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RES MEDICA

THE JOURNAL OF THE ROYAL MEDICAL SOCIETY

Contents

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RES MEDICA

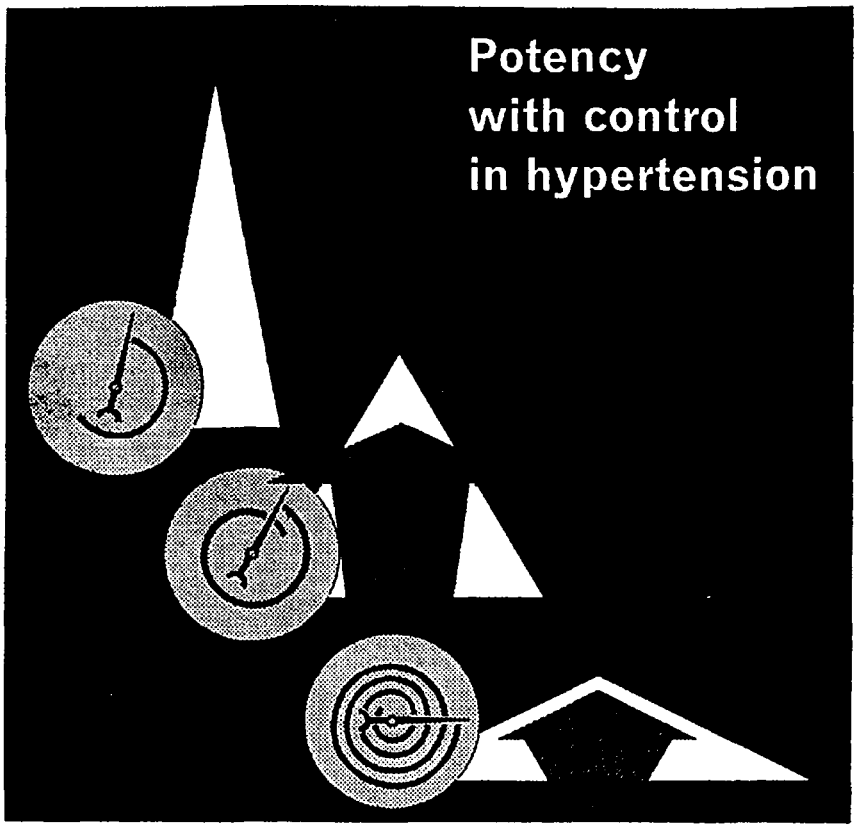
THE JOURNAL OF THE ROYAL MEDICAL SOCIETY

Syllabus 224th Session

(Liable to alteration)

1960			
Thurs.	Oct.	24	PRESIDENTS' ANNUAL DINNER Royal College of Physicians of Edinburgh. 7.15 for 7.30 p.m. Guest of Honour: Dr J. H. GADDUM, F.R.S., D.Sc.
Fri.	,,	25	Dissertation: R. I. LEGGE, Esq. "Parry and Parry's Disease"
Thurs.	Dec.	1	Debate with the Glasgow University Medico-Chirurgical Society, in Glasgow. Motion to be arranged.
Fri.	,,	2	TALK: Dr D. S. MCLAREN, M.D., Ph.D., D.T.M. and H. "Nutritional Blindness"
Fri.	,,	9	Dissertation: A. D. CHALMERS, Esq. "Disseminated Sclerosis"
1961			
Fri.	Jan.	13	ADDRESS: Professor C. S. RUSSELL, M.D., F.R.C.S.E., F.R.C.O.G. "The Unborn Child"
Fri.	,,	20	Dissertaton: J. D. CASH, Esq., B.Sc. "Fibrinolysis and Occlusive Vascular Disease"
Fri.	,,	27	Dissertation: E. B. RITSON, Esq. "Melancholia"
Fri.	Feb.	3	Dissertation: H. M. J. KINDNESS, Esq. "Some Aetiological Factors of Foetal Abnormality"
Tues.	,,	7	SOCIETY'S ANNUAL BALL
Fri.	,,	10	TALK: JOHN HOLT, Esq., A.R.I.B.A. "American Hospitals"
Fri.	,,	17	Dissertation: ROBERT WILSON, Esq. "Auto-Immunisation"
Fri.	,,	24	ADDRESS: Professor W. A. MACKEY, F.R.F.P.S., F.R.C.S.E. "Some Aspects of Cardiovascular Surgery"
Fri.	Mar.	3	Dissertation: H. C. DRYSDALE, Esq. "Epilepsy"
Fri.	,,	10	President's Valedictory Address
Wed.	,,	15	Annual Extraordinary General Meeting

Private Business at 7 p.m. Public Business at 8 p.m. unless otherwise stated. Clinical Meetings, Film Meetings, and Industrial Visits will be arranged during the Session. Due notice of these will be given.



Comment from three important papers in the Lancet, 20th August.

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THE DIAGNOSTIC VALUE OF PAIN

By E. B. FRENCH
B.A., M.B., Ch.B., M.R.C.P.Lond., F.R.C.P.E.

Based on an Address delivered to the Royal Medical Society on Friday, 12th January 1960

Pain is usually the main lead, and often the only clue to diagnosis. For example angina of effort may be associated with a normal ECG at rest, while an ECG may frequently show evidence of myocardial ischaemia in patients who do not suffer from angina pectoris. The clinical history and the response to a controlled clinical trial may make the diagnosis certain, yet mistakes will be made, patients lives altered and their outlook upon the future warped, unless a careful analysis of the various aspects of pain is the rule. This analysis must be made exactly and without the bias of preconceived ideas.

On a ward round conducted conjointly by Sir Arthur Hurst and Professor John Ryle a history of a patient with biliary colic was read out. Dr Ryle remarked to the students that this was the typical *continuous* pain of biliary colic. He went on to say what a pity it was that it could not be called "biliary crisis" because the word "crisis" was already applied to various tabetic manifestations such as the gastric crisis. Sir Arthur pricked up his ears and immediately stated that throughout his experience of cases of gall bladder disease, he had managed to read into the history of his patients the intermittent pain which to most people the word colic suggests. Numerous medical practitioners both in London, Edinburgh and elsewhere, teachers or not, have been under the same misconception as Sir Arthur Hurst. It must be said, however, that they too have readily though perhaps not so rapidly, altered their opinions.

Just as a comprehensive physical examination must adhere to a routine, so should the taking of the history of pain follow a systematic analysis in order to avoid omissions. An excellent system was presented by Ryle in his book *Natural History of Disease*, and it is upon this that this article is based.

(a) Spatial Features

Site. A note of the main *site* of pain should include whether it is localised or diffuse. It is often seen that the patient with a peptic ulcer will locate the pain with the tips of three fingers or the tip of the middle finger of the right hand. Pain from the liver which occurs in some cases of acute hepatitis is usually more diffuse in the epigastrium and indicated by the flat of the hand.

The site of pain immediately narrows down the possibilities. Thus a midline epigastric pain without radiation may arise from the stomach or duodenum, and from the structures developed from the duodenum in the embryo, viz. the liver, gall bladder, biliary tract and pancreas. Some clinicians would include instances of ischaemic heart pain; however such

cases never seem to be clear cut. Maybe such cases attend surgeons; and it must always be borne in mind that unless pain is present at the time of examination the patient's observation or recollection may be at fault. It is true that disorders of the structures mentioned above do not necessarily produce pain in the epigastrium at all, and it is not rare for gallstones, gastric or duodenal ulcers to give pain solely in one side of the back. Then the differential diagnosis begins to include disease of the pleura, chest wall and nerves. That is why the other aspects of pain to be discussed later are so important.

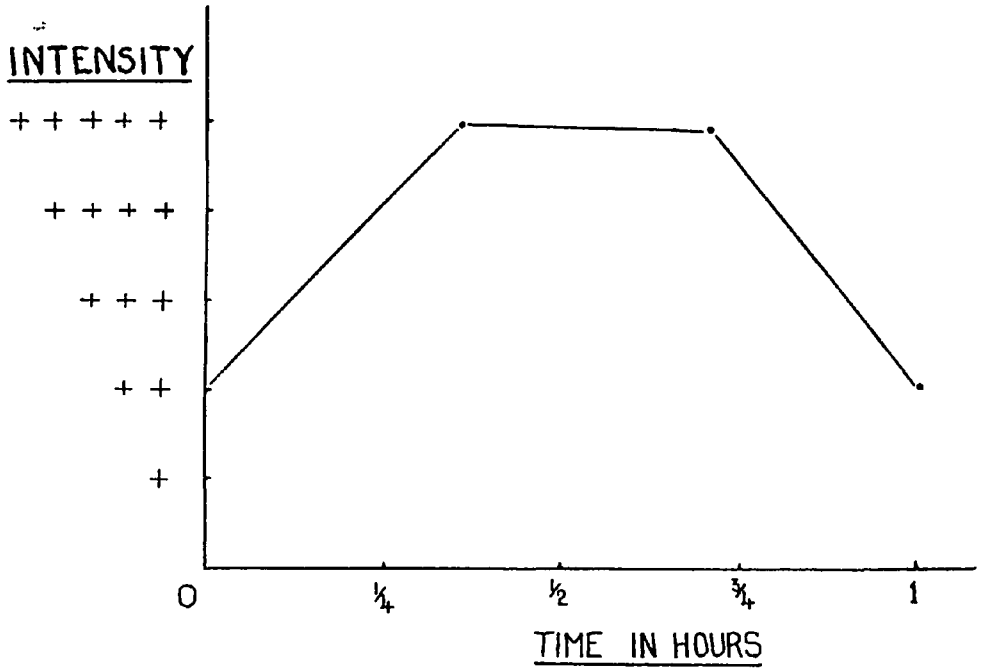
Radiation. Radiation is at once a considerable help, but some inexplicable clinical facts must be borne in mind. Thus radiation to the lower jaw is common in heart pain but is not diagnostic. Two cases which were initially referred to the National Heart Hospital give examples of erroneous diagnosis on this account. One was a man in his sixties with a gastric ulcer, and the other a young girl with a duodenal ulcer, who had such slight epigastric pain that she had not mentioned it because of the much more severe pain in the jaw. Similarly pain in the chest radiating down the left arm can sometimes be caused by hiatus hernia, arthritis of the neck, left sided pleurisy and no doubt other disorders as well as heart pain. Perplexing cases may also arise when the pain of radiation is felt without the primary pain if one may call it so; examples include pain in the left arm alone, occurring in angina of effort; two patients with a gastric ulcer, one complained of pain in the left side of the back alone and the other of a substernal crushing pain. Both these patients had been mis-diagnosed for some years and had been treated psychiatrically for the pain; subsequently both were relieved permanently after partial gastrectomy.

Perhaps radiation is a deceptive word; the clinical facts may be more intelligible if the pain reference is considered more in terms of mal-localisation. If the skin of a subject is pricked with a pin, the pain can be localised by the finger tips, with varying accuracy over different areas of the body surface. For example localisation on normally exposed surfaces is perfect whereas on the trunk the point indicated may be several centimetres in error. Thus it can be seen that the ability to localise pain is increased with constant practice. If 6% sterile saline is injected deep into the erector spinae at about the level of T 9, acute pain will be felt in the back at once which cannot be accurately localised. Within seconds pain will also be felt in the front of the abdomen, somewhere in the region of the ipsilateral rectus abdominis, soon accompanied by muscular rigidity and localised tenderness in this region. Clinically such signs would indicate disease of some underlying viscus. In the light of this experiment it can be seen that disorders of the structures of the body wall may simulate visceral disease as well as vice versa. Pain resulting from visceral disease is also localised quite well in structures from which some sensations are normally received, such as the oesophagus, rectum and bladder. Awareness of any other thoracic or abdominal organs is liminal if at all present. When pain arises in these structures, mal-localisation tends to occur in the extreme forms.

(b) Quality and Quantity

Character. Pain, according to Sir Thomas Lewis, can have one of two qualities. All skin pains have a pricking quality, all deep pain has a dull sensation likened to that produced by pinching the web of the fingers. This is certainly true for skin pain studied under special conditions, but untrue clinically. It is usual to be able to distinguish pain from a pin prick from

that produced by a burn. Experimentally Lewis produced burning by a fine hot wire passed down the centre of a thick brass cylinder which conducted away all surrounding heat. Clinically, most objects that cause a burn cover a wider area than a pin point. Then heat is appreciated by the surrounding unburnt tissue, and thus recognised as a burn. Similarly deep pains may have a distinct quality which is useful in diagnosis. Thus heart pain felt retrosternally has a gripping, tight, crushing or heavy quality. Such adjectives are never used for the pain of peptic ulcer felt in the epigastrium, which is usually described as gnawing or aching. Heart pains felt in the common areas of reference such as the arm are very seldom



The typical "shape" of the pain of biliary colic.

described in the terms mentioned above. Patients commonly just say pain, aching pain or pins and needles or even numbness. Moreover, it is important to recognise that pains referred retrosternally which arise in structures other than the heart also have a gripping quality. Lack of appreciation of this point sometimes results in a failure to recognise a diagnosis of high gastric ulcer. For example a patient with a normal ECG was referred to a psychiatrist and discharged from the R.A.F. After suffering on and off for a further eight years, the correct diagnosis was made and was effectively relieved by operation. Pain in other parts of the chest do not have the characteristic retrosternal quality even if the source of pain is the heart.

Severity. Abdominal pains of great severity are most commonly due to biliary or renal colic, perforated peptic ulcer and acute pancreatitis. One problem is how to assess severity. A male patient was found on his bed on all fours groaning in apparent agony. He was asked to lie on his back so that his belly could be examined. He complied at once, had a pain free expression, no pallor, sweating or vomiting and a normal pulse rate. It was concluded that there were psychological reasons for his overreaction to pain. By watching the behaviour and appearance of a patient it is usually possible

to judge the actual severity of the pain. Relief by a placebo is not satisfactory evidence that the pain was not severe.

If an assessment must be made in retrospect, a detailed account of the patient's behaviour and appearance may be satisfactory. For example if a woman wakes in the night with severe epigastric pain, rises and paces the floor, tries different positions, goes to the kitchen and takes baking soda, applies a hot water bottle, takes whisky, vomits and sweats, then the pain was severe. If, on the other hand, a woman says she had severe pain at work, yet she continued till the usual time, went home in a normal way and tried no method of relieving it, then for diagnostic purposes the pain cannot be rated as severe.

Shape. Shape here is used to describe the form of a graph depicting the course of an attack of pain, the vertical axis being the intensity and the *abscissa* the duration of the pain. This will entail details of mode of onset, whether it then stayed constant, grew worse or better, duration of peak, partial or complete remission and mode of cessation.

(c) Temporal Features

Duration. The duration of pain due to various diseases tends to lie within fairly well defined limits. Thus renal biliary colics generally last for a quarter to one hour but may continue for several hours. Peptic ulcer pain lasts for a quarter to two hours, cut short by treatment, but very rarely continuing longer unless perforation takes place. Lightning pains localised in the legs in tabes dorsalis are so brief that by the time the patient manages to yell the pain is over.

Frequency and special times of occurrence. The pains of peptic ulcer usually occur more than once in 24 hours and on several successive days. Whether or not the pains occur at special times is best assessed by asking the patient. Is he likely to have pain before rising, in the afternoon, evening or night? A rhythm is probable in peptic ulcer, while gallstones, for example, could give pain more than once in a day, though at no special time and intervals between pains may be days, weeks, months or years.

Periodicity. Periodicity is particularly a characteristic of peptic ulcer pains. Not infrequently patients insist that the pains have been present for some years, but on suitable enquiry, attacks of days or weeks duration may be found to alternate with periods of freedom for weeks or months. Periodicity is probably one of the most constant and reliable features in the diagnosis of peptic ulcer.

(d) Features which have a bearing on the determining cause

Aggravating factors. Factors causing aggravation are well illustrated by angina pectoris. Here effort is the principle cause. Not always the same effort is required however. That may be because so many other factors affect heart rate and work. Other factors are a cold wind, anxiety, the effect of a big meal and smoking.

Relieving factors. Many of these are obvious such as rest in intermittent claudication; alkalis, or vomiting in peptic ulcers. There must be one word of caution; patients often say something relieves them but this by itself is insufficient evidence. For example, patients suffering from angina pectoris of effort are often told to suck a tablet of trinitrin and they will claim great relief. They stop, rest and suck a tablet and the pain goes in two minutes. On enquiring into their disability before treatment they often state that they stopped and rested and the pain went in two minutes. The relief of pain

of peptic ulcer by alkalis is a particularly useful guide. If the patient says that relief is immediate or takes place after an hour peptic ulcer can be excluded as a cause of the pain. It is remarkable how patients suffering from the pain of peptic ulcer find relief in "ten minutes," sometimes "five minutes" or "a quarter of an hour" but rarely "half an hour." It is not appropriate to go into the reasons for this now.

Associated phenomena. Ryle gives this last place in his list of observations to be made, he also finds it the least valuable. However, the heading may give a reminder for an enquiry for melaena, family history in relation to peptic ulcer, abdominal colic and so on.

Conclusion

Knowledge and experience accumulate gradually; obvious conclusions should not be jumped to without taking into account any other symptoms. To take a final example of pain in the left side of the chest on breathing; the obvious conclusion is that the patient has pleurisy. However, many cases do, in fact, occur where this is not the right diagnosis: delayed pain from a fractured rib, zoster, splenic infarct, myocardial infarct have all been known to give the same symptom.

A lifelong study of pain will benefit both a doctor and his patients and increase his interest more and more as time goes on. What might at first appear to be a completely dull history of peptic ulceration can assume greater interest by a careful study of all the individual variations in such cases. Also as a consequence of all this study the doctor will find himself in a far better position to reach the correct diagnosis when a more difficult case comes his way.

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THE AETIOLOGY OF HYPERTENSION

By G. W. K. DONALDSON, B.Sc.

Based on a Dissertation read before the Royal Medical Society on Friday, 19th February 1960

The most common cause of death in this country is vascular disease. While it must be admitted that the incidence of vascular disease, and of the other major disease, cancer, increases with age, it is accepted that these diseases proceed often to a fatal conclusion when the victim is still productive. It has been estimated that if deaths due to the results of vascular disease were preventable, life expectancy might increase by some ten years. Were cancer cured, life expectancy would increase by about 2.5 years.

If in the first place we take merely an arbitrary level, say, 150/90 mmHg. above which we can consider pressures to be "high," then we may at once distinguish systolic and diastolic hypertension. Systolic hypertension is due to an increase in the cardiac output or to diminished elasticity of the aorta and large arteries. A rise in diastolic blood pressure if sustained, is usually due to an increase in the total peripheral resistance. The latter is dependent on the degree of constriction of the arterioles. Diastolic hypertension also results in the presence of a raised cardiac output provided that the total peripheral resistance does not fall. Systolic hypertension is not rare and does not appear to have marked deleterious effects. This article will be more concerned therefore with the aetiology of diastolic hypertension, although it must be remembered that the systolic and diastolic blood pressures tend to vary in the same direction. Essential hypertension is due to an increase in the total peripheral resistance without a change in the cardiac output: this causes a rise primarily of diastolic blood pressure, but the systolic pressure also rises.

Currently there is a major controversy regarding essential hypertension: is there a separate clinical entity of patients with high blood pressure? Or do patients presenting with symptoms and signs attributed to hypertension represent merely the upper limit of blood pressures in the general population?

Until about 1955, it was widely accepted that diastolic hypertension—certainly when secondary and probably when "essential"—constituted a clinical disease. But in that year Pickering published the results of statistical surveys of the distribution of blood pressure in a general hospital population. At a given age, the distribution of blood pressures differs from the normal (Gaussian) distribution curve in a positive skewness i.e. more values and wider range of values above the mode than below it. (The mode is that value with the highest frequency). This positive skewness becomes more marked with age, for, although the low pressures tend to persist, the high pressures tend to increase; thus the distribution curve widens. Both systolic and diastolic blood pressures increase with age, so that for an obese woman of 60 years 200/110 might well be accepted as normal. The average systolic pressure increases from 120 mmHg at age

20 years to 170 at age 80 years in man and in woman from 112 mmHg at age 20 years to 190 at age 80 years. The corresponding diastolic pressures are:

In men 70 and 85 mmHg.
In women 70 and 95 mmHg.

The sex difference becomes more marked after the menopause.

Now the distribution curve of all patients at all ages was considered to be unimodal, that is, with only one peak (Fig. 1). Pickering therefore postulated that patients with essential hypertension are merely . . . "that section of the population having arterial pressures above an arbitrarily defined value, and having no other disease to which the high pressure can be attributed . . . the difference is not of kind but of degree."

The other theory is that the difference is of kind: essential hypertension is a disease entity. If this is so, then one would expect a bimodal type

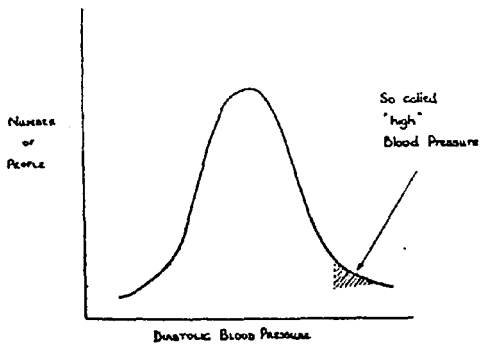

Fig. 1

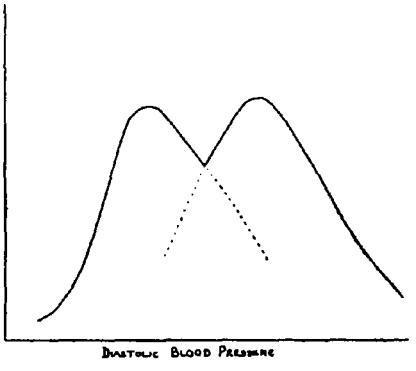

Fig. 2

curve of the blood pressures in the population (Fig. 2). Adherents to this "qualitative" theory maintain that the increased incidence of people with essential hypertension account for the major part of the over-all rise in pressure with age. One must employ special methods of statistical analyses to unmask the bimodality.

Platt has studied the blood pressures of the siblings, aged 45-60 years, of patients with hypertension and found a bimodal curve. On re-examining Pickering's figures, and taking the readings correct to 5mmHg, he has found significant dips in the systolic and diastolic distribution curves at 150 and 90mmHg. Morrison and Morris have shown a bimodal distribution of the systolic blood pressures of London busmen whose parents died between the age of 45 and 64. (Presumably a higher proportion of these parents had hypertension than people who lived longer.) Similarly a bimodal curve has been shown for the children of hypertensives.

Currently, the pendulum of medical opinion is swinging back towards the "qualitative" theory as being the correct one. If correct this indicates that the hereditary factor in hypertension is probably carried by a single, dominant gene rather than a multiple polygenic mechanism as for height, weight, normal blood pressure and so on.

The extent of the influence of the genetic factor has been studied in some detail; figures of from 4 to 64% have been suggested. The effect of the genetic factor appears to diminish with age. If the genetic effect varies a great deal this might be due to:

(1) A multigenic hereditary mechanism if the quantitive theory is correct.
(2) A dominant gene of varying penetrance and expressivity.

The best work has come from a study of twins and the relatives of hypertensives. A dominant gene might be expected to reveal itself in 50% of the children of parents of whom one is hypertensive, and in all children if both parents are hypertensives. In fact, figures less than these have been found, about 35 and 70%. Apart from varying penetrance and expressivity this could also be explained by

(*a*) presence of other diseases.

(*b*) absence of extrinsic permissive factors such as diet and environment.

There is a very close connection between the blood pressures of uniovular twins, and also, but slightly less so, of binovular twins. A few cases of uniovular twins of whom only one was hypertensive have been reported, and it is interesting that in those cases the twins had quite different personalities. Further, the correlation between the blood pressures of twins is not as high in those who have been brought up in different environments.

So much for heredity. Let us consider the psychological and physical aetiology of hypertension. High blood pressure has been named as a stress disease. The psychiatrists have found, in manic-depressive patients, hypotension in the manic phase and hypertension in the depressed phase. Psychologically-minded cardiologists have related the onset of hypertension to some psychological stress, but such retrospective studies are naturally open to deserved criticism. Others have suggested that high blood pressure is associated with a specific type. It is at least widely agreed that hypertensives show restrained aggression and unexpressed rage and hostility, while patients with essential hypertension respond with a greater and more prolonged rise in pressure to unpleasant situations.

Psychotherapy and prefontal leucotomy have a variable effect on hypertension, but most often results in a temporary fall. Acute and chronic stress in the form of earthquakes and front-line war service have been found to cause a persistent, but not very large, rise in pressure.

Nevertheless it has not yet been adequately established whether personality changes and psychological manifestations result in or from hypertensive disease.

The physical aetiology of hypertension is founded on more salient features. Firstly, the kidney has been implicated clinically and experimentally. As early as 200 B.C. Choun-Jon-J wrote: "When the pulse upon depressing is very firm and upon superficial palpitation very tight, then the disease has its seat in the kidney." Bright described the pathology of the kidney in cases associated with high blood pressure.

A tremendous fillip to the role of the kidney in hypertension was given by Goldblatt; he produced experimental hypertension in dogs by clamping the two renal arteries or by clamping one renal artery after removing the other kidney. The renal arteries were not totally occluded; the aim was to produce renal ischaemia by decreasing the arterial blood flow. It was postulated that the ischaemic kidney released a pressor agent which caused the hypertension. However, if the other kidney was left intact and unclamped, no rise in blood pressure occurred: the intact kidney must have "neutralised" the pressor released by the ischaemic kidney. The vasodepressor action of the normal kidney was emphasised by Gollman's finding that bilateral nephrectomy is followed by hypertension; such hypertension is not due to the rise in extra-cellular fluid volume nor electrolyte disturbance, since it occurs when the animal is dialysed.

Byron and Wilson confirmed these findings after producing renal hypertension by partially occluding only one renal artery in the rat. Such

hypertension occurs after a shorter latent period than after total nephrectomy. Removing the clamp will only restore the blood pressure to normal if it is done within two or three weeks. After that time the blood pressure will remain high apparently because an extrarenal mechanism has taken over and become autonomous.

It is noteworthy that vascular lesions only develop in the unclamped kidney. The clamped kidney is "protected."

These experiments at once present some obvious problems:

1. What is the pressor agent released, and what is the necessary stimulus?
2. How does the normal kidney depress blood pressure?
3. What is the extra-renal mechanism?

The pressor agent may be renin which has been isolated from renal venous blood, following clamping. Renin is an enzyme which can be extracted from the renal cortex; on injection it causes hypertension by splitting off the pressor polypeptide hypertensin from the plasma protein hypertensinogen. Unfortunately renin has not been commonly demonstrated in the blood during acute renal ischaemia in man and never in essential hypertension. Experiments involving partial renal corticectomy are purported to show that the origin of renin is in the outer cortical tissue, perhaps in the juxta-glomerular apparatus.

Another vasoexcitatory material, pherentasin, has been isolated by Schroeder from the blood of experimental renal hypertensive dogs and from cases of essential hypertension and hypertension secondary to renal disease in man. It is not directly a pressor agent but sensitizes the vessels to the normal stimulus of sympathetic transmitter. There are reports of increased sensitivity to intra-arterial injection or nor-adrenaline in cases of essential hypertension.

An interesting theory as to the formation of the amine pherentasin is as follows: the kidney manufactures ammonia from the plasma amino acids; this is achieved in two stages:

1. decarboxylation of amino acid to amine: the reaction is catalised by an anerobic enzyme.
2. deamination of the amine; this reaction is catalysed by an aerobic enzyme.

   Now in the ischaemic kidney one might expect the anaerobic but not the aerobic enzyme to continue to function. This would cause an excess of amines such as pherentasin to be produced.

These clamping experiments show that the onset of experimental renal hypertension is associated with a fall in renal plasma flow. Clinically in the renal lesions associated with secondary hypertension, there is usually a fall in renal plasma flow but not in the glomerular filtration rate so that the filtration fraction increases. The one consistent functional alteration in chronic human hypertension is the presence of renal ischaemia. And we may correlate this with Homer Smith's observation that the so-called neurogenic hypertensive patients, after a psychological stimulus or physical exercise, do show a greater than normal fall in renal plasma flow and a slower return to normal.

Congenital renal lesions, of parenchyma or vessels, are often associated with hypertension, and, if the renal lesion is unilateral, the hypertension may be cured by unilateral nephrectomy. Similarly it is not rare to find hypertension developing in a person with severe pyelonephritis. Pyelonephritis appears to increase an existing hypertension and to magnify the

effects of a congenital lesion, for of patients with congenital lesions presenting with hypertension more than half have co-existing pyelonephritis. Yet to be established is the difference between those patients with chronic pyelonephritis who develop hypertension and those who do not. Many patients with severe bilateral pyelonephritis have a decreased renal blood flow but do not develop high blood pressure.

Goldblatt's experiments on clamping the renal artery have often been criticised as not being remotely connected with the aetiology of clinical hypertension. However in 1939 Blackman found at autopsy that in cases of essential hypertension 84% showed atheromatous narrowing of the renal arteries, whereas only 10% of the controls showed this. Pathologists cut longitudinally into the renal arteries; this obscures atheromatous plaques. A 1mm decrease in the radius of a 5mm radius vessel may appear relatively slight, but one must remember that blood flow is proportional to the fifth power of the radius. Thus a 20% reduction in the radius of the vessel causes a 66% fall in blood flow. Blackman's findings may be correlated with the hypertension following aortic thrombosis above the level of origin of the renal arteries.

The hypertension of coarctation of the aorta has long been attributed to the increased peripheral resistance presented by the narrow, long collaterals. (This resistance is in large vessels and causes predominantly a systolic hypertension above the congenital narrowing.) Yet the femoral diastolic pressure often is increased, although the systolic pressure may be normal or less than normal, with a small pulse pressure. Scott and Bahnson (1957) in a classical series of experiments, produced experimental diastolic hypertension in a unilaterally nephrectomised dog by an artificial coarctation of the aorta. Later they abolished the diastolic hypertension (beyond the obstruction) by transplanting the kidney to the neck.

Similarly the hypertension which sometimes occurs in polyacteritis nodosa may also be explained by obstruction in the renal artery leading to ischaemia.

If a rat's renal artery is clamped and left so for several weeks then hypertension will remain after removal of the clamp. However the hypertension may be abolished by adrenalectomy, and restored by feeding high doses of salt.

Ledingham has demonstrated that totally nephrectomised rats develop hypertension only if their adrenals are intact or if there is an excess of salt in their diet. In a totally nephrectomised and adrenalectomised parabiotic rat (the other parabiotic rat being normal) the blood pressure then remains normal, presumably because of the passage of some humoral factor from the parabiotic twin. Adrenalectomy itself has no effect on a parabiotic rat. Selye has produced hypertension in experimental animals by administering D.O.C.A. (deoxycortisone-acetate) plus salt; the hypertension is not due solely to the increase in e.c.f. volume.

Clinically the high blood pressure seen in Cushing's disease is well known. Schroeder has described a group of female patients with hypertension: common factors include obesity, middle age, and the history of some endocrine abnormality. This group constitutes 20% of female hypertensives. These women have a very low salt content in their sweat and their blood pressure is very sensitive to lowering of their salt intake or to diuretics. It would be interesting to observe the effect of anti-mineralocorticoids such as spirolactone on these patients.

Recently renal ischaemia has been correlated with aldosterone secretion by the adrenal cortex. In renal ischaemia in both man and experimental

animals the juxta-glomerular cells, the specialised cells in the wall of the afferent glomerular arteriole, are more numerous and contain more granules. Dietary restriction of salt in animals causes hyperplasia of the juxta-glomerular cells and of the zona glomerulosa of the adrenal cortex. The zona glomerulosa probably is the site of manufacture and release of aldosterone. The stimulus for the release of aldosterone is unknown: it is not A.C.T.H. After adrenalectomy there is also juxta-glomerular cell hyperplasia. It has been postulated that the juxta-glomerular cells may play some part in the control of aldosterone secretion by the adrenal cortex.

It has been suggested that when the cause for secondary hypertension, such as unilateral renal disease, is removed, but hypertension persists, that hypertension is being maintained by an adrenal mechanism which has become autonomous. In fact, in patients with a short history of renal disease, adrenalectomy will often result in normotension after the unilateral nephrectomy has failed. But some cases remain with high blood pressure after unilateral nephrectomy and total adrenalectomy. Adrenalectomy has not yet met with success in the treatment of essential hypertension.

However, in ALL patients with essential hypertension, salt restriction will lead to a fall in pressure if both sodium and chloride are restricted. The importance of salt may lie not in the Na and Cl ions but in the small proportion of unionised sodium chloride and its effects on the cell membrane. There is suggestive evidence of altered sodium, potassium and chloride ratios between the intra- and extra-cellular fluids of the cells of the blood vessels of hypertensive animals.

Finally, countries in which high blood pressure is common also have high salt consumptions. For example, hypertension is rare in the Orient except in Japan where there is a high salt intake.

A neurogenic basis for essential hypertension acting via renal and/or adrenal effector pathways, has been postulated since stress must act via the central nervous system in causing renal ischaemia and increased production of adrenal cortical hormones. Although experimental neurogenic hypertension can be produced by section of the buffer nerves supplying the baroreceptors, the carotid sinuses and the aortic pressor receptors, this state is not at all kin to essential hypertension in which the pressor reflexes appear normal. Conceivably the baroreceptors, by adaptation, might be "set" to a higher level of blood pressure in essential hypertension.

Recently the influence of sex hormones on the sensitivity of the vascular system has begun to be investigated. Women in the reproductive phase of life have a lower mean blood pressure than men; and overall, women with high blood pressure have a better prognosis than men. Dr Mary Pickford and Miss Sybil Lloyd, experimenting on cats and dogs, have found marked differences in the response of the female cat and dog at different times. In late pregnancy and after oestrogen administration oxytocin has a pressor action, as opposed to its normal vasodilator and depressor effects. Yet the pressor response to nor-adrenaline and the depressor response to acetyl chlorine are unchanged. This changed response to oxytocin can also be produced by ganglion blocking drugs and by post-ganglionic sympathetic blockade with Bretylium tolysate (Darenthin). Part of the response to oestrogens appears to be central because of the effect of decerebration or pithing. The peripheral mechanism may involve altered sodium or potassium ratios between the i.c.f. and the e.c.f. of the smooth muscle in the wall of the vessels.

A final observation of interest is that the pressor action of renin but not of hypertensin is absent during late pregnancy.

Summary

1. Hypertension may be transmitted by a dominant gene of varying penetrance and expressivity.
2. The role of the kidney is
   (*a*) the release of pressor agents such as renin and pherentasin in response to ischaemia.
   (*b*) a normal role of keeping down the blood pressure by an unidentified mechanism.
   (*c*) perhaps control of aldosterone production by the adrenal cortex.
3. The adrenals may sometimes provide a secondary mechanism for maintaining long established hypertension.
4. There is at least one other extra-renal mechanism capable of maintaining hypertension. This may include altered responses of pressor receptors and/or vasomotor centres.
5. Other factors include personality type, environment and sex hormones.

But whatever the primary cause in a given case —hereditary, neurogenic, renal or endocrine—it is probable that other factors are necessary for the hypertension to become manifest. We have thus primary and permissive factors. It has even been stated that hypertension would not occur in an individual, both of whose parents were hypertensive, if, from birth he did not add salt to his food.

References include:

"Hypertension" Symposium, Ed. Mayer, Saunders, 1959.
"High Blood Pressure," Pickering, Churchill, 1955.
"The Stress of Life," Selye, Longmans, 1957.
"Hypertension," Ciba Foundation Symposium, Churchill, 1954.
"Hypertensive Diseases," Schroeder, Kimpton, 1955.
Lloyd, Sybil, "J. Physiol," 1959, 148, 625 and personal communications.
Morrison and Morris, "Lancet," 1959, November 28th.
Pickford, Mary, *et al*, "J. Physiol.," 1959, 145, 225 and personal communications.
Platt, R., "Lancet," 1959, July 25th, II, 7091.
Turner, R. W. D., "Lancet," 1959, May 2nd and 9th, 897 and 953.

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Brit. Med. J., 1960, i, 297.

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RES MEDICA

NOVEMBER 1960

HEREDITY AND SOCIAL ORDER

That medical research can be retarded by the limitations of laboratory technique is only too well known. But, once begun, research into a specialised field can advance with startling rapidity.

In the past two years, more reliable methods leading to the identification of individual chromosomes have been developed. A new dimension is being added to the science of genetics, which may provide a variety of of social and clinical implications, typical of this branch of biological science.

It seems that in the course of oogenesis and spermatogenesis, non-disjunction of X or Y chromosomes during meiosis or mitosis may result in the birth of individuals with abnormal genetic constitutions, e.g. XXY associated with Klinefelter's syndrome; XO associated with Turner's syndrome. Among the cases studied so far are examples of primary amentia and true hermaphroditism. More generally known is the association of mongolian idiocy with the usual complement of autosomes and sex chromosomes but with one additional small autosome.

Following a discussion of the presence of some less fortunate groups in the community, I have heard a distinguished member of our University express the following opinion with regard to mongolism; that since a definite abnormality in the genetic constitution can be demonstrated, some reasoned argument can be put forward for the disposal of such individuals. Certainly their inheritance is not that regarded as human. Nor can anyone who has seen for himself how families may devote themselves to the care of a mongol, a cretin or someone chronically insane, find it easy to oppose this argument outright.

But for which reason might a mongol be removed? Simply because of his inheritance? Or because he is a source of heartbreak? On the latter I shall comment, and with regard to the former it has not been shown that chromosome constitutions just as abnormal are incompatible with normal mental and physical development. Patients exhibiting Klinefelter's or Turner's syndrome can be of reasonably high intelligence, and to the world at large appear completely normal.

Nevertheless, when, as a result of inheritance the use of language is never gained, memory is very limited and the implications of any situation never understood, surely foresight and the very human faculty of self-awareness cannot be present.

Chromosome studies will lead to many fields remote from the original researches in leukaemia and immunology. This break-through is a reminder that the science of genetics, though specialist, has implications far beyond itself.

TRANSPLANTATION

During the last few years it has become impossible to look at medical journals and publications and fail to notice the increasing frequency of articles dealing with the problems of tissue grafts and transplantation. Skin grafting subsequent to burns and traumatic episodes and in many forms of plastic surgery is now commonplace and routine, but this has not been achieved overnight. In the early years of such techniques much research and experimentation was necessary to overcome the fundamental problems involved.

Great success has been achieved in these situations and gradually the field has been extended to cover a multiplicity of frequent clinical conditions. Autoplastic transplants of bone from one site to another to restore deficiencies due to fracture or necrosis may be quoted as examples. Successful as the great majority of these procedures are, they are limited in that the transplants must be taken from the patient himself.

Recently, in spite of great difficulties, the field has begun to cover heterologous transplants, but primary surveys indicate that results are far from satisfactory and the work is very restricted. More success has been obtained in the transfer of certain tissues and organs between closely related individuals, especially in the case of identical twins. Progress is slow, but within the past few weeks the first successful kidney grafting operation to be performed in Britain has been reported. Admittedly identical twins provide a unique situation and only certain organs can be transferred, but the experience gained in such conditions is of the greatest significance.

With these advances in mind we must look ahead to the day when organs can be freely transferred from one individual to another. If this ideal could be achieved many patients at present faced with a much reduced life expectancy due to failing and inefficient organs, would be restored and returned to a normal existence. Such a situation seems initially to be impossible or at least very far into the future, but research is striving to obtain just such a goal. It is surely not outside the bounds of reality to visualize the solution to this problem.

TIMES OF CHANGE

Three years have now passed since the first edition of RES MEDICA was published. It may be said that in that period the major teething troubles of the journal have been surmounted thanks to the zest and application of the previous editors and their committees. Our aim in producing the journal remains that of reflecting the events which have of late taken place in the Society particularly in the "Public Business" meetings.

A highlight of the latter part of the 223rd session was undoubtedly Dr E. B. French's address on "The Diagnostic Value of Pain," and it is with great pleasure that we print a digest of this address as our opening article. Also in this edition is the second part of Dr R. W. D. Turner's three-part article on "Auscultation" in which he deals with the topic of "Triple Rhythm." Much praise of the first part of this article has reached us from both postgraduate and undergraduate sources and we have no doubt that our readers will find "Triple Rhythm" at least as stimulating and instructive as its predecessor.

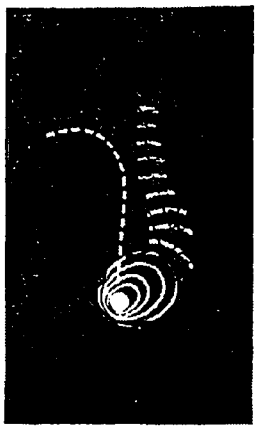
As a Society of about two and a quarter centuries' standing the Royal Medical Society maintains a great interest in the history of medicine, and in particular in the great names which are part of its own history. In this connection we are very grateful to Mr J. B. Wallace, past-president

of the Royal Scottish Society of Arts, for giving us the privilege of publishing an extract of his presidential address to that Society on William Cullen and Joseph Black, who were two of our famous founder members. The interest in historical studies can also be seen in the subjects of several of the dissertations given by undergraduate members in this and the previous session. Mr W. S. Uttley's article on "Sir James Mackenzie—An Introduction to Cardiology" is an example of these.

In this issue are two other articles. That of Mr G. W. K. Donaldson on "Hypertension" is based on his excellent and erudite dissertation given before the Society towards the end of last session. Dr W. L. Ford has for most of his undergraduate life been one of the stalwarts of the Society, and it was with great disappointment that we learned that he was unable to read his dissertation before the Society owing to illness. However, his talent was not lost to the Society in that we now publish his most interesting article on "Constitutional Jaundice."

Any reflection of the happenings within the Society would be incomplete without any mention of the process of revision of some of the Society's laws and customs which is now in the initial stage. This is the result of the work of Mr A. D. Chalmers and his committee and is almost certain to have far-reaching effects in the future conduct of the Society. Among the topics to be brought under review by the Society in this session are the usefulness and purpose of "First Private Business," election to office and fellowship, and the entry of women into the Society. Such topics as these are going to stimulate much thought and discussion and may be even heart-searching amongst the members of the Society. However, we believe that the outcome, in the shape of a Royal Medical Society more useful and used by the medical students of Edinburgh, will make it worthwhile.

The management of Pain



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AUSCULTATION OF THE HEART

II

By R. W. D. TURNER
O.B.E., M.A.(Cantab.), M.D., F.R.C.P.Ed., F.R.C.P.Lond.

This particularly rapid unintelligible patter,
Isn't generally heard and if it is it doesn't matter.
—W. S. GILBERT.

TRIPLE RHYTHM

So sang Gilbert 50 years ago and so might some sing today with regard to triple rhythm, particularly, perhaps, physicians brought up before the days of modern analysis but not, let us hope, the student of today who has the opportunity to start aright.

Triple rhythm signifies that three heart sounds can be heard instead of the usual two and therefore this term should not be used to include splitting of the first or second heart sounds nor for extra-cardiac sounds. The added sound of true triple rhythm falls during diastole.

The extra sounds or "clicks" which can sometimes be heard in systole and are probably due to vibrations arising in a dilated pulmonary artery or aorta are not usually included in the term. It is customary also to exclude the opening snap of the mitral valve. Certainly this is an additional heart sound, not normally heard in health, but it occurs only in association with mitral stenosis and is always followed immediately by a mid-diastolic murmur so that it is unlikely to be mistaken for any other sound and will be described separately.

Triple rhythm may be physiological or may accompany serious heart disease and usually its significance can only be determined by consideration of the associated circumstances. In recording triple rhythm it is therefore important always to state whether it is due to the addition of a physiological or of a pathological sound.

In order to avoid confusion it is suggested that the designations first, second, third and fourth heart sounds should be confined to the physiological sounds which can normally be heard or recorded.

Triple rhythm, then, may be due to the addition of a physiological third or fourth heart sound or under pathological conditions triple rhythm may be due to the addition of an extra sound in diastole similar in position in the cardiac cycle to one or other of these physiological sounds (Fig. 4). Some authors, in order to try and avoid confusion use the term "gallop rhythm" for all pathological sounds. My preference is to use the term triple rhythm whenever three sounds can be heard, adding the qualification physiological or pathological after considering the company it keeps and confining the term gallop rhythm to the appropriate cadence, as discussed below.

Not only is there considerable confusion over terminology but great

variability in the recognition of triple rhythm by clinicians. This is partly due to failure to listen with sufficient care. The added sound in triple rhythm is usually of low pitch and occurs in a frequency range which it is relatively difficult for the human ear to appreciate. By the untrained observer these sounds must be specifically sought and it is necessary to listen intently and as specifically as does the trained ear which can pick out individual instruments in a large orchestra. It is also partly due to unawareness of the various conditions which may give rise to triple rhythm.

It is not always appreciated that recognition is often rewarding not only by giving positive help to accurate diagnosis and guidance on prognosis but also as regards avoiding errors of misinterpretation, for example of physiological sounds. The detection of triple rhythm may often provide

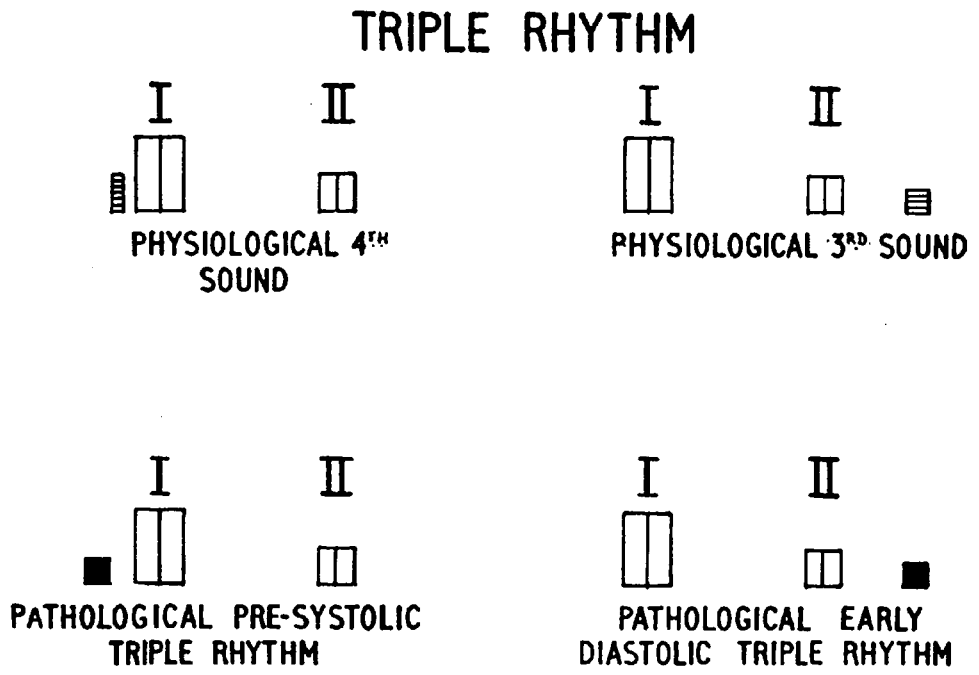


Fig. 4

the first clue to accurate diagnosis when the actual underlying condition has not hitherto been suspected. I have seen this in cases of myocardial infarction, constrictive pericarditis, myocarditis and myopathy.

It will be evident from what has been said that triple rhythm must be discussed as regards timing in the cardiac cycle and as regards its physiological or pathological significance.

By selective electronic amplification and graphic recording these sounds can be intensified and depicted for examination at leisure as already pointed out and in difficult cases phonocardiography is an invaluable aid to precision in diagnosis. However, for most practical purposes interpretation must be made at the bedside.

It is therefore necessary not only to be methodical in examination but to have in mind a clear terminology and classification.

Pre-Systolic (Atrial) Triple Rhythm

Two sounds may result from atrial systole. One (sometimes known as the fourth heart sound) is due to vibrations produced by atrial contraction

itself and the other, although synchronous with and consequent upon atrial systole, is due to vibrations produced in the ventricle.

Physiological Pre-systolic Triple Rhythm

The low pitched vibrations which form the atrial component of the first heart sound are *not usually* audible in health. They occur just after the beginning of the P wave and before the R wave of a simultaneously recorded electrocardiogram (Fig. 5) and are believed to result from actual atrial contraction. That atrial contraction can produce an audible sound is readily demonstrated in patients with complete heart block where there is disassociation between atrial and ventricular contraction. In such cases independent irregular atrial sounds can often be heard. In *some* normal persons, and especially when there is delay in A-V conduction (as reflected in the prolongation of the P-R interval of the electrocardiogram) this sound may be audible immediately before the main first heart sound instead of being "lost" in the louder valvular component. (Physiological fourth heart sound.) It usually differs in quality from splitting of the first sound (from asynchronous closure of the mitral and tricuspid valves) in that the latter is composed of two similar higher pitched sounds.

Pathological Pre-systolic Triple Rhythm

A distinct pre-systolic triple rhythm is frequently heard in patients with left sided heart disease, particularly in those with left ventricular hypertrophy from systemic hypertension or following myocardial infarction. In patients with atypical features which might be due to myocardial infarction, it may give a very useful diagnostic hint. In many patients the clarity of this added sound and its distance from the first heart sound decreases with clinical improvement, and in others, especially with systemic hypertension, there may be no change over many years without clinical deterioration. The sound in fact may often be heard in patients with left ventricular hypertrophy from *symptomless* hypertension. Sometimes too much prognostic significance has been attached to this finding.

Tachycardia shortens diastole and if tachycardia is present this added sound will fall in mid-diastole or be superimposed upon an early diastolic rhythm (see below). In such cases it can only be distinguished by slowing of the heart rate either from pressure over the carotid sinus or as a result of treatment.

In right sided heart disease presystolic triple rhythm may occur from pulmonary hypertension or following major pulmonary embolism.

The pathological sound is believed to be related to ventricular filling but whether from vibrations of the muscular walls or tensing of the valves has not been conclusively determined.

Early Diastolic Triple Rhythm

Triple rhythm from an added sound in early diastole may be due to the physiological third heart sound or to a pathological sound in the same position in the cardiac cycle and probably due to essentially the same mechanism. (Fig. 4).

Two possible mechanisms have been suggested and each has strong proponents. The first is that the sound is produced by vibrations in the ventricular walls and the second that it is produced by closure of the A-V valve leaflets due to the reflux of blood towards the auricles following rapid ventricular filling.

Physiological Early Diastolic Triple Rhythm (Third Heart Sound)

The physiological third heart sound occurs early in diastole, that is shortly after the second heart sound from which it is separated by a readily appreciable gap of .11-.15 second.

Owing to its relative faintness and low frequency this sound can be

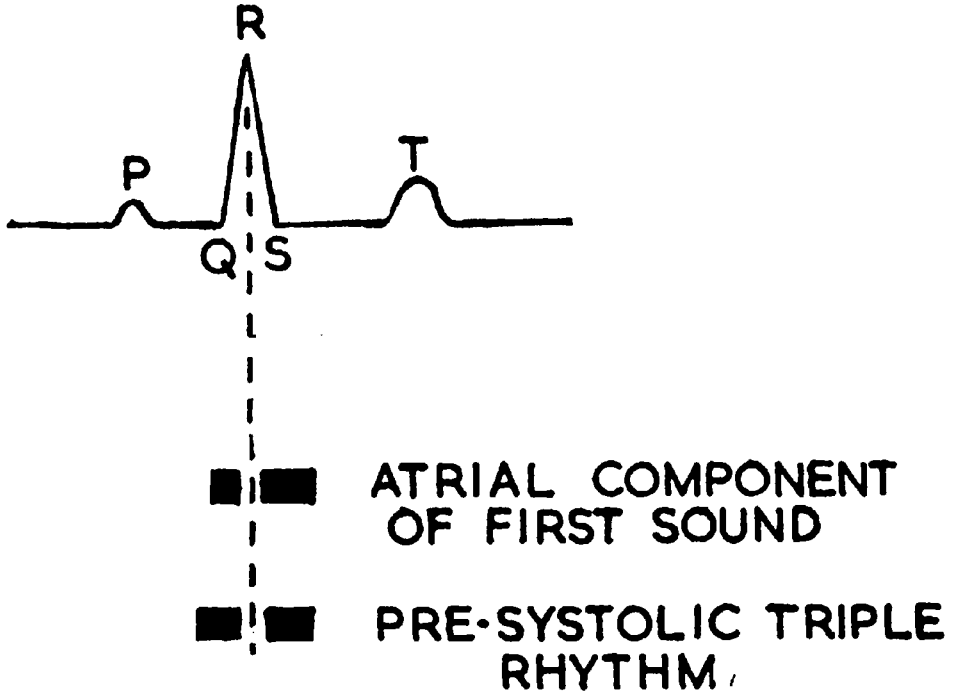


Fig. 5

recorded more commonly than it can be heard but is nevertheless very often audible in young people. In fact it is rarely heard in infancy, occurs more often than not in children, is frequently present in young adults but rarely if ever over the age of 40. It is often present in pregnancy.

It used to be thought that this sound was related to closure of the semi-lunar valves but timing with the carotid and jugular pulses has shown that it is always greater than 0.1″ later than this and constantly coincides with the descending limb of the "v" wave, that is during the phase of rapid ventricular filling after the A-V valves open. (Fig. 6).

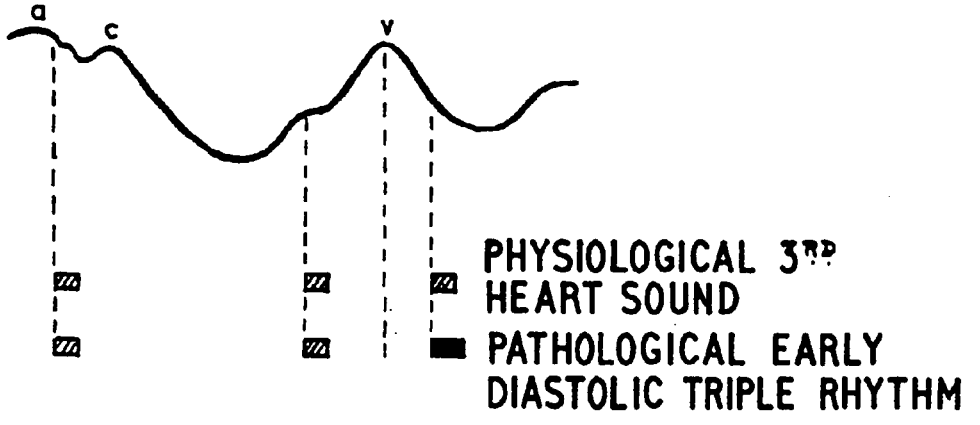
The sound is best heard near the apex beat or between the apex and sternum and in the recumbent posture. It becomes louder or may only be heard if ventricular filling is increased by exercise, emotion or tachycardia from any cause.

Pathological Early Diastolic Triple Rhythm

Pathological third heart sound, ventricular gallop, protodiastolic gallop, rapid filling gallop are synonymous terms for one form of pathological triple rhythm which, as regards timing in the cardiac cycle and probable mechanism, is identical with the physiological third heart sound; that is, at normal heart rates, it is heard early in diastole and shortly after the second heart sound. It may be loudest at the apex or near the sternum depending on which ventricle is involved and also on other factors such as cardiac enlargement, rotation or displacement. It is best heard in the

recumbent posture, especially with the patient lying on the left side and with light pressure of a bell stethoscope or better still by direct auscultation with the ear applied to the chest wall. The sound is of a dull, low frequency quality and is often accompanied by a palpable impulse.

As explained above, it is still not agreed, despite more than 50 years of experiment and discussion, whether this sound is of muscular origin from



PHYSIOLOGICAL THIRD HEART SOUND AND PATHOLOGICAL TRIPLE RHYTHM.

Fig. 6

vibrations of the ventricular wall or results from rebound tensing of the atrio-ventricular valves, but it certainly falls on the descending limb of the "v" wave and corresponds with the period of rapid ventricular filling. For this reason it is apt to be loud when the filling (right atrial) pressure of the ventricle is raised and will not be heard when valvular stenosis precludes rapid ventricular filling.

Triple Rhythm in Constrictive Pericarditis

An added sound in early diastole similar in timing to other varieties of triple rhythm due to rapid ventricular filling is often heard in constrictive pericarditis. It is frequently accompanied by a palpable impulse. Doubtless both sound and impulse are due to a combination of rapid inflow (from the raised venous pressure) and the abrupt limitation of filling produced by the unyielding qualities of the fibrous or calcified pericardium. In fact in quality, though not in timing, this sound resembles an opening snap and the condition is sometimes mistaken for mitral stenosis. However, there is no murmur and examination will reveal the clinical and radiographic features of constrictive pericarditis.

GALLOP RHYTHM

When tachycardia is present the cadence of triple rhythm is often that described as a "gallop" and because of the frequent association with

myocardial failure this sound is of serious prognostic significance. The louder the added sound the more serious the outlook.

Summation Gallop

Summation gallop signifies the super-imposition of atrial and ventricular added sounds. This may occur with prolongation of the A-V conduction time (P-R interval of the electrocardiogram) or, more frequently, with tachycardia. Because of the loudness of this triple rhythm and its ready detection summation gallop is probably the variety of pathological triple rhythm most frequently recognised and its association with tachycardia from ventricular failure is responsible for the gloomy prognosis so often associated with "gallop" rhythm.

Summation of the two added sounds can, of course, only be proved by the demonstration of quadruple rhythm with slowing of the heart rate.

OPENING SNAP OF THE MITRAL VALVE

The opening snap of the mitral valve is a very characteristic physical sign with which all should be familiar. Not only is it frequently and clearly to be heard and present more often than not in patients with mitral stenosis

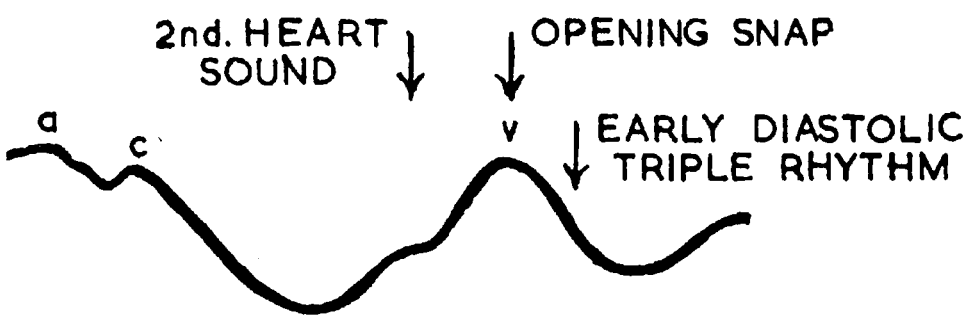


Fig. 7

but its detection may give the stimulus to listen with care for an apical mid-diastolic murmur not previously heard. Also, paradoxically, its *absence* in a patient with signs of mitral stenosis may be more important than its presence and signify that the valve is calcified, rigid or dominantly incompetent. Finally, if not recognised it may be mistaken for some other condition.

In timing this sound occurs earlier in diastole .08″-.12″ after the beginning of the second sound) than a third heart sound or pathological triple rhythm .12″-.15″ and coincides with the peak of the "v" wave, that is to say with the opening of the A-V valves. (Fig. 7).

In quality the sound usually differs from other forms of triple rhythm in being "metallic" rather than "dull." In position it is often heard over a wide area but is loudest at the left sternal border in the third or fourth intercostal space. When heard it is always followed by a mid-diastolic apical murmur but such a murmur may occur without a snap.

In significance it has been claimed that a clear opening snap like a loud first heart sound implies the presence of a "pliant" or ''diaphragmatic" valve with the inference that such a valve will be readily amenable to surgical treatment. Although it does signify a mobile anterior cusp our experience has been that it does not by any means follow that the valve margins will not be rigid or that valvotomy will be successful.

Differential diagnosis is chiefly from splitting of the second heart sound and from triple rhythm. However, two other conditions with which it may be confused should be mentioned. Rarely a similar opening snap of the tricuspid valve may accompany tricuspid stenosis and an added sound similar in quality to a snap but similar in timing to a third heart sound may be associated with constrictive pericarditis.

DIFFERENTIAL DIAGNOSIS OF TRIPLE RHYTHM

The differential diagnosis of the added sounds which are discussed in this section can be appreciated from Fig. 8.

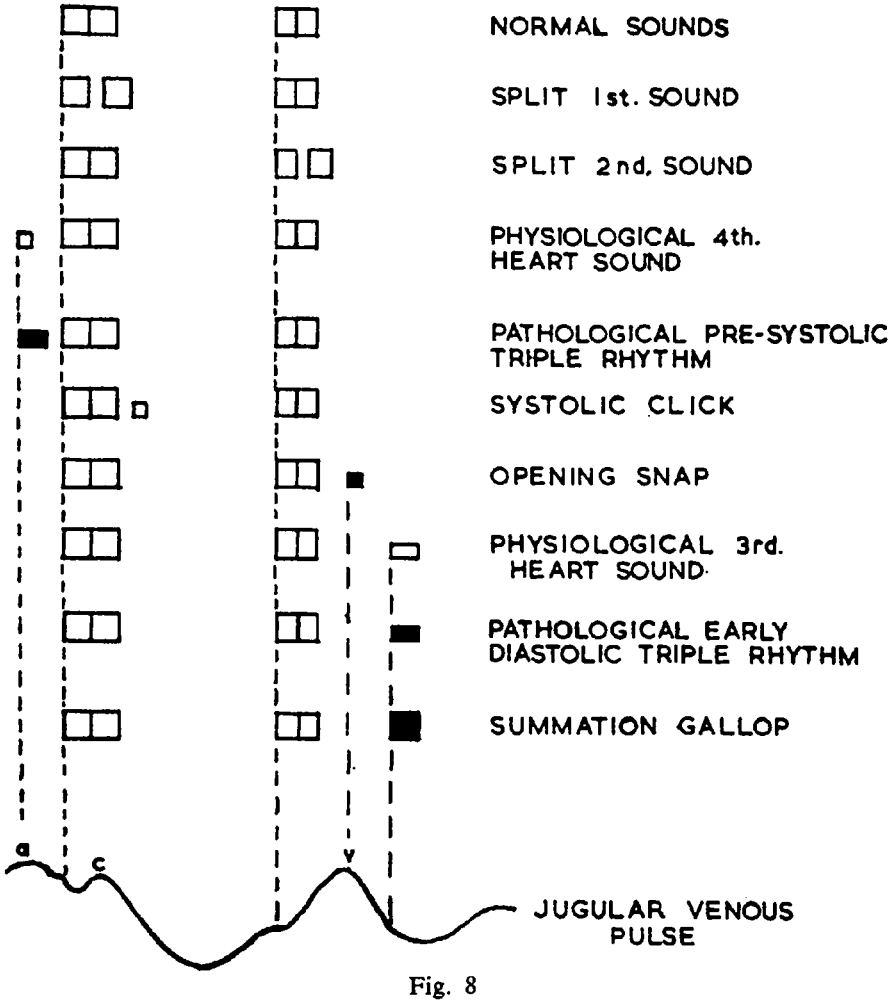


Fig. 8

[TO BE CONTINUED

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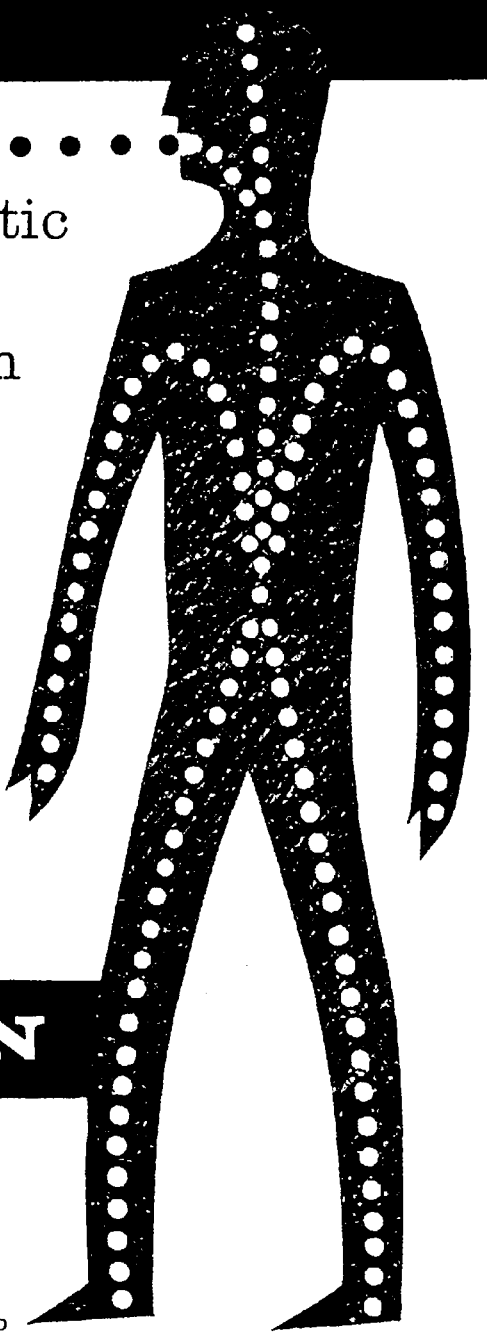

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THE STORY OF TWO PORTRAITS

By JAMES WALLACE
B.Sc., F.R.S.E.

Based on the writer's Presidential Address
to the Royal Scottish Society of Arts

My story begins in the year 1710 in the town of Hamilton where WILLIAM CULLEN was born. His father was an attorney who acted as factor to the Duke of Hamilton. William was the second son of a family of seven sons and two daughters, and the children received their early education at the local Grammar School, the forerunner of the present Hamilton Academy. At the age of 17, William attended some of the Arts Classes at Glasgow University, and shortly after this he decided to follow a medical career.

He was bound apprentice to a Mr John Paisley, a member of the Faculty of Physicians and Surgeons in Glasgow who had an extensive practice in the city. At that time, to serve an apprenticeship was almost the only way in which a knowledge of medicine could be acquired in Scotland. Professorships for teaching some of the branches of medicine *had* been established in some of our universities, but in none of them, except in Edinburgh, had a regular shool for teaching medicine been formed. In Glasgow, although a professorship of medicine had been instituted in 1714 and a professorship of botany and anatomy in 1719, it does not appear that the persons appointed to these offices had ever, during Cullen's time as a student, delivered any lectures upon the subjects they were supposed to teach.

Fortunately for Cullen, his master, John Paisley, was of a studious turn of mind, and had collected a large and valuable library of the medical books available at that time. The young apprentice was allowed to use this library freely and he made full use of this opportunity. It has been left on record by one of his friends of this period that Cullen was distinguished by a lively manner, by an uncommon quickness of apprehension and by a most retentive memory, qualities which were to remain with him throughout his whole career.

Towards the end of 1729, having completed his apprenticeship, Cullen went to London with a view to acquiring practical knowledge of his profession. He was fortunate in being appointed Surgeon to a merchant ship, the Captain of which was a far-out relation, Mr Cleland, whose family lived at Auchinlee near Shotts. The vessel was engaged in trading to the Spanish settlements in the West Indies and Cullen spent a year in this work. In 1730 he returned to London and attached himself to a Mr Murray, an Apothecary in Henrietta Street. Here he helped in the preparation of drugs and chemicals used in the practice of medicine at that time. In particular he became interested in the study of Materia Medica and read all the available books on the subject.

In 1731 Cullen's father died and, as his elder brother had died during his absence, on William devolved the duty of settling his father's affairs and arranging for the education of his younger brothers and sisters. At this time Captain Cleland invited him to come and reside with him at Shotts

and take charge of the health of his son who was suffering from a lingering illness. Cullen accepted the invitation and commenced his medical practice a few miles from his birthplace, Hamilton, and in the vicinity of the residences of many of the families of consequence in the County of Lanark. By a happy chance he met the Duke of Argyll who was paying a visit in the neighbourhood. The Duke was interested in Chemistry and, being in need of some apparatus, this was supplied by Dr Cullen. The Duke was much impressed by the young man's ability and this patronage from Scotland's leading peer was of advantage to Cullen, standing him in good stead at an important later stage in his career.

For the space of two years Cullen resided with Captain Cleland, leading a very busy life, visiting patients, preparing medicines for them, and reading all the medical books he could acquire.

On the death of a relative Dr Cullen succeeded to a small legacy and resolved to give up active practice for a time and devote his attention exclusively to his studies. He decided to go to Edinburgh where the foundations of a new and extended medical school had been laid some ten years before. Here there were available systematic lectures on the different branches of medicine, and here Cullen found among the students others like himself ardent in pursuit of medical knowledge. Some of them formed themselves into a "mutual improvement" society to meet weekly to read essays on subjects connected with their studies and to discuss and debate various topics of a professional character. This was the beginning in 1735 of the Royal Medical Society in whose Hall we meet this evening.

By 1736 Cullen was ready to return to Hamilton to take up his practice once more. He quickly made his mark as a reliable medical adviser, and his ledgers, which have been preserved, show that he was medical attendant to the Duke and Duchess of Hamilton and almost all of the county families in the district. It has been said of him that he became the friend and companion of every family he visited.

About this time Dr Cullen became acquanted with a young man, William Hunter, who was a student at Glasgow University. Hunter had intended to enter the Church but he changed his mind and determined to study medicine. He came to reside with Dr Cullen and stayed assisting him for two years. It was agreed that Hunter should go first to Edinburgh, and then to London to study medicine there. On his return to Hamilton a partnership was to be formed in which Hunter would undertake the surgical work while Cullen would be the physician.

As it happened, things did not work out this way. In London, Hunter was introduced to a Dr Douglas who was engaged in preparing an anatomical work on bones. Dr Douglas was looking for a young man of ability to help him as a dissector. Impressed by Hunter's abilities, he invited him to be his assistant. Hunter let Dr Cullen know about this and Dr Cullen readily gave his consent to the new arrangement, although it deprived him of Hunter's partnership to which he had been looking forward. Incidentally, William Hunter was to attain fame as an anatomist, and his bequest of his museum and library to Glasgow University has made his name a household word there—The Hunterian Museum.

Dr Cullen found himself another surgeon partner and in 1740 he took the degree of M.D. of Glasgow University. Shortly afterwards he married Anna Johnstone, daughter of a Kilbarchan minister. The marriage was a happy one and the couple were very popular in the district. There were seven sons and four daughters of the marriage.

In the midst of his busy practice in Hamilton Dr Cullen still found time to interest himself in civic affairs, and he became a magistrate.

But his genius and energy demanded a wider outlet and his ambition was to be a founder of a Medical School at Glasgow, similar to the schools of Leyden and Edinburgh. With this object in view, he removed to Glasgow in 1744.

In 1744 the Medical Faculty consisted of a Professor of Medicine and a Professor of Anatomy and Botany, but apparently these gentlemen did not deliver lectures on their subjects and it is difficult to find out exactly what duties they did carry out. Into this rather inert atmosphere came Cullen, and almost at once he was lecturing on Medicine in a semi-official capacity. Very soon he became convinced of the need for the teaching of CHEMISTRY within the University. He persuaded the authorities to spend £52 in establishing a suitable laboratory, and Cullen as lecturer was paid £20 per annum.

Cullen was an admirable teacher of chemistry. He inspired enthusiasm in his students and his classes increased in numbers each year. He took a deep personal interest in the welfare of his students and placed at their disposal his knowledge, his library and on many occasions his purse.

As well as lecturing on Chemistry, Cullen lectured also on Materia Medica, on Botany and on Physiology. One medical writer referred to him at this time as "a Medical Faculty in himself."

In addition to all this activity he conducted a busy medical practice so that his leisure moments must have been very few indeed. In 1751, when one of the "inert" professors resigned, Cullen was appointed to the Chair of Medicine and regularly delivered courses of lectures on the Theory and Practice of Medicine.

This busy life, with little leisure, left little time for private scientific studies and those considerations seem to have led to some of his friends proposing that he should remove to Edinburgh when a suitable opportunity should arise.

This oportunity was to come in 1755, but, before proceeding further, let us look at the subject of the other portrait, JOSEPH BLACK.

Joseph Black was born in France of Irish and Scottish forebears. His father, John Black, was a native of Belfast. He was a wine merchant in Bordeaux and he married a daughter of another wine merchant, Robert Gordon from Aberdeenshire, also settled in Bordeaux. (Incidentally, Mrs Black's sister was the mother of Mr Russel who became Professor of Natural Philosophy in Edinburgh. Their aunt was mother of ADAM FERGUSON who became Professor of Moral Philosophy in Edinburgh University, and in due course this family was to supply yet another Professor to the same University.)

John Black was well liked in Bordeaux. He was a cheerful man, contented, benevolent, liberal minded, with no ambitions to be very rich. Later, his son Joseph was to write of him that he was "industrious and prudent in business, of the strictest probity and honour, temperate and regular in his manner of life." Some of these characteristics were inherited by his famous son, and this family of eight sons and five daughters all did well for themselves in later life.

Their mother taught them to read English, and Joseph, who was born in 1728, was sent "home" to Belfast in 1740 to begin his education as a British subject. This he did at a Grammar School where he remained for six years. In 1746 he was sent to continue his studies at the College of Glasgow. Here he wanted to study physical science and in order to do so he chose the profession of Medicine within which his physical studies would have greatest scope. Now, about this time, Dr Cullen had been appointed lecturer in Chemistry in Glasgow. Hitherto the subject had been treated as a curious and, in some respects, useless art and Cullen, taking

a wide and comprehensive view, saw the unoccupied field of philosophical chemistry wide open before him. He was satisfied that with liberal enquiry and investigation the subject could be greatly improved.

It was young Joseph Black's good fortune to come under the influence of such a master and it is little wonder that the student almost at once showed a decided bent in favour of chemical investigation.

Dr Cullen was remarkable for the personal attention he paid to his students and he soon became aware of the aptitude shown by Black for scientific investigation. Very soon Black was assisting Cullen in original experiments and the results of some of his experiments were often publicly quoted in Cullen's lectures as sufficient authority for new facts brought to light.

The friendship between the two men grew rapidly during this period and indeed was never interrupted during their lifetime.

In 1751 Black departed for Edinburgh to complete his Medical Studies there and in 1754 he took his M.D. degree. For this degree each candidate had to present a thesis. At this time efforts were being made to find some solvent for urinary calculi. Many chemicals were tried, including lime water and various alkalies—some of a dangerous nature, and Black became interested in the problem.

He conceived the idea of trying to prepare an alkaline solvent of a mild type starting from Epsom salt, magnesium sulphate. From this substance he prepared a white powder which he called "magnesia alba"—magnesium carbonate. This magnesia alba effervesced with acids. When strongly heated, it changed to a white powder which did not effervesce with acid. Roasting caused it to lose seven-twelfths of its weight. Black showed that the property of effervescence with acids could be restored to the white powder by dissolving it in dilute sulphuric acid and adding pearl ashes—potassium carbonate—to the solution, thus obtaining the original magnesium carbonate.

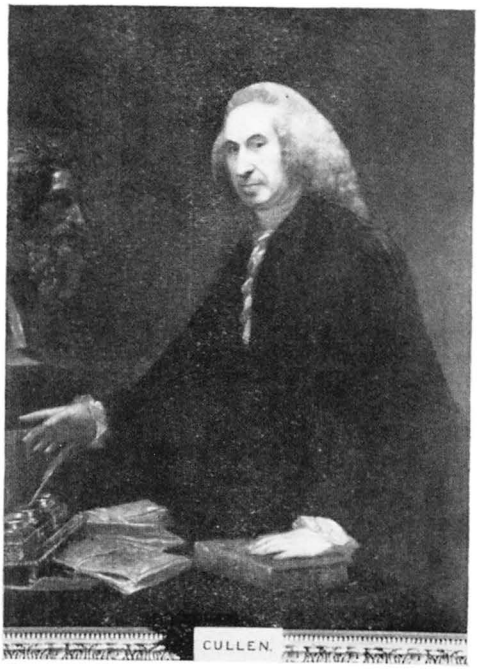
In this work Black did two important things:

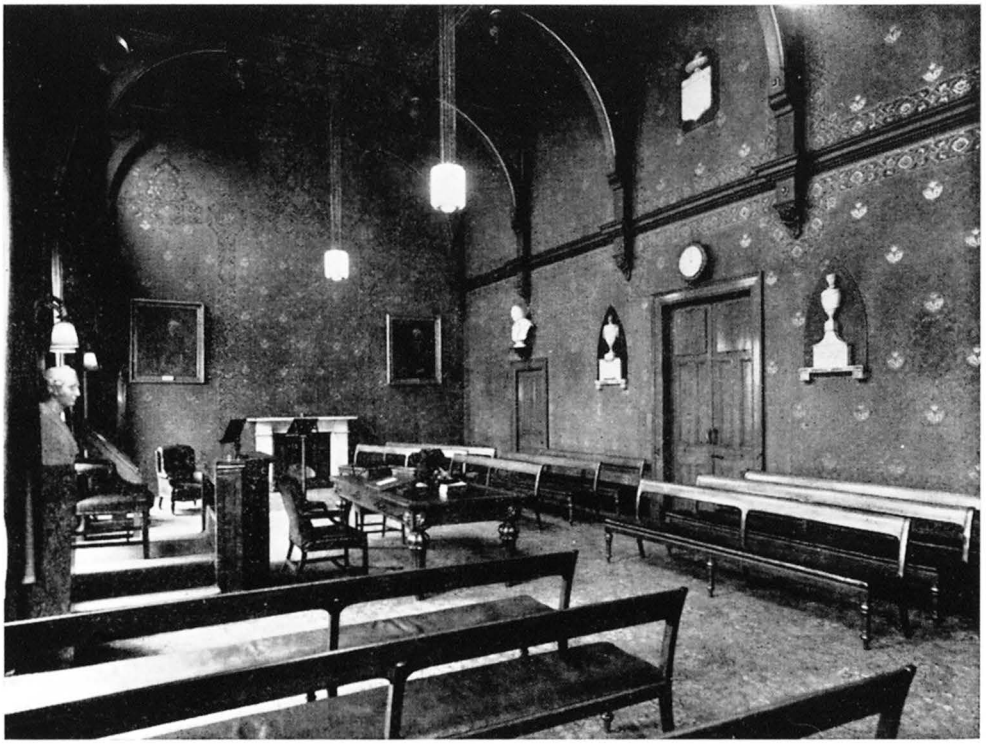
1. He dispelled the idea commonly held that the causticity of alkalies was due in some way to some igneous matter gained from fire—as in the preparation of quicklime from limestone; and
2. By the careful use of a balance, he showed that such calcinations were accompanied by a loss of weight due to some "fixed air" leaving the roasted material.

His "fixed air" was the gas we know as carbon dioxide and the results of his further experiments on magnesia alba, quicklime and other alkaline substances were presented in his thesis for the degree of M.D. One year later, these results were embodied in a paper which he read before the Philosophical Society of Edinburgh who published them in their Transactions. (It is possible to obtain a reprint of this famous paper, published by the Alembic Club in 1944.)

The reputation this work acquired for Black was the means in 1755 of placing him in the Chair of Chemistry at Glasgow vacated by his friend and former teacher, Dr Cullen, when he transferred to Edinburgh.

We return now to Dr Cullen leading his busy life in Glasgow. His lectures on Chemistry continued to attract ever increasing numbers, He did not repeat the same lectures year after year. Manuscript notes taken by students in consecutive years show how Dr Cullen was continually improving the treatment of the subject, incorporating new discoveries—





The Hall of the Royal Medical Society showing the two portraits (reproduced above) hanging on the South wall.

many of them due to original investigations of his own—and spreading among his students the information he had obtained from the latest chemical works as they became available.

His enthusiasm for original investigation infected many of his students with a similar desire and it is little wonder that his classes grew.

During this time he conducted a considerable correspondence with various gentlemen interested in the improvement of agricultural practices in Scotland. He gave several courses of lectures on agricultural chemistry and practised what he preached on a farm at Parkhead, near Glasgow, belonging to his brother. In the meantime his work in medicine continued with regular courses of lectures on the Theory of Medicine and an extensive private practice. One wonders when he found time to pursue any of his private investigations in the midst of all his duties and it was at this time that the opportunity of coming to Edinburgh presented itself.

In 1755 Dr Plummer, Professor of Chemistry in Edinburgh University, became seriously ill and incapable of continuing to lecture. In November of that year Dr Cullen was appointed Joint Professor of Chemistry during the life of Dr Plummer, with succession to the Chair after his death. Dr Plummer died in July of 1756 and Dr Cullen was elected sole Professor, a post which he was to hold for ten years.

Dr Plummer had confined his teaching of chemistry for the most part to Pharmacy, but Dr Cullen took a much wider view and gave the subject much more liberal treatment. He continued the practice he had started at Glasgow University of lecturing in the English language instead of in Latin, and from the start his classes were popular with the students and, as in Glasgow, the numbers attending increased year by year. His classes were attended not only by students of medicine, but by others who wished to study Chemistry as a philosophical subject. We find the idea growing that attendance at such lectures was part of a gentleman's cultural education and many notable personages of the day were members of Cullen's classes.

In 1757 Dr Cullen gave courses of lectures on Clinical Medicine in the Royal Infirmary. This was work for which his experience, habits of observation and scientific training peculiarly fitted him, and his popularity as a teacher and as a practical physician continued to grow. During this time he also had a successful medical practice.

As an example of his popularity and versatility, in 1760 he undertook, at the request of the students, to finish a course of lectures on Materia Medica on the death of the lecturer, Charles Alston. He delivered an entirely new course and notes taken by students during this course were later published in an unauthorised version in London. At a later date Dr Cullen tackled the monumental task of writing a comprehensive Treatise on Materia Medica which left out items of an absurd or revolting character of no medicinal value whatever—animal products such as goose fat, cobwebs, boiled toad dried and crushed to powder, toad spawn, ants (entire), ants' eggs, dried bees, snails, earthworms, powdered pearls, slaters, scorpions, viper's flesh, pieces of human skull, and mummy flesh. This new Treatise on Materia Medica was published in 1789 and continued for a long time to be the accepted guide to Scottish Medical students.

In 1766 Dr Cullen was elected to the Professorship of the Theory of Medicine, while a Dr John Gregory from Aberdeen was appointed Professor of the Practice of Physic and the two professors gave alternate courses on the Theory and Practice of Physic until Dr Gregory's death in 1773 when Dr Cullen was appointed sole Professor of Physic. He was then 63 years of age. Nevertheless he applied himself with energy to the duties of his new office and at the same time continued his consulting practice.

During his teaching life in Edinburgh Dr Cullen maintained a strong interest in the activities of the Royal Medcal Society. This Society, of which he had been a founder member during his student days still met regularly, having been granted the use of a room in the Royal Infirmary of the day, standing in Infirmary Street.

By 1770 need for more space for patients, growth of student members of the Society, and the steady growth of the library of medical books made it clear that the Society would benefit by having a building of its own. Here Dr Cullen's influence was invaluable. He was a leading member of a committee which opened a subscription list, and by 1775 sufficient funds were in hand for the Society to begin building a Hall on ground granted by the College of Surgeons near their Hall on the west side of Surgeons' Square adjoining the old High School.

The foundation Stone of the new Hall of the Royal Medical Society was laid on 21st April 1775 by Dr Cullen who was at that time the President of the Royal College of Physicians. The new building was ready for occupation

SACRED to *MEDICINE*
FOUNDED April 21st 1775
BY THO^{S} M^{c}INNES *MASON*

the following year 1776 and gave accommodation for weekly meetings, a large room for the library of medical books and collection of anatomical preparations, and a third large room suitable for demonstration experiments. There was even a cupola on the roof intended to be used as an observatory, although there is no record of it having been regularly used for this purpose. Dr Cullen's portrait, painted that year by David Martin for the Society, was hung in the main room, and it is that portrait which hangs in the Hall today.

In course of time, the Royal Medical Society had to give up their Hall as much-needed extensions to the Royal Infirmary swallowed up the buildings nearby—including the High School.

When the Hall was being demolished in 1853, the Foundation Stone laid by William Cullen was discovered. It contained a bottle in which was a silver medal and some remains of what may have been paper (which had not survived). The medal now forms the badge of office of the Junior President of the Royal Medical Society. The Foundation Stone was covered by a carved slab bearing the inscription: *Sacred to Medicine. Founded April 21st* 1775. *By Thos. McInnes Mason.* At a later date this stone was built into the wall of the staircase facing the entrance door of the present building in Melbourne Place.

About the year 1778 Dr Cullen purchased a small landed property called Ormiston Hill, in the parish of Kirknewton, eight miles from Edinburgh. Here he put into practice many of his ideas on agriculture. He cleared heathland, reclaimed, levelled, drained, covered gravel with new soil, and planted trees, shrubs, and flowers. The relics of some of this work are still to be traced at Ormiston Hill. In 1789 failing health caused him to relinquish his Chair, and a few months later he died at the age of 80.

Cullen's name is not associated with any epoch-making discovery. He was not a brilliant experimental investigator nor was he a great anatomist.

But he possessed qualities of clearness of perception, accuracy in observing, soundness of judgment and logical precision in reasoning, which gave him the power of distinguishing and selecting from a great mass of heterogeneous material only these facts which were constant and regular, and discarding those which were accidental, unusual or insufficiently substantiated. These qualities permeated all his teaching and exercised a great influence on all the students who passed through his classes. One has only to contrast the state of medical practice in the 1740's with that towards the close of the century to realise how powerful Cullen's influence had been.

When Dr Cullen resigned his Chair of Chemistry in Glasgow to come to Edinburgh in 1756, Dr Joseph Black was appointed to succeed him. He was 28 years of age and during the ten years of his work in Glasgow he maintained a large medical practice as well as delivering regular courses of lectures on Medicine and Chemistry. It was during this period that Black developed his ideas on latent heat and specific heat following a series of careful original researches which he planned and carried out. Black's interest in this work had been aroused when, as a student under Dr Cullen, he had taken part in experiments devised by Cullen to investigate the variations in temperature resulting from various chemical reactions. Dr Cullen had also noted that, when liquids evaporated, a cooling effect was produced and, when ice melted, heat was absorbed without temperature rising. Cullen had been unable to explain this phenomenon, but had directed Black's attention to the problem. In due course, Black's careful experiments, using the balance wherever possible, using thermometers as accurately scaled as was then possible, and with his flair for devising just the right type of experiment to give the required data, yielded results on which he based his theory of specific heats and latent heats. In December 1761 he showed that, when a quantity of water froze, it gave up an amount of heat equal to the amount absorbed (or rendered latent) during the melting.

It was not until three years later, in 1764, that he obtained satisfactory evidence regarding the heat latent in steam. The results of these experiments were given to Black's classes and were not published as a separate work until after Black's death.

This pioneer work on latent heat was to have another far-reaching result. In 1757 there arrived at the College of Glasgow a young instrument maker called James Watt. He and Dr Black became very friendly and on one occasion Watt had to repair a model of Newcomen's water-pumping steam engine, used for demonstrations to students in the Natural Philosophy Department. Black's work on the latent heat involved in making and condensing steam was known to Watt, and the great waste of heat in this engine led Watt to attempt a better method of condensation. Before long he had evolved the separate condenser, a new steam-tight packing and the steam-jacket to prevent loss of heat by radiation. During this period Black's encouragement and generous financial help gave Watt the incentive he needed to bring his steam engine to successful industrial application.

In due course, in 1766, the call came for Dr Black to go to Edinburgh to follow once again in the footsteps of his friend, Dr Cullen, as Professor of Chemistry.

In Edinburgh, Black devoted himself almost entirely to the teaching of Chemistry. During this period he carried out little or no research. He still maintained an interest in industrial applications including the attempts to manufacture alkalies, the bleaching industry, the manufacture of coal tar and a few others. He did not publish anything but continued to give his discoveries to his students in his lectures. Each year his lectures became plainer and more convincing, his experiments well chosen and admirable

for their simplicity and elegance. The number of students and others attending the lectures continued to grow.

Dr Black maintained a light medical practice among his friends throughout this period, but it is left on record that his health was not robust and that exertion easily tired him.

He was precise in speech, neat in dress and appearance, and skilful in manipulation of appartus. It is said that his lecture table was as spotless at the end of a lecture as when he began.

This love of orderliness and precision was one of his leading characteristics. Even his death in December 1799 took a calm, orderly form. He died while sitting at table with a cup of milk in his hand. He had set the cup down on his knees and held it steady with his hand. In this position he was found, with not a drop spilled, as if an experiment had been required to show the facility with which he departed this life.

In his will Black gave further evidence of his orderly precision of thought. He divided his quite considerable fortune into 10,000 equal shares and distributed it according to the degree in which each individual was the object of his care.

In assessing Joseph Black's contribution to science, one would stress two contributions of a fundamental nature:

One in Chemistry—the discovery and identification of fixed air (carbon dioxide) involving work which helped to elucidate the relationships between acids, alkalies and salts; and

One in Physics—the proper appreciation of the relationship between heat and temperature, specific heats of different materials and latent heat of ice and steam.

In two other directions Black's influence on science was far-reaching—his manner of lecturing and his way of inspiring his students. His large audiences testified to the excellence of the former and the work of James Watt in developing steam power is only one example of the latter.

Black's portrait, painted in 1787 by the same artist, David Martin, hangs side by side with that of his master, colleague and friend, Wm. Cullen, and it is fitting that it should be so, for it can be said that together they influenced to a marked degree the trend of scientific thought for generations after they had gone.

ACKNOWLEDGEMENTS

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Constitutional Jaundice

THE MEDICAL STUDENT'S DISEASE

By W. L. FORD, M.B., Ch.B.
House Physician, Western General Hospital.

The common physical sign of jaundice is recognised by yellow discoloration of the skin and sclerae and it is confirmed and measured by estimating the concentration of bilirubin in the serum. Jaundice is rightly regarded as a sign of serious disease but like many other physical signs and biochemical deviations it may be of no pathological significance whatsoever. In such circumstances, to establish with certainty that no serious disease is present and to manage the patient accordingly is clearly more important than to make a precise diagnosis in an incurable case.

The pathological causes of jaundice are classified, fundamentally, as.

1. **Overproduction jaundice**—due to excessive haemolysis.
2. **Hepatocellular jaundice**—due to defective biochemical processing of bilirubin by the parenchymal cells of the liver.
3. **Obstructive jaundice**—due to blockage of the bile duct system at any level from the finest intralobular canaliculi to the common bile duct leading to regurgitation of liver-processed bilirubin into the circulation.

A fourth class of jaundice is conceivable which may be termed constitutional jaundice and this can be redivided into three general types:

1. The congenital hyperbilirubinaemias which are genetically determined abnormalities of bilirubin metabolism. Further subdivisions are now well established.
2. Selective hepatic dysfunction in respect of bilirubin metabolism and excretion following viral hepatitis but without evidence of residual inflammation or diffuse hepatic fibrosis.
3. Subclinical jaundice of 1.0 mg./100 ml. to 1.6 mg./100 ml. may be explained in terms of the individual being placed in the "upper tail" of the normal distribution curve for serum bilirubin levels. The value of the upper limit of normal is highly controversial since the normal distribution curve suggests 1.6 mg./100 ml. as the extreme limit in healthy subjects although most values greater than 0.8 mg./100 ml. have a serious pathological significance.

In the past three years much attention has been devoted to the congenital hyperbilirubinaemias and to jaundice after acute hepatitis. This is a consequence of the recent clarification of the mechanism of bilirubin excretion and also of the development of tremendous activity in the fields of biochemical genetics and auto-immune disease.

THE CONGENITAL HYPERBILIRUBINAEMIAS

Benign familial jaundice was first recognised by Gilbert in 1900. His name is attached to the not uncommon syndrome which is estimated as

occurring in 1 in 300 (0.3%) of subjects of European stock although in practice detected in only a microscopic fraction of these. It is characterised by intermittent jaundice of up to 5 mg./100 ml. and occasionally higher. Biochemical findings are that the bilirubin is entirely unconjugated signifying that it has not been processed by the parenchymal cells. There is no evidence of increased haemolysis and the daily excretion of bile pigments is not raised. All liver function tests including BSP retention are within normal limits. The histology of the liver is normal. Investigation of the patient's family reveals at least one sibling or parent affected in 75% of cases.

Clinically the syndrome possesses certain extraordinary features. Although the condition is a genetically determined metabolic abnormality the vast majority of cases initially present between the ages of 14 and 30 years. Even more remarkable is that in several series more than half of the cases are medical personnel—nurses, residents and especially students.

While it is difficult to conceive that the same sort of genetic constitution makes for both interest in medicine and inability to conjugate bilirubin, a reasonable assumption is that the medical group is more likely to notice slight icterus and to meditate upon its significance. This implies that the great majority of cases of Gilbert's disease are undiscovered and this conclusion is borne out by researches which have sought symptomless jaundice in a healthy population.

In association with the bouts of jaundice certain subjective features are generally emphasised by the patient. The outstanding complaint is ready fatiguability. Gastro-intestinal symptoms—nausea, anorexia with loss of weight and particularly intolerance of dietary fat are next in frequency followed by vague abdominal discomfort often over the liver. The origin of these symptoms is wholly undecided. In favour of the psychosomatic explanation—that the symptoms are expressive of a fear of serious disease, perhaps aggravated by unwise medical advice is that precisely the same group of symptoms appears after acute viral hepatitis with complete objective recovery, the post-hepatitis syndrome as described by Sherlock. Here there is abundant evidence of a predominantly psychological origin.

However, in some cases of Gilbert's disease this typical symptom group is the reason for seeking advice before the icterus is detected and so a a biochemical basis for the fatiguability is not to be easily dismissed.

The marked periodicity of the jaundice and fatiguability is a most striking feature. Almost all of the mild cases have periods completely free of symptoms and of even latent jaundice. Each bout of jaundice lasts from about five to forty days and may occur spontaneously or be precipitated, according to the patients by physical exhaustion, emotional stress or over-indulgence in alcohol. Laboratory experiments have confirmed this effect of alcohol but have been inconclusive with respect to the effect of strenuous exercise.

THE AETIOLOGY OF GILBERT'S DISEASE

Recently much more information about the fundamental mechanisms of jaundice has become available and into this framework the pathogenesis of Gilbert's disease fits most beautifully.

To summarise, bilirubin is formed in the reticulo-endothelial system by the degradation of haemoglobin in a series of reactions involving the removal of the iron and the protein globin and the oxidative disruption of the porphyrin ring. It is quite wrong to assume that haemoglobin is converted quantitatively to bilirubin since it is known that some bilirubin is

derived from extraerythrocytic sources and also a variable proportion of haemoglobin is degraded along alternative pathways.

Bilirubin is transported to the parenchymal cells of the liver loosely bound to the plasm albumen. In these cells the all-important conjugation with glucuronic acid occurs as follows:

Blirubin + uridinediphosphoglucuronic acid = bilirubin glucuronide + uridinediphosphate.

This reaction is entirely dependent on the enzyme glucuronyl transferase and it is lack of this enzyme which is responsible for moderate and severe Gilbert's disease.

In the bile appears a mixture of the mono- and di-glucuronides of bilirubin. This modification of the molecule renders it much more water soluble and, at the same time, less lipophilic. Only in this form can bilirubin be excreted into the bile. This change is the basis of the conversion of the van den Berg reaction from indirect to direct and it also explains why bile does not appear in the urine with haemolytic jaundice as it does with obstructive jaundice since only the water soluble conjugated form is excreted by the kidney. It further explains the occurrence of kernicterus (bile staining of the basal nuclei in infants giving permanent neurological deficits, unless rapidly fatal) in haemolytic but not obstructive jaundice because only the lipophilic, unconjugated bilirubin reaches the site at which this damage may occur.

Now in cases of Gilbert's disease with a bilirubin level of above 5 mg./100 ml. a deficiency of glucuronyl transferase activity in liver biopsy specimens has been demonstrated by a brilliant in vitro method developed by Arias and London in New York. Furthermore the degree of enzymatic defect is roughly correlated with the bilirubin level and indeed the syndrome shows a continuous spectrum extending from the very rare cases with no detectable transferase activity and a serum bilirubin level of 15-20 mg./100 ml. However the majority of cases with a serum bilirubin level which never exceeds 5 mg./100 ml. have no detectable enzymatic deficiency and here the fault is widely supposed to lie in a reduced capacity of the parenchymal cells to take up bilirubin from the plasma. Another possibility is difficulty in breaking the albumen-bilirubin linkage.

THE GENETIC SIGNIFICANCE OF GILBERT'S DISEASE

These recent developments assume added significance in the great vista of human biochemical genetics. Several inborn errors of metabolism exist which are neither truly dominant nor recessive but in which there are important quantitative and qualitative differences between the homozygous and heterozygous state. A fine example is provided by the gene of sickle-cell anaemia. The homozygotes develop haemolytic anaemia because the majority of their haemoglobin is of the abnormal sickle-cell type. Heterozygotes on the other hand show the sickling phenomenon but do not develop anaemia because more than half of their haemoglobin is of the normal adult type and their condition is not biologically disadvantageous.

Now in 1952 Crigler and Naajar described a new syndrome occurring in seven infants from three different but related families. All seven infants had developed deep jaundice after birth with serum bilirubin levels of 10 to 44 mg./100 ml. of which nearly all were unconjugated. There was no excessive haemolysis or significant hepatic pathology in any case. In fact the condition is well described as an extreme infantile form of Gilbert's disease. Five infants developed kernicterus and soon died. Extraordinarily

the other two have survived well into childhood showing no neurological abnormalities and are apparently healthy apart from deep jaundice.

The really interesting feature, however, is that all these children had consanguineous parents which signified that a recessive or homozygous state is responsible. The gene which in a double dose produces a complete failure to conjugate bilirubin as in the Crigler-Naajar syndrome may be identical with the gene which in heterozygous individuals shows variable degrees of dominance resulting in the continuous spectrum of severity notably found in Gilbert's disease. The factors responsible for this variation of dominance, a phenomenon seen in many other genetically determined features, may involve the influence of other genes or may depend on the nature of the external or internal environment. In fact this is an outstanding problem in fundamental biology.

THE OTHER CONGENITAL HYPERBILIRUBINAEMIAS

These new ideas have resulted from improved laboratory techniques. At the same time epidemiological methods have borne fruit by revealing two variants of classical Gilbert's disease which are also classifiable as congenital hyperbilirubinaemias.

The Dubin-Johnston syndrome (1954) is much less common than Gilbert's disease and has the following distinctive features:

1. Jaundice is due to a mixture of conjugated and unconjugated bilirubin. In consequence bilirubinuria is the rule.
2. The liver is also unable to excrete certain dyes including BSP and the media used for cholecystography leading to a non-visualising gall-bladder.
3. There is a very prominent granular black pigment in the parenchymal cells which renders the liver black macroscopically. Its nature has excited much interest for it appears to be a lipochrome—a "wear and tear" pigment—and is definitely not iron-containing.

Like true Gilbert's disease this syndrome is familial, it is associated with fatiguability and it has an excellent prognosis. However it is more likely to be confused with obstructive jaundice because of bilirubinuria and the presence of conjugated bilirubin in the serum. An unnecessary explorative laparotomy is the typical consequence. Clearly a widespread disturbance of hepatic function is involved which is still compatible with normal health and longevity.

Very recently still another variety has been reported which is identical with true Gilbert's disease except that, as in the Dubin-Johnston syndrome, the excess of bilirubin in the plasma is largely conjugated and there is retention of BSP.

Post-hepatitic Jaundice

Acute infective hepatitis is usually followed by complete clinical and histological recovery but there exists several possible sequelae which may begin at once or be manifest only after a variable interval. Of these the most important is diffuse hepatic fibrosis developing into portal cirrhosis. Alternatively persistent or recurrent hepatitis is found which is typified by round cell infiltration of the portal tracts and which produces persistently abnormal liver function tests. The third important consequence is the post-hepatitis syndrome—the diagnosis when the symptoms of the acute attack fail to abate yet liver function tests and liver biopsy reveal no abnormality. Two physical signs are invariably present—mild, fluctuant

jaundice and an easily palpable liver. The latter occurs without hepatic enlargement in some introspective patients who have developed the knack of depressing their diaphragm to an extreme degree thus showing off their lower hepatic border.

Although most of the features of the post-hepatitis syndrome are certainly psychogenic there is little doubt that the virus of infective hepatitis can somehow modify the enzyme systems of the liver to bring about a selective dysfunction in respect of bilirubin metabolism. Consideration of these uncommon cases may shed light on the really important problem of infective hepatitis—why persistent inflammation and fibrosis occur. The old concept that the virus survives in the liver cells, flaring up intermittently over a long period, has gone out of fashion and evidence for the auto-immune theory has accumulated but has still a long way to go. Briefly the theory envisages that during the acute phase of hepatitis the protein components of the liver cells are somehow modified so that they are not recognised by the antibody producing mechanism as "self." Appropriate antibodies are produced over a long period and these have an adverse effect on healthy liver cells. Clearly a self-perpetuating type of situation may arise.

Most points in favour of the auto-immune theory are found in a peculiar type of post-hepatitic cirrhosis (lupoid hepatitis) occurring in young women and having several features in common with systemic lupus erythematosus. These patients have a complement-fixing antibody which reacts with an antigen consisting of normal human liver cells. Also suggestive of an auto-immune mechanism is the very high gamma-globulin level and the frequent clinical response to cortisone.

The crux of this problem is how does a virus modify the proteins of the liver cells to produce alterations in their enzymatic activity and antigenic properties.

Mode of Presentation and Differential Diagnosis of Constitutional Jaundice

The mode of presentation deserves particular emphasis. The majority of cases have a typical attack of infective hepatitis. Months later they are investigated because of persistent jaundice which is suspected to be due to serious liver disease. If the thorough investigation, which should certainly be undertaken, reveals no other abnormality then the alternatives are that the patient has Gilbert's disease, to which the hepatitis was incidental, or that he has an acquired hepatic dysfunction. In a number of cases the search for latent jaundice in the parents and siblings proves negative and then the doubt always remains but the distinction is academic since in both cases there is no treatment and the prognosis is alike excellent.

Since constitutional jaundice is not really common and other cases of jaundice are very common the diagnosis is only tenable after the most rigorous investigations to exclude a less benign cause. Differential diagnosis is from the following conditlons:

1. The haemolytic anaemias have in common with Gilbert's disease mild intermittent icterus, often a familial incidence and normal liver function tests. However they are easily excluded by finding normal values for the haemoglobin level, the reticulocyte count and the osmotic fragility test of erythrocytes.
2. Obstructive jaundice may be diagnosed in cases of Dubin-Johnston syndrome. In the latter the jaundice is intermittent over a long period and the level of serum alkaline phosphatase is usually within

the normal range. Liver biopsy is essential for the diagnosis of Dubin-Johnston syndrome yielding laparotomy unnecessary.

3. Persistent mild hepatitis and well compensated diffuse hepatic fibrosis are, of course, the most likely sources of confusion. The comparatively safe procedure of liver biopsy is always necessary when doubt exists, and of the biochemical tests the thymol turbidity test, the E.S.R. and the BSP excretion test are the most sensitive indices of serious disease. The ACTH test produces a lowering of the bilirubin level in some cases of Gilbert's disease and in obstructive jaundice as well as in active hepatitis for which it was once believed to be specific.
4. Chronic gastro-intestinal disease, particularly chronic duodenal ulcer, may produce mild jaundice through some unknown mechanism. This must be carefully excluded in all relevant cases.

Conclusions

Most cases of congenital hyperbilirubinaemia and harmless post-hepatitic icterus are misdiagnosed for many months or years as chronic hepatitis. This is particularly likely if there has been an initial episode of infective hepatitis. The object of this article is to emphasise the necessity for properly investigating these cases. A brief glance at the literature of this subject yields two most striking impressions. Firstly, all of the recent series have come from Scandinavia and the Eastern United States where the standards of medicine are sufficiently advanced to permit these advanced diagnoses. Secondly, it is grievous that such a high proportion of these intelligent, healthy, young people are consigned to pseudo-hepatic crippledom, a characteristic organ neurosis, which may be life long. This is because of the attitude of the physician who is under the impression that he is dealing with a case of chronic hepatitis. The hapless victim is daily reminded that "he has only one liver" or else that he must "put his liver first now." Even the threat of the dreadful cirrhosis may be used to bully the victim into submission and rest.

In the practice of medicine it behoves us that if we cannot do a patient any good then at least we should at all costs avoid doing him any harm. When dealing with the benign causes of jaundice only the highest diagnostic skill can avoid doing genuine harm in the form of prolonged incarceration, albeit in bed, an unnecessary surgical exploration or an iatrogenic psychoneurosis.

Sir James Mackenzie

AN INTRODUCTION TO CARDIOLOGY

By W. S. UTTLEY

Based on a Dissertation read before the Royal Medical Society on Friday, 21st October 1960

Picture, if you can, a dark grim valley of smoke and chimneys, outlined by a ring of light appearing over the hills. In the streets a clatter of horses' hooves and wooden clogs. In a dingy room the oft repeated scene of a girl in labour surrounded by old women in shawls. The ubiquitous, anxious husband is being solemnly reassured by the confident young doctor newly fledged from Edinburgh University. Her grip tightens on his hand as another instalment of pain is to be paid. Suddenly it is limp and tranquillity passes over her sweating brow. Sudden cardiac failure—the year 1880—and the realisation by that doctor in Burnley, James Mackenzie, that nothing was known about cardiac disease which might have warned him of such an outcome.

Mackenzie was born in 1853, the second son of Robert Mackenzie, a farmer of Scone, near Perth. Here he was educated by that notorious system in which the honours fall to those who remember rather than to those who think, and inevitably he failed to distinguish himself. Leaving school at the age of fifteen he became apprenticed to a local chemist. He apparently soon forgot his experience of educational systems since he entered Edinburgh University Medical School when his apprenticeship was completed. His was a frugal existence, common to many other students at that time. He lodged with a joiner and his family and shared a room with his brother, living off oatmeal, butter and scones from their own farm. Preclinical classes were a repeat in kind of school at Perth—didactic and depressing. Clinical years however brought delight, three gold medals and a house job. Yet his experiences were stored for an attack against that very system of medical education, to be launched many years later.

Following his term of residency in the Infirmary, Mackenzie was invited to an assistantship in the practice of Dr William Briggs and Dr John Brown in Burnley. Now he found himself in a town much removed from the academic atmosphere of Edinburgh. Rough and busy, grim yet vital, the only standard was the standard of achievement. The problems of this busy practice which immediately presented themselves were the same as those we have to face today. In the majority of patients presenting themselves for the first time a firm diagnosis was impossible. Moreover the question was not so much "What exactly is wrong with me?" but rather "How long will it be before I'm well?" or "What is going to happen to me?" The purchase of a large medical encyclopaedia, and the perusal of text-books and notes did not supply the required answers. His senior partners might have been able to produce some of the answers from the wealth of their experience, but Mackenzie had to admit to himself that he did not understand the mechanism or meaning of a single symptom.

Accordingly, within a few years of entering practice Mackenzie had defined his aims:

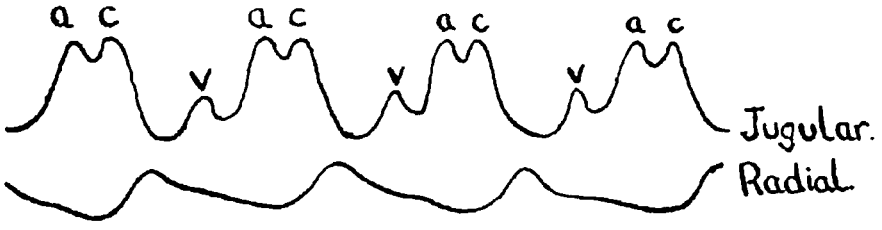
(1) to understand the mechanisms of symptoms;
(2) to understand their prognostic significance.

To effect this he began to make note of every sign and symptom detectable in every case under his care, and to "wait and see" what would be the outcome. These words "wait and see" are to be emphasised as they form one of the main pillars of his thought. The sheer magnitude of this task soon became apparent, and obviously it had to be limited to only certain groups of symptoms. It was incidents like that which is recorded in the introduction to this article, which directed his endeavours into the field of cardiac disorders. He determined to study the common symptoms of fatigue, dyspnoea and pain and to learn their significance by noting their clinical course over a number of years.

The frequent occurrence of irregularity in rate and rhythm of the heart in pregnancy soon attracted his attention. Searching the medical literature of that time he found such statements as "her heart became irregular and she sank and died," yet nowhere did he find any information as to the real nature or meaning of this sign. Many women in pregnancy developed pulse irregularity and delivered their babies normally, so why should others develop heart failure?

Thus began the most classical example of general practitioner research of all time. By employing the Dudgeon Sphygmograph to record the radial pulse, Mackenzie soon realised that there were several types of irregular heart action, but was unable at first to differentiate them. Then he remembered the obscure waves which could be seen in the necks of many patients which were explained as "backwash from the heart," and he attempted to record them.

Once having obtained a recording of these waves, by means of a re-invention of Marey's tambour, the difficulty lay in their interpretation. It was evidently necessary to obtain recordings of some standard movement taken at the same time in order to recognise the relationship of the waves in the jugular vein to the movements of the heart. Mackenzie made a tambour out of a pill box and added this onto the Dudgeon Sphygmograph, thus employing the radial pulse as standard. Two straws were used to trace the jugular and radial pulses on the same piece of smoked paper, and this simple instrument, the so-called clinical polygraph, was used in



domiciliary practice by its inventor for many years. Later this prototype was replaced by a more convenient machine, the ish-polygraph whereby long continuous tracings could be taken on roll paper. This machine was to enjoy widespread use until the introduction of the E.C.G.

A standard tracing consists of the three waves of the jugular pulse (a, c and v), and the radial pulse.

From such tracings Mackenzie correctly deduced the "a" wave to be

due to right atrial systole, the "c" wave to be due to left ventricular systole via the carotid pulse, and the "v" wave to be due to the termination of right ventricular systole. Thus he could now to some extent observe the behaviour of three of the four chambers of the heart, and having obtained a means of differentiating the irregularities, he collected a large number of cases. An analysis of such factors as wave-type, age of the patient and their actual state of health showed that the vast majority fell into one of three distinct groups.

The first form occurred mainly in young persons. All four chambers of the heart participated and the irregularity varied with respiration. The most important observation of all was that the patients remained fit and well. MacKenzie called this the "Youthful Type" of irregularity; we know it now as sinus arrhythmia.

Here was one of his most outstanding advances since, in their ignorance, the consultants of the day created a cardiac cripple out of any healthy child who happened to exhibit this normal and harmless feature.

The second form was that in which the ventricles contracted prematurely, sometimes with and sometimes without initiation by the atria. These premature beats could occur with varying frequency and if they alternated with a normal beat pulsus bigeminus was created. They occurred seldom in the young, occasionally in the middle-aged and frequently in the elderly. To these "extra systoles" was applied the name "Adult Type of Irregularity," and again the pulse was recognised as being of itself harmless.

The third form was found mostly in adults showing distinct evidence of heart failure. The radial pulse is completely irregular in time and force, the "a" wave is missing from the jugular pulse and the vein distends during ventricular systole instead of becoming flaccid.

The reasons for this phenomenon were not immediately apparent but Mackenzie was able by his observations to relate it to a bad prognosis. He therefore at first named it the "Dangerous Type of Irregularity" and described the jugular pulse as being of the ventricular type rather than the normal auricular form. Records further revealed this type to occur most frequently in old people and those patients giving a previous history of rheumatic fever. It was also found to occur in at least 80% of patients suffering from heart failure with the signs of oedema and enlarged liver. As a consequence he gave special attention to those patients in whom the irregularity might be expected to occur, and sure enough one such woman suddenly developed gross dyspnoea with a rapid and irregular pulse.

This classical case was first seen at the age of 31 in 1880, giving a history of rheumatic fever nine years previously, and a pre-systolic murmur was detected. Further attacks of rheumatic fever were experienced, and by 1892 symptoms of angina pectoris were present and an enlarged liver could be felt. Thus in 1898 the onset of the "dangerous" type of irregularity was observed coincident with the disappearance of the pre-systolic murmur. Mackenzie considered that this state was due to the absence of normal atrial systole and because of the post-mortem evidence of dilated and thin walled atria he called it atrial paralysis. The modern term for this state is, of course, atrial fibrillation.

Having obtained data sufficient to recognise the condition as a distinct clinical entity, Mackenzie set about studying its effects on the efficiency of the heart. At the turn of the century the universal theory which was held with regard to cardiac failure was that of "back pressure." By this was meant that valvular damage and incompetence allowed blood to be forced back into the lungs by a contraction of the left ventricle, and ultimately through the right side of the heart into the liver and the great

veins. He noted from his cases that signs of failure followed soon after the onset of fibrillation, and in one particular patient, periodic attacks of fibrillation were coincident with the onset of failure on each occasion. Paradoxically another patient also suffering from similar periodic attacks remained well at all times. However, his heart rate remained about sixty whether the atria were active or not. This suggested that the excessive rate in other cases caused ventricular exhaustion or inefficiency. Thus in 1899 came that flash of inspiration which is now one of the most fundamental facts of medicine. That is . . . *the power of the heart depends on its efficiency and the unimpeded action of its muscular walls.*

Furthermore these observations gave the basis for a sound prognosis to fibrillation, depending on the heart rate, and again a rational treatment could be introduced i.e. any drug which would reduce the ventricular rate to about 80 beats per minute. Mackenzie employed digitalis and tried to find in each case just how much of the drug was required to keep the heart in check. The success of these measures served to establish the use of digitalis in chronic heart failure whereas previously it had only been employed in acute cases.

Finally the true significance of the much feared pre-systolic murmur of post-rheumatic cases could now be judged, not by the severity of the murmur, but by the response of the heart to effort i.e. by observing its efficiency. Mackenzie once said "For want of a guiding principle I spent years and years in muck-raking." In fact the answer to his original quest

of how to foretell danger in cardiac cases, lies not in the detection of an irregularity or murmur *per se*, but in the study of the RESPONSE OF THE HEART TO EFFORT, as indicated by the presence or absence of breathlessness or pain.

This was the "guiding principle," and serves to complete the triad of Mackenzie's philosophy regarding the study of symptoms:

(1) It is necessary to detect the mechanisms of symptoms.
(2) By recording symptoms wait and see their ultimate prognosis.
(3) Try to find a guiding principle.

What of the man himself? He remained in Burnley until 1907, a period of some twenty-seven years and built up a considerable reputation in local medicine. Scottish in appearance, he had a kindly, bearded face, and was well loved if not completely understood by his patients. The novelty and mystery of his polygraph must have savoured of the occult to their simple souls, yet they could well realise his early poverty from the makeshift leather patches sticking to the soles of his shoes. With the publication of his book *The Study of the Pulse* in 1902, came recognition from abroad, mainly from Germany and America. Visitors such as Osler, Ritchie and Wenckebach went to the Burnley practice, but his teachings remained unknown to the leaders of medicine in the South. So, at the age of fifty-four, Mackenzie abandoned his safe and honoured position in the North to impose his views on a reluctant audience in London. His first year there was lean and expenses were high, but during this time he completed the writing of the book destined to bring success. Published in 1908 *Diseases of the Heart* was not merely a good account of disease but an exposition of disorders hitherto unrecognised by medical science, which was accompanied by the proof of instrumental and clinical verification.

Prosperity in practice and profession followed rapidly: a concultancy and department of cardiology at the London Hospital, election to Fellowship of the London College of Physicians and ultimately a knighthood. But insidiously the man was being stifled. He was now regarded as the father of the new school of cardiology, the Neo-cardiologists or Mackenzie School. This latter was regarded as the epitome of scientific observation, and it soon became apparent that all this accord was to his polygraph rather than to his methods. Cardiology might well be split into certain eras, those of the murmur, the polygraph and irregularity, the E.C.G. and infarction, and now maybe the haemodynamic era. Each has its own masters and when thinking of Mackenzie many could see no further than the polygraph. Here is the man who voyages to fresh continents in a new kind of boat, and on his return is hailed only as the inventor of the boat.

At the end of World War I, at the age of sixty-five, he disappeared from London almost as silently as he had arrived and returned to general practice in St Andrews. Space forbids a full description of his work there, or even of his other investigations in London and Burnley. These included investigations into the nature of pain, especially that experienced in angina pectoris from which he himself died in 1925. He also studied the treatment of soldier's heart in conjunction with Thomas Lewis, and his final observations in symptomatology resulted in an attempt to formulate certain basic laws in the book of *The Basis of Vital Activity*.

What now can be learned and gained from the study of this man's life? A philosopher might well think that his methods of work are better than his results. Of general practice Mackenzie wrote "Who is the man that has the opportunity to see the early phases of disease and the circumstances which favour its onset? There is only one such person and that is the

general practitioner." Professor John Hay of Liverpool wrote of Mackenzie, "He is the great example of what can be done and accomplished, not in spite of the burdens of general practice, but in the virtue of the very opportunities afforded by such a position."

It can be seen that these opportunities, and the need to approach them in the Mackenzie manner, are still of vital importance despite the undoubtedly changing face of medical practice. One only has to remember the investigations of Dr Pickles in Wenslydale, or the recent clinical trials carried out in several practices to find support for this. Reduction in practitioner load, availability of the services of a statistician and more widespread facilities for general practice investigations might be required before anything of any great consequence can be done in this field. Yet the truth remains that if we are to achieve the twin goals of finding the early symptomatology of disease and earlier diagnoses, such an approach is necessary.

Sir James Mackenzie placed cardiology on a firm and accurate foundation. He left a demand for the study of symptoms and the elucidation of their prognostic significance; and a study of his principles would lead to the reappraisal of much that has passed for progress in the last thirty-five years.

Retrospect 223rd Session

By J. G. CLARK, M.B., Ch.B.

Senior President of the Royal Medical Society 1959-60.

The 223rd session may one day be regarded as the beginning of an era in the life of the Society. It has been a time when considerable interest has grown among members in the business and welfare of the Society, for which we owe not a little to the office-bearers of the past two or three sessions who by their ardour have saved us from a bed of apathy.

We have concerned ourselves with the position of the Society in the University, and have found that our opinions and our activities as a body do not have the same import as would be desirable. Gone are the days when we could do battle with the managers of the Royal Infirmary for the betterment of teaching conditions for undergraduates.

We have considered the usefulness of the Society to medical undergraduates and have remarked on the reasons which may be keeping so large a proportion of them, including many of Edinburgh's most promising pupils, from partaking of such wealth as may be found in the Royal Medical Society. It is plain to see, if we think about it, that it is not only they who lose, but we ourselves.

The result of this is the Questionnaire, carefully prepared by a committee of four, which was distributed among all present members of the Society and as many recent members as could be traced. It may be argued against such a questionnaire that it denotes an introspective attitude which is not in the best interests of the Society. Any introspection, however, is purely the result of a real concern about the effect of the Society on the world around it, and its value to members. We hope, therefore, that this investigation will be taken most seriously, and that the report of the committee, presented in the autumn, be considered very fully, for in this way the Society may be greatly benefited.

A full and interesting programme kept our attention during the session, beginning with Professor McMichael's historical survey of research in medicine. At the joint meeting with the Royal Scottish Society of Arts We heard Professor Polson, of Leeds, on the "art" of Forensic investigation. It is becoming increasingly difficult, in these days, when the laboratory report begins to usurp the patient's history, to find a situation where medicine may be called an art. The Artists, however, were not disappointed by Professor Polson.

The Annual Dinner was held once again in the College of Surgeons, where Sir Stanley Davidson was the guest of honour. As a social occasion the Dinner was a success, and as a financial accomplishment it shone no less brightly. All credit is due to Dr Nigel Malcolm-Smith and his committee, who toiled ceaselessly with correspondence. His modesty was only exceeded by his surprise when the bank balance turned in our favour.

Other items in the round of winter activities included a visit to Saughton Prison, where work on the rehabilitation of the convicted was shown, and, of course, the perennial visit to a brewery where, to use a popular phrase,

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"A very good all was had by Time." Mr Ian McLaren conducted a most useful clinical evening in the Royal Infirmary, and a film show was arranged but did not prove popular. The Annual Dinner Dance was not held as usual in the Carlton Hotel and our sympathies were with the dinner-dance committee when the alternative accommodation was found not to be up to their expectations.

The Society's library continues to flourish and towards the end of next session the recataloguing should be virtually completed, thus making our fascinating collection of books readily available to the reader. Also we hope that the priceless, the valuable and the useful books may then more easily be separated from the worthless, the valueless and the useless, which seem to be there in the same quantity. Many apparently useless old books do, nonetheless, have a great value to the reader, "For herein may he weave a cushion of velvet upon the oak chair of his medical knowledge." The haematologist may well benefit from such a work as "The Functions of the Spleen, with sundry observations on the Anatomy of the Elephant," written over a century ago.

"The Society's Library," by Dr J. J. C. Cormack, constitutes one of the greatest honours done to the Society in recent years, in that it has been printed in the Bulletin of the Medical Library Association of the U.S.A. The effect of this upon the Society, we feel sure, will be far-reaching, and we congratulate Dr Cormack on his achievement. Reprints from the Bulletin are available from *Librorum Custos*.

Interest in the Society continues the world over, and in the last session we have had enquiries concerning former members from London, Paris, Boston and Philadelphia. We trust that present members will not fail to do honour to their great heritage.

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