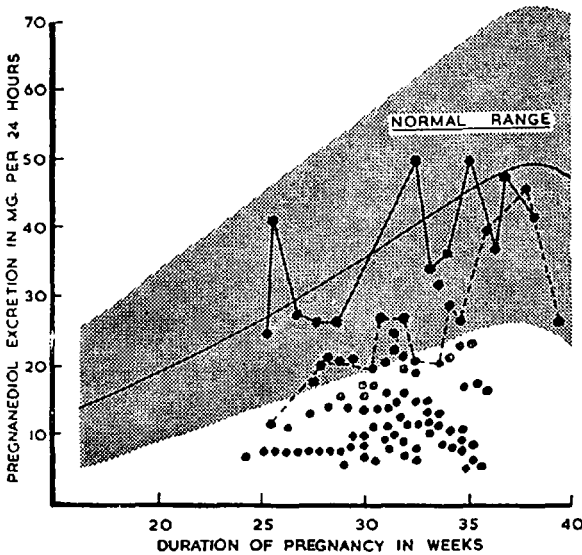
FIG. 4. Pregnanediol excretion in the 16 cases comprising Group 1.

By courtesy of *The Journal of Obstetrics and Gynaecology of the British Commonwealth*.

13 cases supporting our clinical impression ; in one case low readings suggested some placental damage. In Group 3, readings within the normal range but below the normal average showed reasonable placental function in 10 cases ; low readings showed placental insufficiency in 15 cases, while in 3 cases equivocal results were obtained.

Table 1.

CLINICAL GROUPING OF CASES

Total No. of cases in the survey	58
Group 1 (Placental insufficiency)	16
Group 2 (No placental insufficiency)	14
Group 3 (Uncertain)	28

Taking all 3 groups together there were 30 cases with low readings. In all of these there was evidence of enough placental damage to affect the child ; 11 babies were still-born and 2 died in the neo-natal period ; all the babies were below average weight for the stage of pregnancy. The placentae were small and in addition showed evidence of infarction which was sometimes very severe. By contrast, in the 25 cases with normal values, apart from one unexplained death, the weights of the babies and of the placentae were normal.

The pregnanediol assay provided us therefore with confirmation or correction of our clinical diagnosis, or the only reliable evidence of the state of the

placenta when a clinical diagnosis could not be made ; moreover, the amount by which the readings fell below the normal range indicated the severity of the placental damage and the urgency of the problem as it affected the child.

The treatment of an individual case was not based on the pregnanediol readings alone, but on all aspects of the case. The assay was helpful none the less, for although the mode of the delivery was decided almost exclusively on clinical grounds, the timing of induction or operation was simplified by our greater knowledge of the degree of placental damage present.

In a number of cases, the knowledge that there was a severe degree of placental damage made it clear that if the child was to be saved delivery was necessary even although the child was tiny and the duration of pregnancy perhaps not more than 32 weeks ; in such cases without this additional knowledge our inclination would certainly have been to delay interference with the likely death of the foetus in utero. In other instances we were encouraged by good readings to withhold interference until the child was more mature or even altogether : in still others, a number of late pregnancy readings falling just below the normal range suggested that it would be unwise to allow the patient to go overdue.

The assay requires accuracy and precision if reliance is to be placed on the result obtained. A 24 hour specimen of urine is needed and must be collected exactly, and the assay carefully performed. There is some uncontrollable error so second or third specimens should often be assayed. Reliance on the average of more than one assay divides the error of the single assay by the square root of the number of assays.

The Delivery of the Child

Having decided that the foetus is in danger in utero either labour must be induced prematurely or Caesarean Section performed. This choice though superficially straightforward can be most difficult because practice has shown that there is no guarantee that the child will survive its delivery however this is arranged. There is much still to be learnt about normal labour. What aspects of natural vaginal delivery are good for the child? The means by which the baby negotiates the birth canal may be passed over quickly, the descent and flexion of the baby's head, the internal rotation, the extension, the restitution and so on are all important but the slow squeezing of the baby's head and thorax in labour has also to be considered. Is this a hazard separating the robust from the fragile baby? Perhaps the squeezing of the baby's head is a way of showing the baby that life may be hard and that it had better get on with it. The squeezing of the child's thorax in the course of a normal delivery may be an important means by which the chest is cleared of any debris or liquor that may have been inhaled during the practice respirations that we know go on in utero.

These considerations are important because as an alternative to vaginal delivery we may perform Caesarean Section and in this operation there can be no comparable pressure on head and thorax. There is seldom any serious difficulty with the robust foetus of good size but the minutiae of the delivery may be of prime importance when the foetus only weighs 3 - 4 lbs. or even less. My impression is that *normal* labour is preferable to Caesarean Section for the very small foetus but the labour must be normal otherwise different hazards operate ; the closest watch must be maintained at the end of the first and beginning of the second stages because it is then that the foetus is in danger of asphyxia.

Other Hazards to the Unborn Child .

The unborn child may die in utero or it may die after its birth but there are

other hazards. It may be born handicapped, be mentally or physically retarded, or suffer from epilepsy or cerebral palsy, etc. These hazards are also being studied by us and I should like to record our gratitude to the National Spastics Society for their most generous financial support; it is to be hoped that we will be able to throw some further light on these distressing diseases. More needs to be known about the relationship between the foetus and its placenta. What decides the size of the placenta? Is placental growth dependent on the uterine blood flow? Can the foetus make its own placenta grow? These and other questions await answer.

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THE USE OF CONTROLS IN THE ASSESSMENT OF CLINICAL EVIDENCE

By C. VAUGHAN RUCKLEY, M.B., CH.B.

The incorporation of standards or controls into clinical experimentation has become, over the past decade, a widely accepted practice. So much so that there is a danger that the medical profession in general may become uncritical of the practical and, more important, the ethical problems involved. The subject should be under constant review.

Are controls really necessary? How best can they be employed? How is the resulting evidence to be assessed? Under what circumstances can the use of controls be justified on ethical grounds?

THE NEED FOR CONTROLS

Progress in medicine depends upon experiment. Formerly the physician based his belief in the efficacy of his simples and mixtures upon either the dogma of his mentors, hallowed by time and seldom criticised, or his own observations upon individual patients. This has led to the perpetuation, even into this supposedly enlightened age, of many remedies whose true worth has never been accurately assessed.

Although the majority of the remedies inherited from the 19th century and beyond have been discarded with the revision of the pharmacopoea in 1955, the need for objective assessment of the drugs we prescribe has never been greater. The reasons for this are twofold.

The drug houses are pouring out every day a flood of new preparations, many of which are either pharmacologically identical or differ, one from the other, by only a small degree in action or in side effects. This is too much for the practitioner to sort out for himself. Even if he had the time and energy he might not by now have the inclination, for the extravagant claims made on behalf of so many products can breed a cynical indifference, and a reversion to well-tried medicines.

He needs therefore a guide for speedy reference. Though he may not be trained in statistics, if he knows that a drug has been assessed by a standardised scientific procedure, such as a controlled trial, his problems and his scepticism are much diminished.

The second reason is an economic one. That the best treatment should speedily be selected from a multiple choice is very relevant to the cost of the Health Service in this country. Not only should the best be propagated, but the less effective products should just as quickly be discarded.

In diseases where no effective treatment exists, especially when they are either so trival as to inconvenience the patient only a little, such as the

common cold, or are highly malignant, such as acute leukaemia, there may be no necessity or indeed justification for the inclusion of a control group in a trial.

THE CONCEPT OF CONTROLS

The first clear definition of clinical controls has been attributed to Laplace in 1814. " To determine the best of several treatments it is sufficient to try each of them on the same number of patients, keeping all conditions constant . . . the superiority of the most beneficial treatment will manifest itself the more, the greater the number of cases."

This concept has gained widespread acceptance only during the past ten years. It continues to have its foes. Basically it involves the application of a statistical method to experimentation with human subjects in a manner previously applied only to animal studies. Planning the experiment is now recognised to be a major undertaking, necessitating from the start having a clear grasp of the questions it is hoped to answer, and proceeding to detailed specification of the kind of subjects to be included, the treatment to be compared and the measurements to be taken. The points at which different types of trial are particularly vulnerable to bias are more widely appreciated, as is the value of such precautions as randomisation, " blind " comparisons and the inclusion of placebos. The number of successfully completed trials is growing and they serve as models for future work.

ERROR

With the exceptions already mentioned, the inclusion of controls is essential for every kind of clinical trial. Where no control is exercised other than the subjective response of the patient and the clinical impression of the physician, the scope for error is great.

Many investigations into observer variation have emphasised the need to substitute the experimental for the observational approach.

Professor Hill has pointed out, however, that " within the framework of a clinical trial designed to contrast one group with another there is nothing whatever to inhibit the highly gifted clinical observer from observing . . . " The observational and experimental techniques are not mutually incompatible; indeed I believe one advantage of the development of controlled trials in Great Britain has been the need for, and the attempt to improve, observations of disease and disease processes.

" The emphasis placed on objective measurements," writes Oswald Savage, " has already resulted in more careful and accurate studies in these chronic diseases and has already produced new observations on the natural history of conditions such as arthritis."

The principle of therapeutic control is to provide for the group of patients who are to undergo a new and yet untried treatment a parallel group of cases similar in all respects, that is as regards all possible contributing causes except the one factor of treatment ; or if the behaviour of the disease in a particular patient is to be observed before and after treatment, to make conditions the same in both periods except again for the factor of treatment.

Some sources of error may be unsuspected until the control method brings them to light. They represent all conditions which may be important for the origin as well as for the further development of the disease. Sources of error, or " concurrent causes," are divided by Herdan into ' internal ' and ' external ' causes.

Among the internal causes are firstly, the characteristics of the patient.

These include sex, age, nutrition and genetic constitution—all of which may influence profoundly his response to disease and its therapy.

Secondly, there are the characteristics of the disease itself. At different periods of time and in different subjects, particularly in chronic diseases, or in trials covering several months or years, the disease may vary in its stages, in its degree of severity, and in the virulence of an infecting organism. Delay in treatment will also allow evolution in the disease process, and will alter its response to treatment.

Among external causes are firstly environmental factors such as financial conditions, family affairs, conditions of employment and various physical disturbances which may substantially affect the progress of the disease.

Causes may be introduced through the treatment itself. These include the effects of transition from home to hospital — the very fact that a patient is moved into a hospital environment can evoke new mental and physical responses, as also can the attitudes of doctors and nurses. For example, in an organic disease such as ulcerative colitis where psychical factors are known to play an important part, even a dummy tablet, if recommended with conviction and enthusiasm by the physician, may evoke a perceptible clinical improvement. Thus in certain trials neither the doctor nor the patient should know whether he belongs to the trial or the control group, nor even, in the case of the patient, that such a dichotomy exists; hence the use of the ' double blind ' method and dummy tablets.

It is not correct to assume that by introducing clinical controls into a trial we automatically eliminate error. However large a trial, and however similar control and trial groups may be, owing to the operation of concurrent causes it may lack generality. That is to say that the results, although true for a particular time, place and trial, may not be universally true.

The science of comparative therapeutics involves the study of just such larger problems. However, comparative therapeutics apart, it is probably true to say that the larger and more widespread a trial, the more reliable are its conclusions. Examples of two such experiments are the M.R.C. trial of ACTH, cortisone and aspirin in acute rheumatic fever, 1955, which involved the co-operation of many centres in the United Kingdom and the United States, and secondly the trial of the Salk polio vaccines which involved many thousands of patients.

THE CONSTRUCTION OF CONTROLLED TRIALS

According to the type of disease we are studying, so a particular type of trial is adopted and a particular statistical method applied to the analysis of the results. There are two broad categories : " within-patient " trials, where the patient is his own control, and " between-patient " trials, where control and trial are different patients.

It seems agreed by most authorities that in clinical trials, as in experimental pharmacology, when feasible, comparisons of treatments should be made within subjects rather than between subjects. If each subject receives all the treatments, variations in level of response from subject to subject cancel out when treatment averages are compared. The gain in precision is often striking (5).

A within-subject trial is a simple example of grouping. The general principle is to divide the patients into groups such that differences between groups represent important sources of variation that may inflate the experimental errors—that is, they are stratified according to known concurrent causes— then, if the experiment can be conducted so that each treatment is represented

equally often in every group, differences between groups are automatically eliminated from the comparisons of the treatment averages.

There are various designs by which grouping may be applied. A basic form is the simple cross-over pattern where the patients, and the duration of the trial, are divided into two for the comparison of two drugs. For example, 100 patients are included for the testing of 2 drugs over a period of 6 months. For the first 3 months 50 patients, who may either be randomly selected or subgrouped according to some common characteristic, are given drug A and 50 patients drug B. For the second 3 months the treatments are reversed. The patients are their own controls.

The same principle can be applied in various more complex designs. An example of a trial may illustrate the method. The relative values of Phenmetrazine and Dexamphetamine in the management of obesity have recently been compared (6). A 'double blind' procedure was used. Three series of tablets of similar appearance were prepared:— Phenmetrazine, Dexamphetamine and a control placebo, containing principally Lactose. A crossover technique was employed on the latin-square pattern.

<div align="center">1.   A.B.C.   2.   B.C.A.   3.   C.A.B.</div>

The patients were allotted to a particular treatment by a random sequence using a table of random numbers (Bradford Hill, 1955). Thus the two treatments under review were compared one with the other, and in addition, each patient was his own control. With the use of such control grouping far more information can be gained than simply the quantitative success of one treatment over another.

All patients throughout the trial were on a similar low caloric diet. As is always the case with the initiation of a reducing diet, regardless of the drugs given, the weight loss in all groups was greater during the first 6 weeks, due to initial dehydration. Since the precise effect of a treatment depended upon two things, namely the kind of tablet taken and whether it was administered in the first, second or third period, a more accurate result could be obtained if these two influences were disentangled. Grouping made this possible.

Thus an important concurrent cause could be eliminated, namely the evolution of the disease process at a particular time in the trial—in this case the regression of weight loss—and appropriate statistical correction terms could be applied. The conclusions drawn at the end of such a trial are therapeutically and statistically reliable.

In general, it is seldom possible to apply these within-subject methods to acute or rapidly progressive diseases. In fact, in clinical practice, as Doll has pointed out, the opportunities are few for using the patient as his own control because " when one drug has been tested the patient's condition is likely to be so altered, whether by the drug or by nature is immaterial, that nothing is to be gained by repeating the treatment with another drug." (7).

The majority of trials therefore have to be conducted by giving trial and control drugs to different patients, that is between-subject trials. The groups of patients should be similar in all respects except the treatment they receive.

In the past, controls were often retrospective, that is to say, attempts were made to compare the effects of a new drug on a group of patients over a period of time with the effects of a previous treatment and a different group of patients. This, as Armitage (8) and others have pointed out, is a practice which should be avoided because other factors may be operating.

For example, patients treated with anticoagulants for coronary thrombosis have been compared with ' control ' groups treated prior to the introduction of anticoagulants in 1948. It has been shown that these two groups can not be fairly compared. The very fact that a specific treatment for thrombosis was

available meant that after 1948 a larger number of coronary thromboses of only moderate severity were admitted to hospital than previously. This alone was sufficient significantly to improve the survival rate of cases treated in hospital.

To avoid these and other difficulties in between-patient trials a variety of methods of random selection have been devised. Randomisation precludes the possibility of conscious or unconscious bias on the part of the clinician who is allotting patients to the trial.

Randomisation does not ensure that all groups are exactly equal; nothing can do this. It does ensure that they differ by an extent that is predictable and can be allowed for in the statistical analysis.

It may be thought preferable to take into account all the concurrent causes over which we have some control by methods of sub-grouping or stratification. This is particularly valuable where the numbers involved are small and where it is less likely that 'by chance' the two groups will be homogeneous. This sub-grouping can be incorporated into the system of alternates—known as compensating alternates—or can be combined with the random numbers method, especially if more than two sub-groups or strata are contemplated.

Two or more groups which at the commencement of a trial appear to be quite comparable may show, on reassessment at the end, to differ in important respects. In the M.R.C. trial in 1955, some 500 children were divided into three groups to compare the value of ACTH, cortisone and aspirin in the treatment of acute rheumatism. It was found that most of the concurrent causes were strictly comparable, but a marked difference happened to be present between groups in the numbers presenting with chorea (ACTH, 5.6%: cortisone, 11.4% : aspirin, 15.5%) and with congestive heart failure (ACTH, 14.2% : cortisone, 9% . aspirin, 6%). This difference is statistically significant and could therefore influence results, and it illustrates the value of sub-grouping.[9]

Doll points out, however, that it is seldom necessary to have more than a few subgroups, and that if it seems necessary to have a large number it suggests that the treatment is being tried on too heterogeneous a group of patients.

A statistical method which has been increasingly used in recent years is Sequential Analysis. The usual practice in trials is to postpone conclusions until final measurements from all subjects have been gathered. In a sequential trial on the other hand, a continuous statistical analysis is made as the data from each subject comes in. The trial is stopped as soon as the analysis indicates a clear-cut verdict of statistical significance.

This method may allow a reduction in amount of experimentation by 10 - 50% as compared with a fixed-size trial of the same discriminating power. For its suitable application there are certain requirements :—

 (i) Patients enter the trial in sequence over a period of time.
 (ii) Results should be quickly available.
 (iii) There should be potent reason for wishing to stop the trial as soon as possible.
 (iv) The primary object should be to perform a test of significance between new and standard treatments rather than a quantitative assessment (10).

The controls in sequential trials are the patients on the standard treatment.

Sequential Analysis is the method used in the Stilboestrol-Oestriol trial in metastatic mammary carcinoma, which is currently being conducted in Edinburgh. It provides a good illustration of the technique.

It is designed to show whether there is any significant difference between therapy with a synthetic oestrogen, stilboestrol, and a naturally occurring one,

oestriol. The former is the standard control. Patients are allotted to one or other group by a ' double blind ' method. The tablets, similar in appearance, are distributed by the sealed envelope system using a table of randomised numbers and applied by a statistician.

In order that progress can be assessed with some accuracy the criteria of admission to the trial are clearly defined, principally definite skin recurrence and/or metastases clearly seen on X-ray.

Each patient is seen at monthly intervals. The nosographic criteria of progress are based on X-ray changes, measurements of skin lesions, including photographic records and biochemical tests. They are assessed not by one but by a panel of doctors. As soon as it is clear that a patient is deteriorating despite the hormone therapy she is withdrawn from the trial.

THE STATISTICAL EVALUATION OF RESULTS

The construction of therapeutic trials implies a twofold control. The two control concepts may be distinguished by the names of ' clinical controls ' and ' chance controls '.

Having arrived at the end of a trial with a quantitative difference in results between trial and control groups, the question then arises as to whether such differences can be regarded as significant. The alternative is that the differences observed are caused by fluctuations of the many causes which comprise ' chance '.

Hence just as important as the clinical control is the control of the observed differences, and this is affected by application of a calculated standard error or standard deviation.

There are three main types of fluctuations or variations of numerical quantities which obey the laws of chance :—

1. Random sampling fluctuations of numbers and of relative frequencies (percentages).
2. Biological variations of counts and measurements.
3. Experimental and observational errors.

Once a difference has been observed between the findings in the control group and in the trial group, a statistical significance test must be applied. The appropriate test depends upon the particular nosographic criterion by which the effect of treatment is being assessed. For example, differences in relative frequencies or of percentages of outcome are assessed by the standard error of a percentage and by the chi-square test, and differences between average duration of a disease by the standard error of the mean test.

For most practical purposes, having established a distribution curve from one control group we can draw an arbitrary line at a distance of two standard deviations from the mean. If an observed value from the trial group lies outwith this line it has a 95% chance of being statistically significant. If it lies beyond thrice the standard deviation it has a 99.7% likelihood of being significant.

ETHICAL PROBLEMS

The foregoing discussion has centred upon some of the problems which arise with the use of controls, their application and assessment. Considerations remain of far greater importance. They arise in clinical experimentation because of our belief, with Kant, that every human being, irrespective of his mental or social stature, should be regarded as equally important.

It has been said that many of the great men of history were great because they were bigots ; that is to say they could only see one side of a problem, their

own side. In the same way, anyone, whatever his sphere of activity, dedicated in the pursuit of a policy or line of investigation, may become blind to points of view differing from his own.

Since this may be a quite subconscious process, such a person may bitterly resent the imputation that he is not fit to assess objectively the ethical implications of his own work.

Since the use of controls has assumed an integral part of clinical experiments it is very relevant, in discussing their use, to consider the ethics upon which human experimentation as a whole is based.

Can we justify experiments on humans at all ? I have discussed earlier some of the material reasons why controlled trials are necessary in the propagation of new therapy. These trials cannot be confined to experimental animals. Findings in other species may have general or specific validity for man, but the ultimate establishment of such validity must rest in each instance upon direct observations upon man.

Shimkin has advanced important considerations for the justification of such experimentation. He points out that an unwillingness to experiment carries with it as much moral responsibility as active experimentation. He says, " . . . to do nothing, or to prevent others from doing anything, is itself a type of experiment . . . " and goes on :

" As much knowledge and as weighty reasons are required for one course of action as for the other, and it should be demonstrated that the proposed experiment is more dangerous or more painful than the known results of inaction " (11).

The Nuremberg Medical Trials resulted in the formulation in 1947 of the oft-quoted rules which serve as a guide, though not necessarily as an infallible credo, for the experimenter. Shimkin has reduced these rules to two primary principles :—

1. " Investigators must be thoroughly trained in the scientific disciplines of the problem, must understand and appreciate the ethics involved, and must then be competent to undertake and carry out the experiment.

2. The human experimental subjects must agree to the procedure and must not be selected upon any basis such as race, religion, level of education or economic status. In other words, the investigators and their subjects are human beings with entirely equal, inalienable rights that supersede any considerations of science or general public welfare."

How can the use of patients as controls be reconciled with such principles ? Guttentag has drawn a distinction between the ' physician-friend ' and the ' physician-experimenter '. The former has a personal relationship with his patient, sharing his distress and wanting to assist him. " Objective experimentation to confirm or disprove some doubtful or suggested biological generalisation is foreign to this relationship. This would involve taking advantage of the patient's cry for help and of his insecurity" (12).

There is no doubt that among medical research workers in this country there is a tendency to regard patients as experimental objects, rather than human beings, and since this attitude is principally to be observed in the teaching hospitals it may well be spreading.

The responsibility for care of the patient, and for intensive investigation or experimental procedures on that patient, should be in the same hands, not necessarily the hands of an individual but preferably of a group. The more extensive and potentially dangerous the experiment, the more widely should the responsibility be divided. The nature of the doctor-patient relationship is such that nothing ought ever to be done to the patient except to his direct advantage, unless he gives his consent. As Fox has put it, " it is this consent

that changes his status to that of volunteer, in which he becomes the legitimate object of experiment." (13)

Greiner has listed the circumstances under which he considers that a compromise may fairly be reached.

" In the first place, the risk of drug toxicity must not exceed that run by thousands of patients under conventional treatment. In the U.S.A. this means drugs and doses that have already been accepted by Government agencies.

" Secondly, each patient-participant shall have a medical condition which, in the ordinary course of events, would be treated by the test agent or another drug with similar action.

" Thirdly, the experimental design shall not permit deterioration of the medical condition.

" Finally, it is apparent that a number of trials would be impracticable if the patient understood exactly the nature of the experiment, or even that he were participating in an experiment at all. A rigid ethical ideal may be too restricting when facing real-life problems." As Greiner succinctly puts it, " a workable standard appeals to me even more than lip-service to a remote principle, however perfect." (14)

The very fact of an experiment being necessary implies that one treatment is inferior to the other, and therefore that one group of patients will derive more benefit than the other. As long as it is only known for certain to be true in retrospect, then the experiment can be entirely justified on ethical grounds.

While the trial group receive the new treatment the control group are given the best orthodox treatment. Crofton has said that since the control group receives the best treatment previously available, it is the safest group from the patient's point of view to belong to. " He may be denied the still improved advantage of the new treatment but he avoids its possible side effects. And, of course, the new treatment may prove to be inferior to the old."

Finally, if we reject controlled clinical trials as ethically inadvisable, what are we to propose as the alternative? Without controls, trials are unreliable; without trials the distribution of drugs may be haphazard and potentially dangerous. To quote from Hill, " in many settings the carefully designed controlled trial is far more ethical than the uncontrolled experimentation with unproven products to which patients are frequently exposed." (15)

It is not sufficient simply to take a passive role nor to obstruct those who are active in the development of new experimental methods. We have an obligation not merely to reap what has been sown, but to plough-under a little more untilled land for the next crop.

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"THE SLIMY MUD OF WORDS"

Language and New Concepts in Medicine

By H. C. DRYSDALE, M.B., Ch.B.

Based on a Dissertation read before the Royal Medical
Society on Friday, 24th February, 1961.

Out of the slimy mud of words,
Out of the sleet and hail of verbal imprecisions,
Approximate thoughts and feelings,
Words that have taken the place of thoughts and feelings.
There springs the perfect order of speech,
And the beauty of incantation.
                    —T. S. ELIOT, *Choruses from "The Rock."* *

The condition of man requires that he communicate with his fellows. Yet language may be a distorting glass, and may often accentuate the isolation rather than the communication. For the doctor, the need for personal communication is as great as for other men but there are, in addition, two spheres of his professional work in which it becomes paramount.

In the first place, the doctor has to contact his patients. " *I am by trade a dealer in words, and words, as you know, are the most potent drugs known to man.*" The saying is attributed to Rudyard Kipling and contains a truth familiar to all who come in contact with patients. Words acting as drugs influence the irrational and the emotional, and their power is amply demonstrated by the positive results so often produced by the pharmacologically inert tablets used in double blind clinical trials.

Apart from the therapeutic use of words, however, the doctor has often to transmit facts to his patients, and here grave difficulties may arise. There is little to be gained from prescribing a precise and accurate diet unless both the patient and the doctor mean the same thing by ' dinner '; for the patient any disease which is ' pernicious ' must be dire and dreadful in its outcome, no matter if, to the practitioner, it only means a fortnightly subcutaneous injection ; when the patient says he is ' better,' is he improved—or cured ?

When dealing with patients, the doctor tends consciously to use non-technical terms, and when he does impart information he is generally at some pains to make sure that he is correctly understood. In the second situation where communication is of paramount importance to the doctor, such pains are often absent. This is the situation of communication between doctors, as men of science. If Medicine is both a science and an art, perhaps part, at least, of the artistry lies in the use of language. Certainly if we doubt

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* " Collected Poems," Faber & Faber Ltd., London.

the importance of this artistry it is to the professional writer that we should turn. Sir G. Pickering [1] in his recent comments on this subject, quotes W. Somerset Maugham : " On taking thought it seemed to me that I must aim at lucidity, simplicity and euphony. I have put these things in the order of importance I assigned to them." Perhaps we may examine a little more closely the first of these desirable attainments.

Dr. Richard Asher [2, 3, 4] has conducted a penetrating analysis into the distortions which the meaning of a word may undergo. He demonstrates three separate meanings in each term ; the entymological meaning, the derivation of the word ; the implicational meaning, upon which the derivation is based ; and the referential meaning, the simple objective fact which is eventually associated with the term. An example may serve to show both the utility of this analysis and the importance of the confusion which can arise.

The clinical entity Epilepsy has been known from ancient times, and the dramatic nature of a fit ensured that an accurate description was made early in its history. Theories as to its causation were many. One of the components of the fits which was recognised early was the premonitory subjective sensation, and catalogues of the various manifestations were drawn up. At this time the popular theory of causation was that evil humours passed from the limbs to the head and there evoked the fit. The term ' aura,' from the Greek, meaning a cold breeze, was first used of a single patient whose premonitory symptoms were described in this way ; this description was taken as confirmation of the humour theory, and it was but a short step from there to calling all such premonitory symptoms auras—and assuming a similar cause. [6]

Thus we have the entymological meaning—a cold breeze, and the implicational meaning—the passage of humours to the brain immediately before a fit. Once the term had become generally accepted, all further thought upon that particular subject was bedevilled by the implicit assumptions of the terminology, until eventually, aura acquired a referential meaning—the subjective sensation preceding a fit. In this case it was several centuries before it was generally realised that the aura was the result of an initial central disturbance, and, in the interim, various measures, ranging from cautery to hideous medicinal concoctions had been persistently applied to the limbs to prevent the spread of the hypothetical humour.

The example is from the past, but there is ample confusion in the use of terms today, confusion within the implicational meaning. Take, for example, the very basic word disease. Does this mean overt dis-ease ? Surely not, since so much time in present-day medicine is spent in discovering subclinical states. Shall we then define it as a deviation from the normal ? Immediately the word ' normal ' clamours for definition. Even with accurate observations, precise measurements, numerous patients and all the aids which statistics can offer us, this may be a difficult task. Always there will be patients who hover at the extremes of any ' normal range ', or worse still, occupy the limbo of overlap so charmingly labelled ' equivocal '. How, then, are we to know what to treat ?

As well as forming a bar to action, the imprecision of the term disease is also a bar to thought, for a single disease may contain within it many different pathologies or aetiologies. As long as peptic ulcer is a disease, then the fact remains concealed that one such ulcer may be associated with a parathyroid adenoma, another with a beta-celled tumour of the Islets of Langerhans, and a third with undue consumption of corticosteroid hormones. There has been therefore, a recent tendency to substitute the term " syndrome ' for disease ; such a symptom complex represents the result of a " *chain of physiological processes, interference with which at any point produces the same impairment*

of bodily function. The same syndrome may thus arise from many different causes." [5] So simple a substitution as this has, in the words of Sir Harold Himsworth, produced a 'liberation of medical thought.'

Dr. Asher has demonstrated two ways in which words further limit out thinking. In the first place, once a concept has become sufficiently established to be given a name, it becomes most difficult to eradicate, and an apt name may perpetuate a non-existent entity. Pituitary cachexia, defined in my dictionary as the weakness and emaciation caused by the removal of the hypophysis has its existence doubted in Davidson's *Textbook of Medicine*: "Wasting (pituitary cachexia) is not a common sign, and when present is often due to some intercurrent disease". Similarly the delightful Osgood-Schlatter's disease of the tibial tuberosity is gradually being ousted from its pride of place among the osteochondritides, and the arch iconoclast Dr. Asher tells us that both Messrs. Pel and Ebstein wrote about patients with chronic remitting fevers probably due to brucellosis, and certainly not associated with lymphadenoma.

Conversely many a syndrome must escape general recognition simply for lack of an appropriate title. This has been demonstrated by the simple expedient of naming two, and in the future no textbook of psychiatry will be complete without a mention of the Munchausen syndrome, or cardiology book without a mention of precordial catch (Trexidor's twinge).

In summary, therefore, a word may come to enshrine a dead idea, its meaning may change with the passage of time, or it may come to possess more than one meaning so that precision in its use is for ever lost. "Once a word has been mishandled consistently, it is useless for scholars to try to preserve its correct meaning. Like a bolt screwed into the wrong socket, it forces a place for itself and, at the same time, spoils the thread of the seating so that the correct fitting will no longer go in properly." [2] We may gain a sad measure of consolation from the reflection that this debasement is not peculiar to medicine for, as Thurber ruefully quotes : "Love has become a four letter word ".

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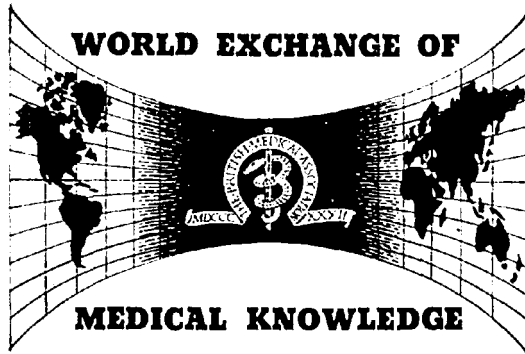
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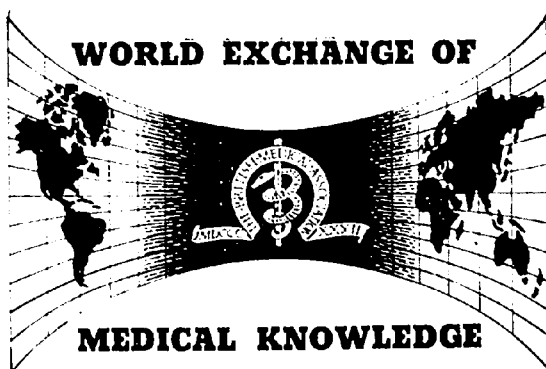
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HARVEY THROUGH THE MINDS OF OUR GENERATION

By J. K. SLATER

O.B.E., M.D., F.R.C.P.(Ed.), F.R.S.(Ed.)

including comments on present-day medical education

From the Oration delivered to the Harveian Society, June, 1961.

"The return of one Harveian Festival recalls from the subconscious a host of feelings to each of us, in the forefront the sense of profound reverence towards one of the Di Immortales of medicine ; in little less degree, the sense of pride—national pride—that the unraveller of the enigma of the circulation was British born. For it is not we alone, who, on the day of celebration, stand bareheaded before the perpetual monument ; in every school of medicine the world over the same impulse is felt, whatever the outward expression."

These words were spoken in this place thirty-five years ago by one of our most distinguished and worldly-wise physicians. As a neophyte in that year, 1926, I listened enthralled as the learned oration flowed in the resonant tones of the great Sir Robert Philip, and in fact, the vague name of that mediaeval character, William Harvey, became real and fascinating to at least one of the new boys that evening. Sir Robert was my first orator and now, when inexplicably I find myself at the same lectern, there is perhaps a natural tendency to look back and attempt a brief and partial review of all the discourses that have been given during my membership of the Society.

Never can so much have been written by so many about one man, but such is the variety of human approach or, (as they would say in Yorkshire, there are " nowt so queer as folk") that even a close scrutiny of the material available fails to discover the slightest suspicion of plagiarism—a tribute perhaps to the English language which provides so many ways of saying the same thing. All are agreed about the time and place of his birth, the manner of his demise in his brother's house and his burial in Hempsted, Essex, and indeed about much that happened in between these events,—the influence of Padua or the inspiring Fabricius whose work on the venous valves probably gave Harvey his needed clue,—the love of his London College and Bart's Hospital, his romantic association with two monarchs, his frequent travels at home and abroad, often in distinguished company. All these matters are authentic and well annotated. All of our orators have accepted these basic facts with uniformity, the intriguing part of the individual approach comes when speculation is allowed full rein.

Sir Robert Philip in his most masterly oration deduced that Harvey's association with James I and later Charles I brought him repeatedly to Edinburgh

and thus into contact with the leading educational circles in which the former monarch had long been much interested. In these visits Harvey had great influence in many spheres, or, as the couplet put it —

> " He dwelt among men : Physician and Sage
> He served them, loving them, healing them."

And so, says Philip, this influence must have had bearings on the history of Edinburgh and particularly of the Edinburgh Medical School. It should be remembered that at this time he had, as a leading member of the Faculty and of the University Court, taken part that very year in the bicentenary celebrations. Moreover, he was President-elect of the B.M.A. It is therefore safe to assume that his alert mind had harnessed all the slants pointing in the way he surmised. " It is therefore of my great interest to recall that the first move towards the foundation of the Royal College of Physicians of Edinburgh was made in 1617 on the occasion of the King's visit to Holyrood. If nothing immediate came of it, it seems hardly conceivable that the endeavour failed from lack of interest of the King." At least it initiated much coming and going, at first of Harvey and the King, and later Scarborough, his successor as Chief Physician, until all the various forces and counter forces were ironed out and the difficulties removed with the granting of the Royal Charter in 1681, that is 24 years after Harvey's death.

Great orations must inspire thought and research in others who follow, and not surprisingly we find a year or two later Dr. Robert Thin—another President of this College—giving an account of Archibald Pitcairne whom he describes as " physician, philosopher, poet and wit, with his virtues and his failings, the latter not a few." His name ought to be held in reverence by all Scottish Harveians, as he was their first kinsman to grasp the full meaning of Harvey's great discovery, the first to defend his claim to that work, and, following in his master's footsteps to blaze the trail of scientific inquiry through uncharted Continents, and thus add to the sum of human knowledge and by his practice based on that knowledge, to diminish the sum of human misery.

Harveians turned out in large numbers for the Festival in 1930. George Lovell Gulland's title—" The Circulating Fluid ", seemed to promise something pithy to those who knew him well, " Uncle George ", as he was affectionately known to thousands of students before and long after the First World War.

Unexpectedly to many, his talk was confined to the blood and in his most serious vein. He discussed the earlier views on the nature of the blood, and the development of our modern notions, then speculating on the possibilities, ridiculing Galen and the Roman empire as the main reason for little research, then the deadening hand of the Church as the unchallenged successor to Hippocrates and Galen's accepted doctrine which was that of the three spirits, the natural, vital, and animal which had held the stage and convinced the uncritical for much too long. Apparently, as few will remember, the origin of the vital spirit was the heart and of the animal, the brain. Harvey gave the death blow to all this and, as stated by Gulland, a wave of scientific interest passed over Europe from the middle of the 17th century. He puts it thus : " Harvey foreran it and his vivifying genius had much to do with its start. It coincided with the Puritan revolution which was in its essence a re-examination of authority much the same in kind as the scientific revolution, and it culminated in England in the formation of the Royal Society." His summary and conclusion is extremely interesting : " All the vast mass of knowledge which we call Haematology we owe to Harvey, not because he foresaw it, that he could not do, but because he opened the door to it. He was the first to cast off

authority to experiment for himself and he had the vision to see, the brain to understand what he saw, and the courage to stand by his beliefs."

Let me now draw your attention to a charming piece of partisan reporting. In 1934 Edwin Bramwell discussed " Sir Charles Bell. His Life and Work." True to form as a founder member of the mutual admiration club, otherwise known as the Association of British Neurologists, started in the previous year, he reasoned, argued and finally claimed for Bell as high a pedestal in neurology as Harvey holds in cardiology. The precedent for this kind of approach came from no less an authority than our founder, Andrew Duncan, who gave several orations in the commencing years, all of which, except the first, were devoted to biographical sketches of eminent men. There seems little doubt that Bell, two centuries later, did for the nervous system what Harvey had done for the circulation—he opened up a new vista for his successors. (For the unenlightened it should be said that Bell gave his name to the palsy, the long nerve and many other things besides). Furthermore, as a claimant to immortality he had the supreme advantage of being an Edinburgh graduate.

Before me stands out a truly authentic document by a master of the History of Medicine packed with facts obtained not by reading or hearsay alone, but first-hand on-the-spot information fully corroborated and annotated by one skilled in the art. During his year in this office, Dr. Douglas Guthrie spent a great deal of time in fruitful travel : to Folkestone, to Canterbury, to Cambridge, to Padua, to Barts' and the London College of Physicians as well as to many other places at home and abroad, linked to the life and career of William Harvey, culminating in a unique oration which was a joy to listen to and much appreciated by a large gathering. No wonder, with a year so packed with interest and travel and activity, that he warned me some time ago that June always came round much too quickly ! This oration, conveniently available in the B.M.J. (March, 1957), should be made compulsory reading for all neophytes, and thus kindle an understanding spirit in our members at the outset, incidentally avoiding such a gaff as one horror made to me some time ago when he remarked *sotto voce*, " Who was this *John Harvey* anyway ? " An outcome of Guthrie's approach was his bringing to light of new facts and putting them into line with the rest. He tells us that Harvey's masterpiece, " The Anatomical Disquisition of the Motion of the Heart and Blood in Animals ", often called for short, " De Motu Cordis " was published at Frankfurt in 1628, and " was printed on poor paper and was full of printer's errors. As an example of book production it ranks very low, but as a clear, brief and logical account of the author's researches it is beyond praise." Why was it not immediately accepted? Guthrie discussed this perplexing problem, that Harvey did not rush into print. In his, Harvey's, own words : " I teach anatomy not from books but from dissection ". In truth the real significance was probably not apparent for nearly two centuries. There is much to learn and appreciate from this reticence of many great men to publish; for example, Darwin waited 20 years, Jenner 18, and Lister 8, and even then their work was not appreciated for a considerable time. As Guthrie reminds us ; " the discovery of a principle is always more important that the discovery of a fact, as it leads to further advances." What better example of this type of evolution than Erhlich's chemotherapy and Lister's antiseptic method.

In his conclusion Guthrie expresses himself thus : " The experimental method of investigation, a **novel** to Harvey's critics is now familiar to the most junior medical student. It has long since ceased to be a matter of argument. Moreover, increased facilities of transport and communication have made it possible for a new discovery to be known throughout the world in a matter of hours ; within a few weeks, or months at most, each addition to the

existing knowledge is examined and assessed at its true value. Indeed, the speed of integration of new discoveries and new ideas has become almost terrifying."

Last year Ian Hill deplored the tendency for the phrase " doing research " to carry overtones of implied superiority to those who simply treat the sick— as though the very word " Research " carried a talisman of virtue. Truly original minds with an aptitude for research and with ideas are rare indeed and these should seldom require Hill's new unit of currency—the mega-buck. He likened Harvey to a part-time consultant—a postulation that obviously pleased and flattered many of his audience, but would probably have deeply wounded the great man himself. Returning to experimentation he debated very skilfully and with learned opinions the reaction if it were thought that experiments on man were planned or carried out. So much happens even in a brief twelve months that we now know the answer at least in part. In theory man can refuse, and perhaps it matters less if that man is a Russian or even an American ! Hill left us pondering deeply, with the well known couplet of an Edinburgh Academical—" To travel hopefully is a better thing than to arrive, and the true success is to labour ".

<center>*   *   *   *</center>

SOME COMMENTS ON MEDICAL EDUCATION TO-DAY

As a clinical teacher of some little experience I have long felt that the training offered to the medical student was too haphazard and ill-balanced, frequently resulting, after six years, in jaded young men and women not knowing where to turn. In Edinburgh we have always despised cramming and drawn a sharp distinction between its objects and that of genuine teaching. Yet now the Universities thrust back at the schools the onus of creating a youth with a one track mind instead of the broad English culture obtained by our fathers. Too often these young people carry into their University the distorted idea that they have no time for anything but techniques and technology. They have a vast vista of instruments and electricity interspersed with more than a little biochemistry. Furthermore, they may well lack the shrewd and balanced mentality to sort it out. Solutions, of course, are easy to suggest, but difficult to provide, and always controversial in a generation when planning itself has become a career. Big planners succeed where little planners fail. It is much easier to plan a University or a Cathedral or even a hospital than say, an egg-cup or a wine glass. Few are prepared to dispute with the genius, whereas every housewife knows a better egg-cup. Probably it is something of this that has allowed the medical course to become top-heavy with science in the early formative years. In my view the first four years training should be basic in the proper sense of the word, that is to say pruned of anything that in the slightest degree could be called specialist—great care being taken to see that everything has a practical application and a ' patient ' flavour as distinct from that of the laboratory. At the end of this period the future doctor would be assessed and asked to declare his preference for a career. He might be granted a preliminary qualification—an M.B. or call it what you will, he would then proceed in his chosen branch, rather in the manner of apprenticeship at present adopted by the B.Sc. candidate in physiology or pathology. Residencies would be available in all specialities for varying duration according to the subject and the need of the individual. This ' second period ' would preferably have an indeterminate length, but at the end a stiff assessment called for with the object of granting a doctorate in medicine.

That, broadly speaking, would be my plan, unembellished and without

detail, reviving as is seen, the senior qualification of the university in medicine which has been so widely neglected in recent years, at least in this school ; a development which must be contrary to the prestige and best interest of the University. Some may suspect that all this would interfere with the present status of the diplomas granted by our Royal College. I do not think so. On the contrary, provided the selection of intakes is in experienced and competent hands, those with special aptitude and skill would soon be recognised. For these, in their particular grooves, a Fellowship would be, as now, a *sine qua non* ; and the College of General Practitioners, always gaining in prestige and power, may be depended upon to protect and enhance the interest of those who have decided upon the most exacting of all branches—that of family practice:— " To cure sometimes, to relieve often and to comfort always." It will come to be recognised that talent is just as essential for the practicing physician as for the research fellow ; the question resolves, as in the nursery and at school, of spotting and providing scope for the advancement of the individual gift. The reputation of the Edinburgh School was built up to a large extent on the quality of its teaching and the type of doctor that was exported throughout the Kingdom and the erstwhile Empire. With modification to suit the changing needs this must continue. The flourishing post-graduate school will inevitably grow and perhaps the undergraduate one will diminish. Time alone can show, but clearly, since the war the clinical staff have carried a much too heavy burden which can be relieved only by a proper infusion of fresh teachers and to gear this to future requirement will necessitate most careful thought by those responsible. My plea is to emphasise that a really good teacher is always interested in advancing knowledge, but too often the dedicated research worker regards his teaching commitment as irksome—an attitude that is quickly detected by his discerning students—with unfortunate reactions.

In his Harveian oration to his London College in 1956, entitled " Practice, Teaching and Research ", Crighton Bramwell reviews very ably the inter-relationship between these as he has witnessed it and indeed played a part in its development since the end of the first world war. " The hospital ward is the laboratory of clinical medicine," and he goes on to observe " that deductions drawn from careful and accurate observation at the bedside are no less scientific than those based on work with a microscope or a test tube in the laboratory." Then this contrast—" The pure clinical scientist is interested chiefly in the disease—the clinician in the patient. In two patients suffering from the same disease the clinical scientist studies the features they have in common, but the clinician is no less concerned with the way they differ in their reaction to the disease. For him the soil is as important as the seed." What exactly was achieved, when, after the last war throughout the country all the part-time Professors in Medicine, Surgery and other clinical subjects ceased to be and were replaced by full-time Chairs? There can be no doubt that it did help to integrate the clinical and pre-clinical sciences and provide a career for people with certain types of ability who hitherto would have been called physiologists. Thus it is a matter of opinion whether the east or west side of Middle Meadow Walk is to play the predominant part and enjoy the favours. What of course, leaves no room for doubt at all is the vast amount of time devoted to administration by highly trained and well paid people with little aptitude in this direction, but who too often grow quickly to enjoy it for what can only be its power and escape qualities. Who should be our administrators? If there are an insufficient number of our experienced senior colleagues in retirement then we must cultivate an increased bond of understanding with the bureaucrats who are now fully trained and much more

co-operative than in our first tentative contacts over twelve years ago. Certainly the present system is intolerable and must cease. It is too wasteful of a limited number of people whose whole interest should be focussed on a quite different ambition.

My time has almost evaporated but I should like briefly to reconcile what may seem to have been a biased exposition of one aspect in the present scene in our profession. Recently, Francis Fraser pled for a much greater degree of co-operation among the different branches within the profession—by which he means hospital, general practice, and public health—and suggests a greater collaboration with the clergy. He stresses the problem of discovering and training future research workers, apparently scarcer than one might suppose, cutting our coat according to the cloth. William Harvey's great achievement has been a challenge that has too often been made an excuse for a one-sided approach according to the current fashion, whereas a reorientation of our problems is required at frequent intervals ; lest, as at present, there is a tendency to self-deception and complacency—resulting in a misuse of our man power. There is abundant opportunity within our profession for every type of mind, but the legislators in their preoccupation with one aspect are too apt in their ignorance of others to adopt an attitude of denigration. And—old hat, but true—" the onlooker sees most of the game." It is a research world in medicine, and it always has been, especially since Harvey's stimulating impetus. But now, in medicine, we tend to make a fetish of research as though it were something quite novel—not very flattering to the ghosts of Harvey and other illustrious scientists of the past. Furthermore, it has often been shown that the over-organised people can be outstripped by the amateur who has the native wit and training to understand the meaning of his observation. In a talk of this length it is only possible to scratch the surface of a deep and fascinating subject, but my contention is that if we in Edinburgh can remain true to our inheritance and great tradition we will continue to discover and develop the many and diverse flares lying latent in our pupils, thus allowing our contribution to advance on a broad front. The alternative is the danger that scientists will cease to be human. With the widespread modern tendency to worship them as demi-gods, some at least are bound to succumb to the temptation to accept this blind worship, and to think of themselves as being on a moral and intellectual plane perceptibly higher than that occupied by those who are not initiated in their mysteries. As medical science progresses, so inevitably the specialist finds his field becoming narrower. He is no longer a Harvey with all the circulation lying open before him ; he is concerned perhaps with one single detail of one single auricle. This kind of thing is bound to narrow the mind ; therefore if the future management of our affairs is not to be entirely unbalanced, we must ensure that from the earliest years and throughout the scientific discipline is properly garnished with education in others of culture and the arts.

Last year Ian Hill left us with Stevenson's famous dictum. Tonight I am going to fall back on the advice of a much older thinker, confident, at least, that no-one can disagree with St. Paul.

Whatsoever things are true,
Whatsoever things are honest,
Whatsoever things are of good report.

If there be any virtue, and if there be any praise, think on these things.

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MELANCHOLIA

By E. B. RITSON, M.B. Ch.B.

"Melancholy," meaning "black bile" or "black despair," designates aptly
that spiritual blight which has vexed mankind from the earliest time. Play-
wrights and philosophers have long been intrigued by the spectacle of cause-
less melancholy, and, more recently, pathological melancholy, rechristened
"psychotic depression" has been the subject of clinical definition.

The indaquacy of our language is recognised as a major stumbling-block
in many spheres to-day where rapid progress is being made and this is parti-
cularly the case in psychiatry. While awaiting improvements, one must try to
name conditions as accurately as possible with existing terms. In describing
the condition in question, "melancholia" seems a preferable word to
"depression." "Depression" is part of the common coinage of everyday
speech and, as such, has an individual meaning for every member of the public.
In their experience, it constitutes a normal, if undesirable state of mind, and
to give the same name to a recognised pathological condition is as confusing
as calling angina pectoris, heartache. Furthermore, not all patients who may
be diagnosed as suffering from depression will admit to feeling depressed. To
call a disease after one of its symptoms and not an invariable one at that, seems
irrational and very liable to mislead.

Burton in "The Anatomy of Melancholy" defines melancholy as "a kind
of dotage without a fever having for his ordinary companions fear and sadness
without any apparent occasion." This, written at the time when the humoral
concept of physiology was unchallenged, served admirably as a nidus on which
later definitions might grow.

Kraeplin, in his classification of the psychoses, regarded melancholia as a
disorder of mood and a form of manic-depressive insanity. He stressed the
periodic nature of attacks and their propensity for spontaneous cure.

In summary melancholia may be described as a disorder of emotion inexplic-
able in terms of external events and without apparent organic cause, which is
characterised by a sad anxious mood and psychomotor retardation. The con-
dition usually remits spontaneously and completely but there is a tendency to
recur.

As so often happens, what begins as a definition ends as a description. This
emphasises the truth that until we know the cause, we cannot accurately define
the disease. What then is the cause? Essentially it is unknown. However,
from a devious and intensive study of its aetiology has emerged what Einstein
called "the feeling for order behind appearance." It is this feeling which

suggests that soon the disease will yield its secrets and its exact nature be known.

It has long been felt that the tendency to affective instability is inherited. Kallmann collected statistics of morbidity from manic-depressive psychoses in Europe and America. His conclusions were that in no case did the incidence in the general population exceed one per cent. Yet it had been shown that morbidity rates for parents, siblings or children of manic-depressive index cases were of the order of twelve per cent or more. In a series of 27 monozygotic twin pairs. Kallmann reported a hundred per cent incidence of affective psychosis. Among these twins it is interesting that there was no concordance of form or timing in the mood swings. It seems from this that the genotype sets the balance but some other as yet undetermined factors determine which way and when it will swing.

The form of this genetic transmission remains undecided. Slater and Kallmann contend that it is inherited as a single autosomal dominant while others postulate a multifactorial genetic determination. Much remains to be clarified, perhaps the outcome of investigations into the molecular structure of genes will be a more exact understanding of the disease and even a hint as to its cure. Even the facts which are established indicate that it is essential to take a full family history in all cases of this kind.

Kretschmer's types have become part of our psychological tradition and from his studies he has shown that the pyknic habitus is more frequent in patients suffering from affective disorders than could be expected by chance. Such typing although an absorbing exercise has proved of little practical value. When chromossome maps have been plotted it may be found that the predispositions to pyknic appearance and affective disorders are genetically linked.

A passing acquaintance with European history makes it clear that it is impossible to speak of racial characteristics in any meaningful way. However, it is reported that the Jews show a higher incidence of affective psychosis than average. The disease is commoner in Britain and Bavaria than in Norway and Prussia. An incidence of 0.3/1000 was reported in a Finish population of 400,000 and one of 3.5/1000 in a Scottish rural population of 56,000.

These figures have not been explained. It must always be borne in mind that each community has its own criteria for normal and abnormal behaviour and the pressure exerted from without to encourage a sick man to seek treatment will vary accordingly. Moreover, the difficulty in finding any uniformity of diagnosis must affect the interpretation of results.

Manic-depressive insanity is commoner in the female, the ratio being 3 : 2. Any conclusions drawn from these figures have met with a certain scepticism because the male is notoriously liable to show atypical features, particularly alcoholism which mask diagnosis.

Periodicity is a feature of the female metabolism and this cycle of hormonal activity produces changes of temperament in even the normal woman. The occurrence of menstrual and premenstrual depression is well established, as are the affective aberrations of the puerperium and menopause. It is also worth noting that amenorrhea is a frequent feature of depression. All this naturally prompted a search for some hormonal key to the aetiology of affective disorder. To counteract this enthusiasm, it has been pointed out that puberty and adolescence, times when the hormones are at their liveliest, rarely show an affective psychosis.

Many of the cyclic variations in human behaviour are initiated by the influence of the hypothalamus on the prefrontal cortex. Furthermore, it has been shown that in animals with both cerebral hemispheres removed, the periodic discharges affecting all divisions of the vegetative system persist.

Foerster produced elation by stimulating the hypothalamus in a patient under local anaesthetic. This and the effect of leucotomy which severs connections between the primitive brain and the cortex both augment the view that the diencephalon has some role in determining the affective disorders.

It is perhaps in the light of damage to the primitive brain that we should regard the various neurological diseases commonly associated with affective upset. Among such are general paralysis of the insane, arteriosclerosis, disseminated sclerosis and Parkinson's disease. In persons predisposed, affective illness is not an uncommon sequel of infections such as pneumonia and particularly, influenza.

To support the view that melancholia represents a regional disorder of brain function we may quote Hughlings Jackson in his essay on "The Factors of Insanities":—

"In every insanity, more or less of the highest cerebral centre is out of action temporarily or permanently from some pathological process; for my present purpose it matters little what that process be. It only matters as the pathological process produces loss of function, that is, dissolution of more or less of the highest centres. I do not use the term 'function' in the sense often given to it in clinical accounts of nervous maladies as for example, when it is said of a patient that his case is entirely functional. I do not believe that there is such a thing as loss or defect of function of any nervous elements without a proportionate material alteration of their structure and nutrition."

This essay written in 1894 which was referred to at the 1960 Gowers Memorial Lecture retains its relevance to the present day.

To attempt the elucidation of this disorder of function whose presence we feel but cannot see, we must journey to the world of the biochemist. Here we may cull from their intricate geometries a pattern which seems both comprehensible and hopeful.

It is well known that many drugs such as alcohol, opium or mescalin can alter our mental state. More particularly, certain drugs, notably reserpine, can produce a condition clinically similar to melancholia. Brodie (1957) showed that reserpine caused the depletion of brain serotonin—this is thought to be due to the release of bound serotonin. Vogt has shown that the concentrations of nor-adrenalin and serotonin in the hypothalamus, midbrain and floor of the fourth ventricle were higher than elsewhere in the C.N.S. Both these substances are concerned in the transmission of nerve impulses. Furthermore, reserpine has also been shown to liberate adrenalin and related amines from these areas of high concentration.

Such revelations naturally led workers to speculate that depletion of brain serotonin and catechol amines was in some way associated with depression. Apparent confirmation of this view arose when it was shown that the mono-amine oxidase inhibitors were clinically effective in depression. These drugs inhibit the enzymes which are at least in part responsible for the breakdown of serotonin and adrenalin.

In recent years it has become increasingly well recognised that it is the subcortical brain which is concerned with our awareness and response to surroundings. This activating system co-ordinates autonomic, somatic and psychological activity. It has been suggested that this system has two components, one sympathetic and promoting active go-getting behaviour, the other akin to the parasympathetic and largely responsible for recuperation causing drowsiness and loss of interest (a state likened by some to hibernation). It is hinted that some of the afore-mentioned amines play a part in arousing these systems.

From all this confusion emerge certain trends, none of them universally

accepted, which hint at the possible nature of melancholia. We have a disorder which appears to be genetically determined. It appears predisposed by a biochemical lesion centred in the activating system of the primitive brain. As in so many physiological systems normality is a precariously held equilibrium and release of inhibiting forces or overstimulation of the opposing system results in the appearance of a pathological state. What seems so difficult to explain is the periodicity of the disease—why does the balance tilt when it does, without apparent occasion ?

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SYLLABUS 1961-1962

OCTOBER 1961

13. INAUGURAL ADDRESS
8 p.m. Sir Walter Mercer, F.R.C.S.E. " The Edinburgh Influence on Early American Medicine."

20. Dissertation: J. A. R. Friend, Esq., B.A.(Cantab.) : " The Failing Heart."

27. Dissertation: J. S. Kelly, Esq., B.Sc. " Chemical Transmission."

NOVEMBER

3. Dissertation: R. Butler, Esq. " Sir Charles Bell."

10. Dissertation: J. F. Peutherer, Esq. " Malabsorption."

17. ADDRESS: Professor A. G. R. Lowdon, O.B.E.. M.A., F.R.C.S.E. " Acute Ischaemia of the Limbs."

23. PRESIDENTS' ANNUAL DINNER
Royal College of Surgeons, 7.15 for 7.30 p.m. Guest of Honour: Professor Sir Derrick Dunlop, B.A., M.D., F.R.C.P.E., F.R.C.P.

24. Dissertation: C. E. Hope, Esq. " Respiratory Inadequacy."

DECEMBER

1. TALK: Dr. W. I. Card, M.D.. F.R.C.P.E., F.R.C.P. " Gastro-intestinal Hormones."

8. Dissertation: J. A. Calvert, Esq., B.Sc. " The Treatment of Renal Diseases."

JANUARY 1962

12. ADDRESS: Professor W. L. M. Perry, O.B.E.. M.D.. D.Sc. " Laboratory Investigation of Hypersensitivity."

19. Dissertation: P. J. Swarbrick, Esq. " Congenital Dislocation of the Hip."

26. Dissertation: M. C. Grayson, Esq. " Why Medicine ? "

31. Film Show.

FEBRUARY

2. Dissertation: W. H. Leach, Esq. " Atherosclerosis."

7. ANNUAL BALL, in Carlton Hotel.

9. TALK: Mr J. H. S. Scott, F.R.C.S.E. " Evolution—the Orthopaedic Excuse."

16. Dissertation: N. A. Boyle, Esq. " Physiology, Neuropharmacology, and Therapeutic Use of the Monoamine Oxidase Inhibitors."

22. Debate with the Glasgow Medico-Chirurgical Society, in Edinburgh. Motion to be arranged.

23. ADDRESS: Professor Ian Donald. " The Development of a New Diagnostic Technique by Ultrasonic Echo Sounding."

MARCH

2. Dissertation : R. A. Bailey, Esq. " Mongolism."

9. PRESIDENT'S VALEDICTORY ADDRESS.

14. Annual Extraordinary General Meeting.

PRIVATE BUSINESS at 7 p.m.   PUBLIC BUSINESS at 8 p.m.

Clinical Meetings. Film Meetings, and Industrial Visits will be arranged during the Session.

RETROSPECT

224th SESSION

Our Society had no premises of its own until 1775, when the First Hall was built in Surgeons' Square; the Society was fortunate then in having such men as Cullen and Andrew Duncan to plan such a historic step and to raise money for its completion. Again in 1852, when extensions to the old Royal Infirmary made it necessary to vacate the First Hall, a distinguished committee including Syme, Christison, and Simpson negotiated the purchase and adaptation of our present premises.

THE HALL

The Society has now decided that another move is necessary; for the Midlothian County Council wish to buy our premises within the next ten or twenty years and have already bought property around us with a view to expanding their office accommodation. The County Council have power to effect the purchase compulsorily if they so desire. It would therefore be unwise to spend much money on our premises, for although the decaying splendour of the Hall is very dear to us, the rooms have become grossly inadequate as regards the housing of the Library, the furnishings, and heating.

As in the past, we could hardly be more fortunate in the Committee elected to deal with the question of a New Hall. Under the wise leadership of Sir Derrick Dunlop, the Committee has already investigated the possibilities, and as a result space has been reserved for us on the so-called ' Island Site '—the block which includes the Pollock Hall and the shops facing the McEwan Hall. The University plans to demolish buildings on this site, and to use it for new buildings such as a new Students' Union. On this site we should be able to maintain our independence and yet be even nearer to the centre of the Medical School than we are at present. Sir Derrick's Committee deserve our congratulations and thanks for having made such a successful start in the negotiations.

The Society is indeed fortunate in its senior members and friends—not least in Dr. W. A. Alexander, who continues to look after our precarious finances and, by his kindly advice and presence at Council Meetings, does so much to maintain the best traditions of the Society.

THE APPEAL

To build a New Hall comparable with our present premises we shall have to find not less than £75,000. This is a very large sum, but we are optimistic that senior members and friends will consider the Society an institution worth perpetuating and supporting in this new venture. There is no doubt that new premises are essential for the survival and expansion of the Society, and just as our predecessors have laboured to keep the Society well housed for our benefit, we feel it our duty to maintain the Society and its traditions for those who will follow us.

Sir Derrick Dunlop, as Convener of the Appeal Committee, will launch the Appeal at the Annual Dinner of the Society in the Royal College of Surgeons, on 23rd November; appeals for one cause or another are common enough nowadays but we hope that the cause of a historic and virile body such as the Royal Medical Society will commend itself and be successful.

Since we would like to raise as much of the money as possible from

individuals, copies of the Appeal will be sent to our Fellows and Life Members; we hope that others who would like details will write to the Secretaries of the Society.

NEW LAWS

At the Triennial Extraordinary Meeting held in April to consider the Laws of the Society, a number of minor changes in the Laws were made. To the relief of many, and the disappointment of a few, a proposal to admit women to the Society was firmly rejected. The franchise for the election of Presidents was enlarged to include members who have at least ten attendances, although those eligible for the Presidency must still have twenty. It was also decided that those eligible for other offices should require ten attendances. It has been made simpler for a prospective member to petition for a seat in the Society, in that now only two proposers are required instead of six. These petitions are, of course, still ballotted on by the Society.

These are the only changes which have emerged from the Questionnaire and the protracted discussions of last year. The fact that there are so few changes probably indicates that the active members are well satisfied with most of the Laws, and that the liveliness of the Society depends not so much on the Laws themselves as in the way in which they are applied, and in the enthusiasm of individual members.

JAMES A. R. FRIEND,
Senior President, 1961 - 62

BOOK REVIEWS

TEXTBOOK OF MEDICAL TREATMENT. Edited by Sir Derrick Dunlop, Sir Stanley Davidson, S. Alstead. Eighth edition. Edinburgh: E. & S. Livingstone. 1961. Pp. 983 and XIX. Price 60s.

New editions of this textbook have been appearing regularly and frequently since its first publication just twenty-two years ago. This is undoubted proof of its popularity and a reflection of the steady advances Medical Treatment has made over the years.

It has been written for students and practitioners by an eminent group of clinicians but yet maintains a very high standard of uniformity and clarity. Careful and skilled editing has played no small part in achieving this.

The systematic arrangement makes consultation very easy and the style allows for pleasant reading. Reliable and current methods of treatment are presented without the nuisance of discussing the latest fads in therapeutics. The clinician can feel sure that the information he obtains is sound and worthwhile.

With the prominence of the geriatric problem today it was decided to enlarge the section devoted to the Care of the Aged. Much of it includes simple daily habits and everyday routine. One might even dare to say—commonsense. But it is these small points which make all the difference to a successful end and which are so easily overlooked. It is as well that they should be so thoroughly explained.

There is also a new chapter on Analgesics and the relief of pain. Seeing that it is pain which frequently brings a patient to his doctor and which causes him the greatest concern, it is surprising how seldom its relief is ever dealt with in adequate detail. This addition sums up all the applications of the reliable analgesics, and puts the patient's problems in a better perspective.

For the anxious student hoping to pass his finals and the worried practitioner wondering what next to do, this book is a necessity. The editors must be congratulated on a publication of tremendous value.

E.S.Q.

THE MEDICAL MANAGEMENT OF ACUTE POISONING. by Gordon Cumming. B.Sc., Ph.D., M.B., Ch.B., A.R.I.C. Cassell. 10s. 6d. net. Pp. 120.

This little book is intended for the casualty officer or G.P. and the final year student. It outlines the main physiological principles and then spends a chapter each on Carbon Monoxide, Barbiturates, Salicylates and Alcohol, that is the poisons most commonly met. Public Health and Paediatric aspects are also dealt with. Although such an immense amount of ground is covered in a very short space clarity is never lost and the book is most readable.

Dr. Myre Sim's chapter on the psychiatric aspects of poisoning is as concise and clear as the rest of the book and can be read with benefit by all psychiatry students.

This is just the book to have beside you when you are informed that a new admission, suffering from poisoning is on his way.

R.A.B.

THE PATHOGENESIS OF ESSENTIAL HYPERTENSION. Proceedings of the Prague Symposium 1960. State Medical Publishing House, Prague, 1961. Price 50s.

This volume contains the proceedings of a symposium arranged by the Czechoslavak Cardiological Society and the World Health Organisation, under the chairmanship of Professor C. Heymons.

The lectures tackled the problem over a broad front, embracing the epidemiology of the disease and the influence of nervous vascular control and higher nervous centres, as well as alterations in haemodynamics and vessel wall and general metabolic factors underlying its causation. The diversity of these topics emphasises the widespread dislocation which accompanies a disease too frequently considered simply in terms of raised blood pressure.

However, although the Symposium discussed many questions it provided few of the answers. The first session, devoted to considering whether essential hypertension was a disease entity or

merely embraced levels at the high end of a normal distribution curve of blood pressures, led to no agreement on this basic point. A most valuable point brought out again and again during the conference was the inadequacy of present data and the need for more research. The Symposium, however, was more notable for the discussion of old problems than the presentation of new work.

This volume is essentially a reference book and of little general appeal to medical students or practitioners. Nevertheless it could provide anyone approaching the subject of essential hypertension with an insight into present views on its pathagenesis.

The book is poorly produced by current British or American standards.

J.A.C.

THE RED CELL, by T. A. J. Prankerd, M.D.   Published   by   Blackwell Scientific Publications Ltd. Price 32s. 6d. net.

This compact little text book is intended for those interested in the academic study and research into problems of the red cell. In his preface, the author points out the great division that has grown up in work on this subject, namely, that between the experience of the physiologist and the interpretation of the pathologist.

An attempt is made to combine the two in a single volume, but the related sciences still stand very far apart, and the bridges thrown over the gap are few in number.

In dealing with this difficult subject, the author has been faced with the problem of extracting information from the large number of references, and has chosen those which reflect his own view. This is however made plain. It represents a clear and concise picture, not over-complicated by the mass of conflicting evidence usually found in such publications.

Throughout, the separate chapters are well set out, and follow logically one to the next. This enables the reader to follow the information, which in places is highly technical, a vital test in a book dealing with such a complex subject.

On the whole, the book is not suited for ordinary undergraduate study, being more for those interested in the special study of physiology or pathology of the blood, and in this respect is made more valuable by the long list of references.

In conclusion, the book definitely deserves a place in any medical library, not for an initial understanding of the subject, but for reference and verification purposes.

D.H.K.S.

THE USE OF DRAWING IN THE STUDY OF ANATOMY AND PHYSIOLOGY, by Charles R. Bannister, M.C.S.P.   Pp. 39, numerous illustrations.   Published by E. & S. Livingstone Ltd., Edinburgh and London, 1961.   Price 17s. 6d.

One of the most formidable difficulties facing the pre-clinical student is the amount of hard memory-work involved in learning anatomy, and there is no doubt that drawing is a most effective, economical method of study. Moreover, the ability to produce a good drawing on an examination paper is especially valuable.

In this little book, Mr Bannister suggests methods of study involving drawing, advising different techniques for different purposes — initial study, revision, and for presentation in examinations. He thus attempts to provide a rational scheme of work for learning by drawing. The artistically untalented will be particularly interested in the section dealing with the technique of actually making a picture—it is emphasised that anyone can draw well enough for these requirements.

Since this is in no sense a text-book, is seems questionable whether many people will want to pay so much as 17/6 for it. However, the quality of printing and of the almost too profuse illustrations is excellent, although the wire binding leaves something to be desired. Certainly, students beginning the study of anatomy and perhaps feeling a little overwhelmed may well find the methods advocated very effective.

R.L.M.

SYMPTOMS AND SIGNS IN CLINICAL MEDICINE, by E. Noble Chamberlain, M.D., M.Sc., F.R.C.P.   Seventh Edition, published by John Wright and Sons, Ltd., Bristol.   Pp. 569, many illustrations.   45s.

This book comes from the same publishers as Hamilton Bailey's 'Physical Signs in Clinical Surgery', but it is not such a useful or interesting book. It is probably easier to illustrate surgical lesions than to explain breath sounds or heart murmurs—but even allowing for this difference, Hamilton Bailey succeeded in giving his book a very personal sort of distinction which Chamberlain's book lacks. Perhaps it is unfair to compare this book with one so exceptional as Hamilton Bailey's; after all, Chamberlain's book is now in its seventh edition since 1936, and is well known, especially in the south. In general, the physical signs as well explained and many of the photographs and diagrams are excellent. A few are in great need of replacement, such as an appallingly unrealistic drawing of the different

Collectively Speaking

Do you talk of a *dosage*
Of Doctors, or *cure*?
Or is it a *consult*,
Or *temperature* . . . . ?
Whatever they're called
In the mass, they're agreed
That, after work, Guinness
Is just what they need.

after work you need a
GUINNESS

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varieties of sputum. One would have thought that the illustrations of the optic fundus in optic neuritis and optic atrophy could have been replaced more usefully by diagrams of hypertensive and diabetic retinopathy—the latter is not even mentioned in the text. Percussion of the heart is advocated although many physicians now feel this is worthless as a routine procedure. There is a section on clinical chemistry which gives useful details of side-room tests and an inadequate selection of the routine laboratory tests.

In this latest edition a short chapter on medical history has been included, together with a number of drawings of famous men of medicine in the text; but somehow the author has not written such a fascinating account as Hamilton Bailey. who enlivened his text with biographical footnotes, anecdotes and case histories.

One cannot help feeling that a book of medicine in which the theoretical background must be omitted or minimised is in some way unsatisfactory. Whether a book of this sort is a substitute for good bedside teaching and clinical experience is doubtful; but for all of these criticisms and reservations, this is a good book filled with practical and accurate information. For those who feel the need of a book on clinical methods this can be recommended as the best available.

J.A.R.F.

ANATOMY OF THE EYE AND THE ORBIT, by Eugene Wolff. 5th edition. revised by R. J. Last. H. K. Lewis & Co. Ltd., London, 1961. £4 4s—pp. 489.

This new edition of the late Eugene Wolff's well known book has been efficiently revised by Last without impairing its essential qualities. It is a type of monograph which may well come into more general use to save students and clinicians from the difficulty of coping with the many separate and often compressed sections found in comprehensive text-books.

An acquaintance with the basic medical sciences is naturally assumed but the descriptions in this book are clear, concise and and adequate. A few items which at first sight seem redundant, such as the description of the paranasal sinuses, are soon shown to have clinical applications. The terminology has been brought up to date without being too rigid and eponyms are used where they are necessary or informative. Only a few additions have had to be made so as to include such things as electron microscopic and bio-microscopic work.

The scope of the work goes beyond the orbit to anything which may be of importance to those working on it. The illustrations are excellent and the work can safely be recommended to undergraduates or to graduates taking up the speciality.

R.G.I.

ASSESSMENT OF THE ACTIVITY OF DISEASE. J. S. Lawrence. M.D., M.R.C.P. 252 pp.; 34 tables, 37 illus. H. K. Lewis & Co. Ltd., 1961. £2 2s.

This volume can claim to be the first really comprehensive work dealing with the Erythrocyte Sedimentation Rate to appear in the English language.

The first half of the text considers the theoretical aspects of changes in E.S.R. in relation to overall changes in the plasma constituents. occurring in disease situations. A chapter summarising laboratory methods of determining these changes follows.

The remainder of the book consists of a systematic discussion of the changes occurring in individual diseases, and it is this part that will probably be of the most interest to the average student.

Throughout, the author maintains a very lucid style of writing, in spite of the large numbers of figures he has to convey at times.

As will be gathered from the above. this is a work of prime interest to the clinical pathologist. although a perusal of it will help to clarify not a few problems in relation to general medicine.

The diagrams all make their point clearly, while the printing and binding are of a high standard.

P.J.S.

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