MAY, 1947

THE ULSTER MEDICAL JOURNAL

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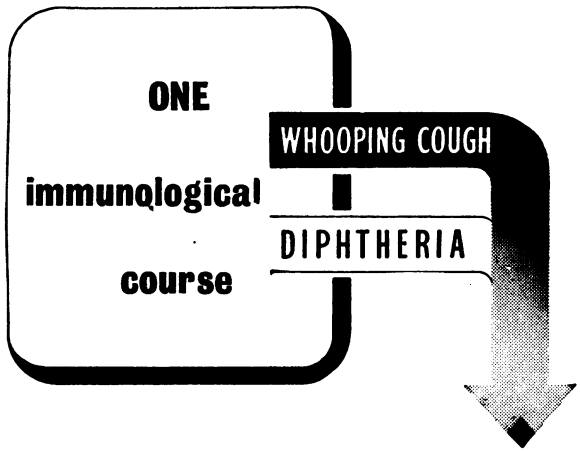

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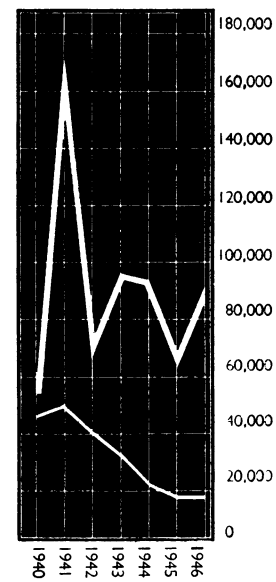

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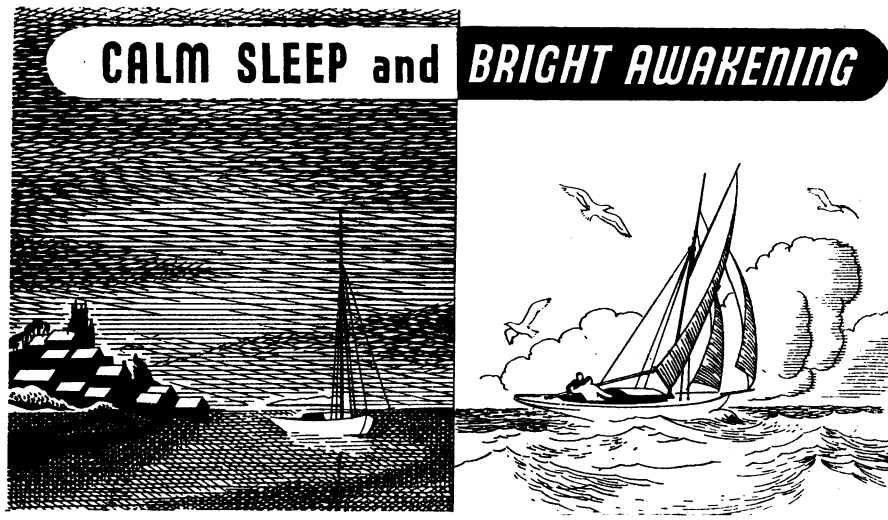

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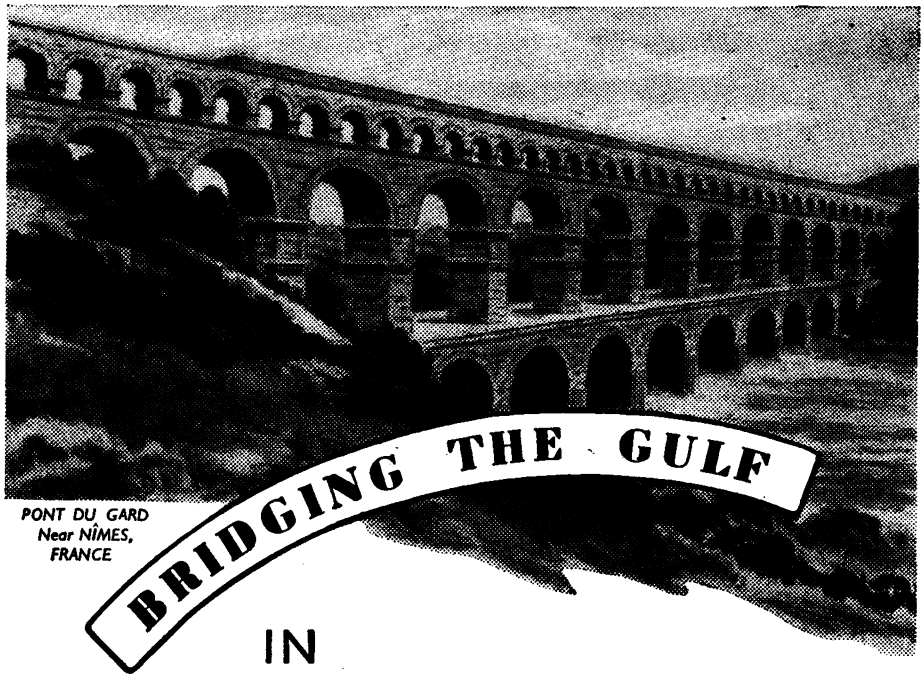

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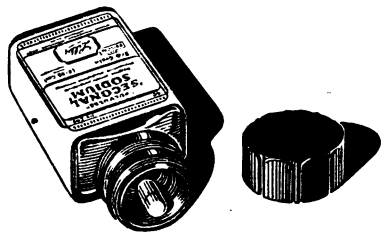

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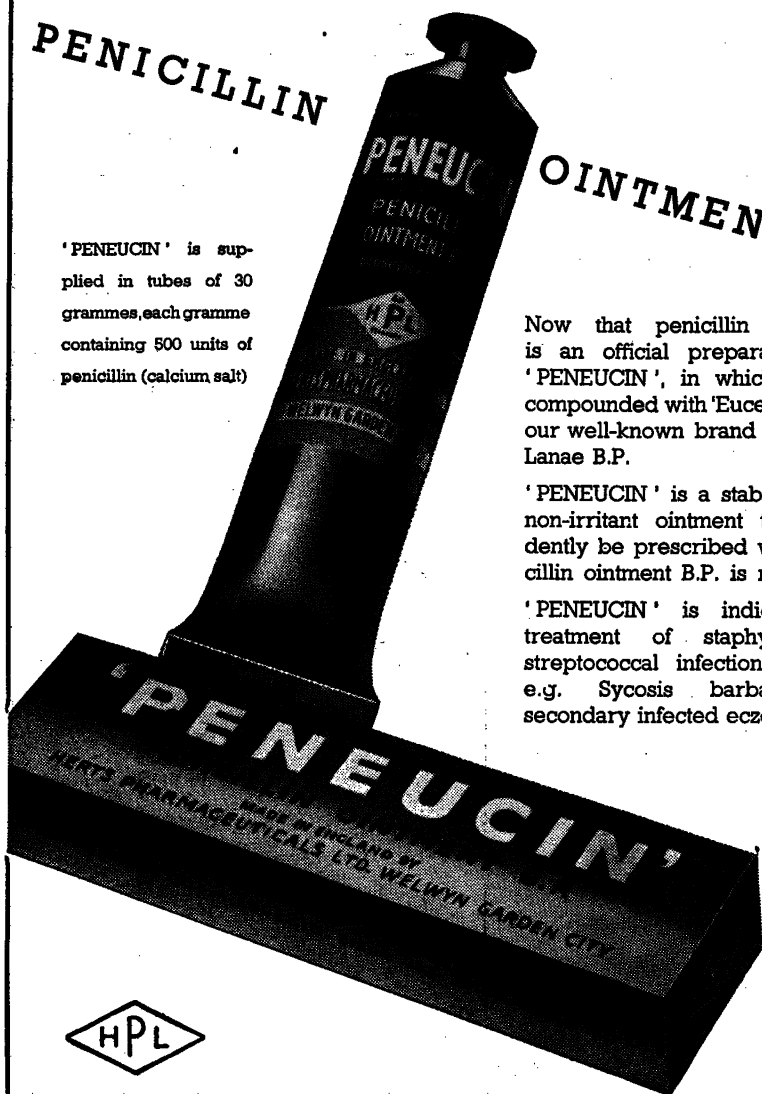

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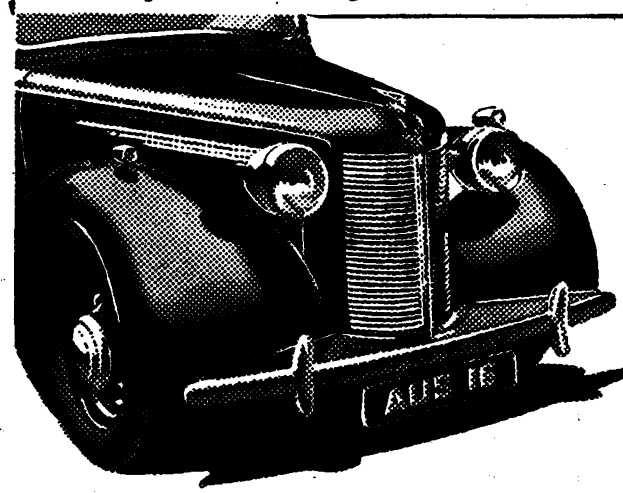

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THE
ULSTER MEDICAL JOURNAL

PUBLISHED ON BEHALF OF THE ULSTER MEDICAL SOCIETY

Vol. XVI 1st MAY, 1947 No. 1

Ophthalmology: Advances in Treatment, with Special Reference to Penicillin

By J. R. WHEELER, M.B., F.R.C.S.EDIN.

OF all the ailments which the human being is called upon to suffer in advancing years, perhaps loss of vision is the worst.

The commonest cause of this visual defect is cataract— an opacification of the lens which varies in degree from a slight opacity, which prevents one seeing small print clearly, to total opacification, when light alone will penetrate through to the retina.

Up to a quarter of a century ago few surgeons would operate on a case of cataract until it was mature, i.e., lens completely opaque.

The length of the period from the partial incapacity of the immature cataract to the total incapacity of the mature cataract is very variable—months to years.

If one eye only is involved, most conservative surgeons will wait until the cataract is approaching maturity before operating; but frequently the condition is bilateral, and it is these cases which are so greatly incapacitated.

To-day, thanks to improved technique, this period of incapacity can be eliminated completely, as we judge the correct time to operate is when the patient is no longer able to carry out his normal occupation.

The intracapsular extraction of the lens is the operation of choice for the immature cataract. In this operation the lens is removed intact in its capsule after rupturing the suspensory ligament.

The safer operation for cases of mature cataract, especially in the very elderly and the young adults, is still the extracapsular extraction of the lens. Here the anterior lens capsule is opened and the lens expressed through this opening. The lens capsule is left behind in the eye, and in about fifty per cent. of cases it will be necessary to incise it (perform a capsulotomy operation) in six to eight weeks' time.

There is no doubt about the fact that the intracapsular operation requires greater skill in manipulation of the lens than the extracapsular operation, but in the hands of a skilled surgeon who is in constant practice, the intracapsular operation carries no greater risks.

The intracapsular operation should not be attempted until the surgeon has attained efficiency and dexterity in the extracapsular operation.

There are two types of cases where the intracapsular operation has very definite advantages over the extracapsular operation—the cases of immature cataract and the cases of hypermature cataract.

In immature cataract there is much clear lens matter still present but a comparatively small central opacity may greatly reduce visual acuity. The technical difficulties of removing this immature lens by the extracapsular method are considerable and much lens cortex may be left behind. This lens cortex is apt to cause considerable intraocular reaction. A successful intracapsular operation on the other hand produces little or no intraocular reaction, the patient is left with a beautifully clear pupil, and obviously no subsequent "needling operation" will be required.

Hypermature cataract is not a common condition, but its removal is always difficult. The extracapsular operation is contra-indicated, and the intracapsular should be tried, but it may be necessary to remove the lens with a vectis or "scoop."

The extracapsular operation is possibly a safer operation for mature cataract, and certainly it is a safer operation for cases of cataract complicated by posterior synechiæ or other evidence of old iridocyclitis.

I find my result of intracapsular operations show just as high a percentage of good results as do my extracapsular operations.

And so I repeat that the time to perform a cataract operation is when the patient is no longer able to carry on in comfort.

PENICILLIN IN OPHTHALMOLOGY

PHYSIOLOGICALLY and pathologically the eye is a double organ. The lids, conjunctiva, and sclera are freely supplied by blood vessels (as most other tissues) and substances circulating in the blood stream readily reach them. In contrast, the cornea and the interior of the eye constitute (as does the brain) a largely insulated system. These tissues depend largely, not upon blood bathing the tissues, but upon highly selected filtrates of the blood (i.e., aqueous humour, which nourishes lens and cornea, is a derivative of plasma). This shields these highly specialised tissues from many constituents in the blood stream.

Penicillin belongs to a group of agents which does not readily penetrate the interior of the eye. Thus systematic administration of penicillin in intraocular infections is unlikely to give good results.

One must also consider the modern view *re* the causes of these intraocular inflammations. In cases where the outer protective coats of the eye have been perforated, an exogenous reaction may result within the eyeball, producing an iridocyclitis in the injured eye, and this reaction may spread to the non-injured eye in cases of sympathetic ophthalmia.

Much more commonly there is no perforation of the eyeball, and the iridocyclitis is a result of endogenous causes which are not truly infective in nature. The intra-

ocular reaction is due to a whole series of irritants which may be of a bacterial, virus, allergic, or metabolic nature. These include focal sepsis, syphillis, gonorhœa, tuberculosis, rheumatism, diabetes, etc.

Thus penicillin may occasionally give good results in clearing up a general infection which is causing intra-ocular inflammation.

We know that the sulphonamides given systematically readily penetrate the interior of the eye and are occasionally useful in cases of low-grade intra-ocular inflammation of endogenous origin.

It has been clearly established that penicillin and sulphonamide can often be used together with advantage—there is no incompatability.

It would therefore seem to me that where no cause is to be found in cases of intra-ocular inflammation, it is worth while giving a full course of sulphonamide plus penicillin, but do not be surprised if it proves to be of little or no value.

While penicillin is of very limited value in intra-ocular inflammation, it is ideal for extra-ocular infections. Thus, pencillin in ophthalmology is largely confined to infections of the outer eye and ocular adenexa. As these parts are readily accessible, local therapy is the main method of administration. In appropriate concentrations it is harmless to delicate ocular structures. It is lethal to sensitive bacteria in low concentrations, and to slightly sensitive bacteria in high concentrations. It acts well in the presence of pus and has no lethal effect on leucocytes. Very occasionally a local reaction has been observed.

Local sulphonamide therapy on the other hand is of little value, as the drug is inactivated by pus and breaking down tissue products.

In using penicillin, Florey's dictum must be observed :—"Penicillin must be kept in contact with all infective tissues until the natural body defences have time to deal with the infection. Organisms must be tested for penicillin sensitivity."

Drops are rapidly washed from the eyes, and therefore frequent application is essential. In severe infections instil at intervals of one to five minutes, in moderate infections half-hourly or hourly, and in mild infections three-hourly.

When drops are freshly prepared they should retain their activity for seven days if stored in a cool place. Guttæ Penicillin (B.P.) has 1,000 units per c.c. In practice it has been found that this strength is well tolerated and effective. Professor Sorsby states that up to 2,500 units per c.c. can be used, but personally I think this high concentration is apt to cause conjunctival hyperæmia.

In theory it would seem that penicillin ointment should lessen the need for such frequent application of drops—Oculentum Penicillin (B.P.) contains 1,000 units per gramme. Stored in a cool place it is said to retain its potency for six months.

In practice there is still difficulty in obtaining a suitable base which will not destroy the penicillin and will not irritate the patient.

A subconjunctival injection of penicillin is said to be the best method of getting some concentration in the cornea, iris, and ciliary body—this method gives no concentration in the posterior half of the chorio-retinal layer. The dose suggested is two minims twice daily of a solution strength 1,000 units per c.c.

Intraocular injection of penicillin is not well tolerated, and the method is still *sub judice*.

I will now detail the modern views *re* treating a case of ophthalmia neonatorum.

The causative factors are :—Gonococcus in about 25 per cent., Staphylococcus 35 per cent., Other cocci 5 per cent., Bacilli 20 per cent., Virus 10 per cent., Undetermined 5 per cent.

Prevention can be carried out by treatment of the expectant mother and the careful washing of the baby's eyes immediately after delivery. The use of conjunctival antiseptics is benificial. There is no evidence that silver nitrate is superior to some of the organic silver preparations such as argyrol, while it may cause undesirable and even disastrous sequelæ.

In the treatment of ophthalmia neonatorum, local application of sulphonamide therapy is ineffective, while sulphanilamide and sulphapyridine tablets may cause toxic symptoms. Sulphamezathine, thiazole, diazine, are all well tolerated.

In the routine management of a case a swab is taken for smear and culture, the eyes irrigated with bland lotion as half normal saline at room temperature, and guttæ atrop. sulph. 1 per cent. and guttæ medicinal paraffin instilled. Sulphamezathine, 0.25 gm. (half tablet) given by mouth (crush into powder and give in teaspoonful of water or milk). Continue "drug" (dose 0.125 gm.) every four hours day and night until forty-eight hours after clinical cure is obtained. For adults an appropriate dosage is given.

The purulent discharge usually disappears within twenty-four hours. While discharge is present, three-hourly irrigation of the conjunctiva followed by a drop of liquid paraffin should be carried out. In seventy-two hours the eyes are usually dry. If there is any corneal trouble, continue with guttæ atropine three times daily.

In penicillin therapy all common causal organisms respond and penicillin is well tolerated. Swab is taken for smear and culture. May also instil a drop of ardenaline 1 : 1,000, and take a scraping from palpebral conjunctiva for examination for inclusion bodies (virus). Instil guttæ atrop. 1 per cent. Penicillin (2,500 units per c.c.) instil one drop. Continue one drop every five minutes until no discharge (generally a half to three hours). Continue half-hourly until all swelling and moistness have gone (six to twelve hours). Continue hourly for further twelve hours and two-hourly for further twenty-four hours.

The results obtained by intensive application of penicillin locally are almost as strikingly superior to those obtained by sulphonamide therapy as these in turn were over the classical methods : but if penicillin drops are not readily available then sulphonamide therapy is a reasonable substitute.

In penicillin we have a drug which, when given in appropriate dosage, acts quickly. If it is to be used, use it whole-heartedly over a short period and it will kill all organisms which are sensitive.

In infection of the lids like styes, blepharitis, etc., penicillin will reach the invading organism by either general or local administration, and it usually depends on circumstances and the virulence of the infection which method is adopted.

It is always well to remember that penicillin only attacks the organisms and gives

no immunity to the patient against repeated attacks. That being so, it is still essential to do everything possible to raise resistance by all generally accepted means.

Infections of the lacrymal sac respond well to local penicillin therapy—repeated washing of the sac and instillation of a solution of penicillin may cause an early case of dacryocystis to completely resolve and leave a patent nasolacrymal duct. With long-standing cases where fibrosis is causing a stricture of the duct, it is obvious that some surgical procedure is necessary to either drain or remove the lacrymal sac before one can hope for a cure.

For chronic conjunctivitis which may be due to chronic irritation rather than infection, the astringent drugs like zinc. sulphate or hamamelidis are still the best.

In these cases one must look for the cause of the lesion. This may be a direct irritant like a foreign body, eyelash, dust, bad ventilation, etc., or a reflex irritant like refractive error, heterophoria, working in bad light, etc. Allergic, metabolic, and constitutional causes also play their part.

Trachoma is probably second to no disease as a cause of human suffering, blindness, and a national economic loss. In countries like Egypt, where it is endemic, it is said to be as old as the Nile or the desert.

There is now positive evidence for the belief that trachoma is of virus origin—the only virus disease strictly localised to the eye.

It is known that sulphonamides favourably influence some infections due to large viruses, and it has been found in practice that sulphonamides have a direct and powerful action on trachoma virus and that it can be eradicated by their exclusive use.

It will still be necessary, of course, to treat the well-known local pathological lesions as follicles, lid deformities, etc., in the old-established manner.

The sulpha drug of choice is thiazole, diazine, or mezathine, and as ever, in using these preparations, the invading organisms or virus must be killed and not just maimed. A full systemic course must be given and, if necessary, it may be repeated after a short interval.

The use of penicillin in trachoma is still so limited that it is not possible to offer any real opinion. The fact that the virus of ophthalmia neonatorum responds satisfactorily to penicillin gives some promise that the virus of trachoma may also be sensitive.

Corneal Ulcers.—Ulcers which are infected by a virulent organism (hypopyon type) respond well to intensive local penicillin therapy, and, apart from the use of atropine, it can be employed exclusively. On the other hand, ulcers of the dendritic type which are possibly due to a virus, or of the neuroparalytic type due to tropic change, cannot be expected to be helped by penicillin, and, in fact, are not helped.

Finally a word about ophthalmic surgery. To-day no ophthalmic surgeon would perform an intraocular operation without first using penicillin drops, to be certain of an operative field free from organisms. In the immediate post-operative period the penicillin is continued until the wound is firmly healed.

Recent Advances in Oto-Rhino-Laryngology with Special Reference to Penicillin Therapy

By KENNEDY HUNTER, M.B., F.R.C.S.EDIN., D.L.O.

THE advent of chemotherapy has forced physicians and surgeons to change their views on the prognosis and treatment of many injuries and diseases.

The greatly improved results following the introduction of the sulphonamides has been further advanced by the discovery and use of penicillin.

Previously, surgery's main function in many cases of infection was to provide drainage, leaving the defences of the body to deal with the infecting organisms. Now the defences can be greatly supplemented by chemotherapy.

This short communication is mainly concerned with penicillin.

I shall not deal with the history, chemistry, pharmacology, or bacteriology of penicillin, but will devote my remarks mainly to the methods of administration and the accepted and proved uses.

It cannot be too often repeated that for penicillin to be of any use, the infecting organism must be susceptible.

Bacteriological examination should be carried out as soon as possible, but this does not mean to say that the commencement of treatment with penicillin need be delayed until reports are received. If the examination proves the infection to be due to a non-penicillin-sensitive organism, penicillin therapy should be discontinued and other appropriate measures substituted.

Administration of penicillin may be by the systemic, intra-thecal, or local routes. For systemic use, the penicillin salt is dissolved in sterile, re-distilled water. For intra-thecal use, the pure crystalline penicillin should be used. For local use, the following preparations are in common use:—creams and ointments, powders, lozenges, sprays, and drops. The Cremor Penicillini (B.P.) rather than the Cremor Penicillini Sterilisatus (B.P.) should be prescribed for the patient's own use, because it contains 1 per cent. chlorocresol. This prevents penicillinase-producing organisms growing in it. If pyocyaneus infection complicates the picture, 2 per cent. phenoxetol may be added to the cream. Only enough cream to last a week should be prescribed at one time. Sprays and drops are used in strengths of 1,000 to 2,000 units or more per c.c. in sterile distilled water or sterile normal saline. These lose their potency in five or six days, so only small quantites should be prescribed. The dropper or spray should be boiled frequently.

Powders are prepared by mixing a sterile sulphonamide or lactose with calcium penicillin in strengths of 500 to 10,000 units per gramme. The dry powder retains its potency for about six months.

THE EAR

Staphylococcal and streptococcal infections of the skin of the pinna may be treated with penicillin cream. The results of treatment of furunculosis of the external

auditory meatus with local penicillin have been rather disappointing, but a very early lesion may be aborted and in late cases spread of the infection to other follicles and galnds may be prevented. Certain cases of chronic external otitis may be improved, but relapses still occur. Many cases are due to non-sensitive organisms.

The meatus is packed tightly with plain half-inch ribbon gauze and kept saturated with penicillin solution by dropping on the gauze every two to three hours. The packing is renewed every twenty-four hours.

Injuries to the meatus should be treated in the same way. This will often prevent the onset of an acute external otitis following accidental injury of the meatus whilst syringing an ear for wax.

Injury to the drum, when not complicated by infection, should *not* be treated by syringing or drops. No attempt should be made to clean or wash out the blood-clot. A wick of sterile gauze should be inserted into the meatus and nothing more done, unless infection supervenes, when it should be treated as an acute otitis media.

Practically all cases of acute otitis media are due to a penicillin-sensitive organism, so most cases could be cured by systemic penicillin, if given early enough. The general practitioner is the one likely to see these cases in their early stages. I think all cases should be given systemic penicillin. Three-hourly injections of 25,000 units for adults is the ideal method at present, but this is not always possible. Probably most early cases can be cured by massive dosage at less frequent intervals. I would suggest 250,000 units night and morning for adults and corresponding dosage for children, say 50,000 units night and morning for a child of one year old, 100,000 units night and morning for a child of four years old, and 150,000 units night and morning for a child of twelve years old.

If the condition is well established and pus is present in the middle ear with a bulging drum, a paracentesis must be done.

If the ear has commenced to discharge or if a paracentesis has been done, local treatment with penicillin drops should be instituted. The meatus is cleaned with dry wool three, four, or five times daily, depending on the amount of discharge, and drops put in each time. This may be combined with systemic penicillin.

The results of penicillin therapy in chronic suppurative otitis media are disappointing. This is due to several reasons, the principal ones being a non-sensitive organism, gross hypertrophy of the mucous membrane, or actual polyp formation, cholesteatoma or chronic bone disease. If a swab reveals only a penicillin-sensitive organism, gross hypertrophy of the mucous membrane or actual polyp formation, chronic bone disease, penicillin therapy should be tried. Operation may be averted in some early cases of acute mastoiditis by the use of systemic penicillin, but these cases require very careful observation. Unless a rapid response is obtained, operation should be done. Penicillin has proved extremely useful in the post-operative treatment of acute mastoiditis. It eliminates the long and painful dressings and greatly reduces the stay in hospital. After all the mastoid cells have been opened, the mastoid antrum drained and all bone chips removed, a fine rubber catheter—No. 3 or 4—is inserted into the antrum and the end brought out of the lower end of the wound, which is tightly stitched round it. A suture fixes the catheter to the

skin edge. One or two c.c. of penicillin solution, depending on the size of the cavity, is injected through the catheter every six hours. The end of the catheter is closed with a wooden spigot, usually a piece of a wooden applicator. The outer end of the catheter lies under the superficial dressing, so that the wound is not exposed for each injection. The discharge from the middle ear usually dries up in three to six days; when the catheter is removed. The wound will be completely healed in another day or two. By this means, the chances of the return of normal hearing are increased, as deafness is due to the middle ear discharge continuing for a length of time, so giving rise to intra-tympanic adhesions.

Lateral Sinus Thrombosis

Systemic penicillin should be commenced immediately a diagnosis is made, but I think the lateral sinus should be exposed, opened, and the septic clot removed. If this is not done, a relapse will probably occur when the penicillin is stopped. It is probably not necessary to ligature the internal jugular vein in the neck.

Meningitis

The primary focus is attacked with systemic penicillin, but as this does not reach the C.S.F. in sufficient concentration, intra-thecal penicillin should also be given. After withdrawl of C.S.F., about 10,000 units of the pure crystalline penicillin in two to three c.c. of double distilled sterile water is injected slowly. The solution should be slightly warmed to remove the chill. This is repeated every twenty-four hours for about five days in the average case. As sulphonamides are excreted in the C.S.F., they should be given in addition. It has been found that sulphadiazine gives the highest concentration in the C.S.F., so this preparation should be chosen. Relapses should be treated in the same way; several may occur before complete cure is obtained. Operation on the primary focus, e.g. the mastoid, should be delayed until the meningitis is under control. Indeed, in some cases due to acute mastoiditis, operation may prove unnecessary.

On the other hand, if examination of the C.S.F. reveals a sterile culture plus an increase in the cellular content, etc., where an extra-dural abscess is suspected, intra-thecal penicillin should be withheld and operation performed immediately.

Brain Abscess

Systemic penicillin and sulphadiazine are given before operation. The abscess, when found, is treated by inserting a fine rubber catheter into the cavity and, after the pus has drained away, penicillin solution is injected through the catheter. 1 c.c. of thorotrast is mixed with the penicillin; this makes it possible to follow the diminution in the size of the cavity by repeated x-rays, so giving a guide as to when the catheter may be removed. The catheter is closed with a wooden spigot and opened every twenty-four hours, the pus being allowed to drain away and more penicillin injected.

Cairns recommends repeated aspiration and injection of penicillin without drainage.

Nose

Sycosis and furuncles of the nasal vestibule may be treated with local penicillin. If cavernous sinus thrombosis should occur in a case of nasal or labial furunculosis, systemic penicillin in very large doses will save many cases. This condition used to be almost one hundred per cent. fatal.

Acute catarrhal rhinitis or common cold.—In the stage of secondary infection, i.e. when the discharge thickens and becomes coloured, the instillation of penicillin solution four times daily may shorten the duration and may prevent the complications which may arise from the secondary infection, such as sinusitis and otitis media. Ten to twelve drops of the solution should be put into each nostril, with the patient lying on the back and a pillow under the shoulders, so that the head is extended to such an extent that a line from ear to chin points vertically. All breathing should be done by the mouth to prevent the solution being sucked from the nose into the throat. This position should be maintained for three to four minutes before sitting up. If there is much congestion of the mucosa, half per cent. ephedrine in normal saline may be mixed with the penicillin solution.

Sinusitis

Severe acute purulent multi-sinusitis should be treated with systemic penicillin. Acute infection of the antrum with pus in the cavity requires wash-out and injection of penicillin solution into the cavity. The one operation may suffice. In subacute cases it will have to be repeated. A specimen of pus should be aspirated from the cavity on the first occasion for bacteriological examination. In chronic cases, a similar technique is worth trying, but here it is best to put ureteric catheters into the antra, fixing the ends to the forehead with plaster. The penicillin solution can then be injected three times per day with no discomfort to the patient. This should be combined with systemic penicillin in full doses, i.e. 200,000 units in twenty-four hours. I would suggest that this be continued for seven days before giving up. If the organism is not penicillin-sensitive or the lining is very thickened or polypoid, a radical Caldwell-Luc operation will be necessary, with complete removal of the lining.

Infection of the sphenoid sinus may be treated in the same manner, puncture, wash-out, and instillation of penicillin.

Acute infection of the frontal sinus, which fails to resolve quickly by simple conservative measures, may be treated by drilling a small hole in the floor of the frontal sinus, through which a small catheter is passed. The wound is closed around the catheter, which is fixed to the skin with a stitch. Penicillin solution is injected three times per day. At first, none will enter the nose because of the swelling of the mucosa blocking the fronto-nasal duct. When this swelling subsides in a few days, the penicillin will be found to flow freely into the nose. If this does not happen, lipiodol may be injected via the catheter and x-rays taken. This will reveal the thickness of the lining or the presence of polypi, which would require major surgery.

Ethmoiditis

The ethmoid cells cannot all be individually punctured and washed out, so penicillin cannot be used locally as in the other sinuses. Instillation of penicillin and ephedrine solution into the nose in the proper position may be tried. In the subacute case, Proetz suction-replacement technique may be given a trial. The very acute ethmoidal infection, which is seen in young children and babies, should be treated with systemic penicillin. If an orbital abscess forms, this should be drained.

Osteomyelitis of the facial and skull bones arising as a complication of sinusitis is best treated with large doses of systemic penicillin. Surgery may or may not be required. Collections of pus, such as extra-dural, sub-dural, or cerebral abscess, will require drainage.

Mouth and Throat

Vincent's Angina.—Mild cases can be cured with penicillin lozenges, but severe cases require systemic penicillin. To prevent recurrence, dental treatment is often necessary.

As a troublesome glossitis follows the use of penicillin lozenges in a considerable percentage of cases, I would reserve their use for such conditions as Vincent's infections. I do not think it is worth using them in cases of slight sore throat, and the results are not particularly good, at any rate.

It is worth remembering that extraction of septic teeth always produces some degree of bacteræmia, and in a sick patient or one with endocarditis, this may have serious consequences. One injection of systemic penicillin, about fifteen minutes before the extraction, will kill off most or many of the liberated organisms.

Tonsillitis

I doubt if it is worth treating the ordinary case of acute tonsillitis with systemic penicillin, unless it fails to respond to sulphonamides. Penicillin lozenges have practically no effect on tonsillitis.

Peritonsillitis in its early stages may be cured by systemic penicillin, but when pus has formed incision is necessary.

A severe septic mouth or throat, with signs of laryngeal œdema or Ludwig's angina, should be given systemic penicillin immediately in full doses. A tracheotomy or neck incision *may* be averted.

Penicillin is of great value in operations on the pharynx or larynx, such as removal of pharyngeal pouch or total laryngectomy. One of the great dangers of operations involving the opening of the pharynx is infection of the wound and sloughing, or mediastinitis. With the pre- and post-operative use of systemic penicillin, combined with penicillin locally via small catheters, primary wound-healing can be expected in most cases. The removal of an œsophageal pouch can be done in one stage instead of the more usual two-stage method.

Perforation of the œsophagus by foreign bodies or instruments used to lead to a fulminating mediastinitis. Prompt use of systemic penicillin combined with rest of the œsophagus now offers a fair prognosis.

DEAFNESS

Deafness is a very common, distressing, and disabling affliction.

In children, the prompt and proper treatment of diseases of the nose and throat, together with the skilled use of penicillin in the treatment of acute infections of the middle ear, should greatly reduce the incidence of deafness.

In young adults, apart from the results of infection, one of the commonest causes of deafness is otosclerosis. This is a disease of the otic capsule and affects mainly the bone round the oval window and the foot-plate of the stapes. The bony changes result in limitation or complete loss of movement of the stapes in the oval window. This results in the blocking of sound vibrations which should reach the inner ear. The condition is often hereditary, but the cause is still unknown. Until a few years ago, practically nothing could be done to improve the hearing of these unfortunate people.

The onset is usually between twenty and thirty years of age and is very insidious. The first complaint is often tinnitus. When the patient first seeks advice, there is usually a well-marked middle-ear deafness. Paracusis is usually present; this means the ability to hear better in a noisy place.

The diagnosis is made partly by the exclusion of other causes of middle-ear deafness. The ear-drums are normal in appearance. Audiometric examination reveals the loss of hearing to be at the lower end of the scale, the high notes being almost normal.

For some years various attempts have been made to provide another route for the sound vibrations to reach the inner ear and so by-pass the immobile stapes. Thus the fenestration operation has been evolved and it is now past the purely experimental stage. Here again, chemotherapy and especially penicillin therapy has played an important part, as post-operative infection defeats the aim of the operation. As the name implies, the operation consists in making an artificial window into the inner ear.

The first stage of a modified radical mastoidectomy is performed. The attic is exposed and the incus and head of malleus are removed. A flap of skin from the meatus is cut so that it remains attached only to Shrapnell's membrane. This is turned aside and the lateral semi-circular canal exposed. The remainder of the operation is carried out with the aid of an operating microscope and a dental electric drill. The area is kept under continuous irrigation and suction to remove all bone-dust. By means of various types of drill an opening, four to five mm. long, is made through the bony wall of the canal over the ampulla of the membraneous canal, great care being taken not to injure the latter. Some surgeons place a cartilage stopple in the opening to try to prevent closure by new bone. The prepared flap is now placed over the new window. The sound vibrations, on reaching the drum, are transmitted from the drum to the attached flap and so through the new window to the inner ear.

The operation never gives normal hearing, but in successful cases about a 25-decibel gain is obtained. Thus it will be seen that not all cases can benefit from the

operation, and cases must be very carefully chosen. A decibel is the smallest change in intensity or loudness which the human ear can appreciate.

The two most important frequencies for understanding speech are the 1024 and 2048 cycles per second, and the 30-decibel line appears to be the critical one. A patient with 25-decibel loss suffers only slight inconvenience. A patient with 35-decibel loss suffers great inconvenience and feels deaf. It will thus be seen that a patient with a loss of 50 decibels may, if the operation is successful, be able to hear again, as her loss will then be less than the critical 30-decibel line.

On the other hand, a patient with a loss of say 70 decibels, even if the operation were successful, would still have a 40/45-decibel loss and would still be deaf. The only advantage might be that a hearing-aid might now be used where it was useless before.

In selecting a suitable case, many factors have to be considered, apart from the *degree* of deafness. Changes in the inner ear would contra-indicate operation. Apart from the audiogram, these changes can be suspected from the patient's voice. Deaf people who speak in a loud voice usually have inner-ear deafness. Disappearance of the paracusis and intolerance of amplification also mean inner-ear changes.

The drum must be intact and there must be no history of otitis media

A suitable case may be told that there is a fifty per cent. chance of permanent and useful improvement in hearing, a five per cent. chance of hearing being worse and a two-and-a-half per cent. chance of complete loss of the hearing in the operated ear. For these reasons, the worse ear is usually chosen for operation in the first place.

In some cases, the new window becomes closed with new bone formation, and so the improved hearing disappears. This usually happens within six months, but may take place up to two years after the operation. The closure is usually manifest by disappearance of the fistula sign. A case which has closed may be re-opened and the chances of subsequent closure are greatly reduced.

The mortality from the operation is negligible. Some vertigo is always present for a few days. It may last several weeks before completely passing off. Facial paresis may occur, but is usually transient.

The patient will require about three weeks hospitalisation, but the cavity takes eight to twelve weeks to heal, during which time dressings are necessary.

Return to work is usually possible in eight weeks.

The Results of Sympathectomy

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THIS paper deals only with sympathectomy for the extremities and includes the results of three operations. For the lower limb, an excision of the sympathetic chain, 3 to 6 cm. in length, centred opposite the third lumbar vertebra, has been the standard procedure. This includes the fourth lumbar ganglion and in many cases the third ganglion also. The extraperitoneal route is used, with spinal anæsthesia, and in bilateral conditions both sides are done at one session. For the upper limb, cervicothoracic ganglionectomy was given up in Manchester in 1935, when Professor Telford introduced his preganglionic section. In this operation the sympathetic chain is sectioned opposite the third rib, by the anterior approach, and after division of the rami from the second and third thoracic ganglia, the upper end is turned up and sutured to the scalenus anterior. No Horner's syndrome follows this procedure.

The results can be considered under two headings, physiological and clinical.

PHYSIOLOGICAL

There is an increased blood flow in the extremity from abolition of vasoconstrictor tone, and to this increase are due the beneficial results such as abolition of ischæmic pain, healing of ulcers, and rapid separation of dead tissue. The increase is greatest in the distal parts of the limbs because :

1. The greatest vasoconstrictor tone is in the skin which forms a greater proportion of the bulk of the digits than of any other part of the limbs.
2. The presence of arteriolo-venous anastomosis in the digits permits great increase in the blood flow.
3. Normal limbs have a skin temperature gradient, with the distal parts coldest because of greatest vasoconstrictor tone; after sympathectomy this gradient is abolished or even reversed.

The immediate result is a hot and dry extremity, with the skin temperature only slightly below blood heat, in the absence of severe organic arterial obstruction. The heat is not maintained, however, and the hand or foot begins to cool, often at the third day and with a pronounced fall in temperature on the fifth or sixth day. This fall is partly accounted for by the return of autonomous tone in the musculature of the arterioles, but to some extent it is due to the disappearance of the pyrexial reaction to the operation, caused, no doubt, by the absorption of products of tissue damage. Is this cooling an indication that sympathetic denervation is complete? To answer this question, tests for sympathetic activity must be applied.

The most sensitive test which I have found has been the measurement of the skin electrical conductivity of the digits, before and after procaine block of the ulnar and posterior tibial nerves. Sweating skin, containing water and electrolytes, has a high conductivity, while dry skin offers a very high electrical resistance. In a normally innervated limb, peripheral nerve block results in a profound fall in electrical conductivity in the cutaneous distribution of the nerve because the sudomotor fibres are paralysed. In the early weeks after sympathectomy the electrical conductivity is low and is unaltered by peripheral nerve block, an indication that sudomotor activity is absent. Since sudomotor and vasomotor fibres pursue identical pathways, vasomotor activity will also be absent. This is confirmed by the observation that no rise in skin temperature of the little finger follows ulnar nerve block in an extremity recently treated by sympathetic section.

This freedom from sympathetic activity after operation is not, unfortunately, permanent in the great majority of cases. I have tested by the above methods forty-six upper and thirty-eight lower limbs from one to fourteen years after sympathetic section, and have found some degree of sympathetic activity in all the upper limbs and all except seven of the lower limbs. It must be emphasised, however, that the tests employed are very delicate indicators and that the return of activity was very slight in many cases; clinically, the hands and feet, especially the latter, often remained warm and free from sweating. Nevertheless, some improvement in blood flow, as indicated by a rise of skin temperature, could be produced by nerve block. A further useful test is paravertebral sympathetic block. This has been carried out in the upper thorax by a technique described elsewhere (Haxton, 1947) and it has been possible to produce sympathetic paralysis in the upper limbs, in cases in which return of activity had occurred, without causing a Horner's syndrome or any sensory or motor change in the upper limb. The only suitable explanation of this finding is regeneration of sympathetic fibres from either the divided rami communicantes or, more likely, from the lower cut end of the chain. In confirmation there is voluminous evidence from animal experiments which testifies to the uncanny power of regeneration possessed by these fibres. As already explained, however, the regeneration is often very incomplete and the clinical benefits of warmth and dryness remain.

Clinical

Turning now to the results obtained in the treatment of various disorders by sympathectomy, through the courtesy of Professor Telford, to whom I am most grateful, I can report on 496 cases treated in his neurovascular clinic at the Manchester Royal Infirmary between 1931 and June, 1946. Most of these had two or four limbs treated, so that the total number of sympathectomies must be in excess of one thousand. Of these cases, four died while in hospital, two from pulmonary emboli, one from alcoholic delirium, and one from hæmatemesis. When it is borne in mind that many of the cases have been elderly arterio-sclerotics, some with angina pectoris, this mortality must be recognised as very small indeed.

Only a few cases are untraced. The remainder have been followed up over a long period and the late results of operation assessed as good, fair, and failed. Cases are

classed as good when marked improvement has resulted and the patient has been able to resume work, fair when there has been sustained improvement but not complete relief of symptoms, failed when improvement has been merely transient or even absent, the limb often coming to amputation for gangrene. Beginning with the occlusive vascular diseases, I turn to

Thrombo-angiitis Obliterans

This disease is seen in its severest form in men under the age of thirty, and, in general, the prognosis varies inversely with the patient's age, cases beginning in the early twenties frequently coming to double amputation of the lower limbs and early death from coronary or mesenteric involvement. After the age of thirty we are now inclined to suspect early arterio-sclerosis as a more likely diagnosis.

Sympathectomy was formerly performed in the belief that thromboangiitis obliterans is predominantly vasospastic in character. Now, the beneficial effects of sympathectomy are considered to be due to the abolition of normal vasoconstrictor tone in collateral vessels, and the operation is now reserved for the stage at which it does most good, that is the stage of pain in the feet when warm in bed, intractable ulceration or onychia of the toes, and gangrene localised to the toes. Ischæmic pain is abolished and healing is speeded up.

The late results are satisfactory, considering the progressive nature of the disease. Out of 105 cases, 12 are untraced, and of the remaining 93, 49 have given good, 18 fair, and 26 failed results. In some severe cases the disease appears later in the hands, and upper limb sympathectomy seems to have arrested or slowed the spread there, except in two cases who have lost the greater part of both hands.

Arterio Sclerosis

The results have been published in detail elsewhere (Telford and Simmons, 1946) and only the main points will be mentioned. Sympathectomy has produced only slight improvement in intermittent claudication in the great majority of cases, and a worth-while improvement cannot be guaranteed. The stage at which sympathectomy is of most value is, as in thromboangiitis obliterans, that of severe ischæmia in the foot, characterised by rest pain with marked rubor in the dependent position paling rapidly on elevation. Cases with gangrene confined to the toes often do well, but if the mortification is spreading on to the foot, sympathectomy is not helpful and sometimes accelerates the spread. On the whole, the markedly beneficial results of sympathectomy in this common malady are not sufficiently well-known. In eighty-three traced cases out of eighty-eight, the result was definitely good in forty-seven, fair in fourteen, and failed in only twenty-two.

Raynaud's Disease

This group of primarily vasospastic disorders is one of great interest because it presents the baffling problem of relapse after a completely satisfactory immediate result. Out of a total of fifty-three upper and thirty lower limb cases I have carefully investigated forty upper and twenty-eight lower limbs. Seventeen upper limbs

had been treated by cervicothoracic ganglionectomy, and of these five were good, five fair, and seven failed. Of the twenty-three upper limbs treated by preganglionic section, nine were good, three fair, and eleven failed. There is, therefore, little difference in the late results of these two operations. Of the lower limbs, sixteen were good, eight were fair, and four failed. The results are much better than in the hands, but not one hundred per cent. successful.

I believe the explanation of relapse to lie in the nature of the disorder which is an exaggerated response of the digital arteries to cold, a susceptibility which remains after sympathectomy. The fact that relapse does not as a rule appear until from six to eighteen months after operation is due to the superadded vasoconstrictor tone which results from regeneration of sympathetic fibres. Our results are not so bad as the figures would imply, because even in those labelled failed, all except two of the patients admitted benefit from the operation and stated that they considered it worth while. Another factor to be taken into account is that only severe cases have been subjected to operation since the milder cases often show spontaneous improvement. The former, presumably, have a greater local sensitivity to cold and will relapse more readily than will the milder cases. By operating on the latter as well, much better figures could have been obtained.

In Manchester we have seen many examples of severe Raynaud spasms in the fingers, resulting from the use of vibrating tools. This is a distressing trouble which greatly handicaps the workman and which neither responds to treatment nor clears up when the work is stopped. A good account has been published (Telford, McCann, and MacCormack, 1945).

Acrosclerosis

This serious trouble which, by gradual spread of subcutaneous fibrosis, converts the hands into rigid claws often with ulcerated and painful finger tips, is frequently ushered in by Raynaud attacks, and in the early stages at least, there may be no trace of the sclerosis that is to follow. The results of sympathectomy are not good; out of twenty-one traced cases in a total of twenty-three, fourteen have failed, six have been fair, and only one good, and that an early case. The operation is not worth while unless done at an early stage.

The more widespread fibrosis of dermatomyositis causes similar circulatory trouble in the digits, but sympathectomy in three cases has produced no benefit.

Acrocyanosis

This condition, in which the superficial capillaries of the digits are dilated and filled with almost stagnant blood, is akin to Raynaud's disease in that it is due to an abnormal degree of local sensitivity of vessels to cold. It is manifest by cold and blue, often moist and swollen extremities. The results of operation are similar to, but rather better than in Raynaud's disease. Out of nine upper limb cases, six are good, one fair, and two bad, while all nine lower limb cases have been good.

Anterior Poliomyelitis

The palsied limbs in this disease have a poor blood supply and an excess of subcutaneous fat. These factors combine with cold to produce hard and tender nodules

of fat necrosis, most commonly on the backs of the legs above the ankles, which frequently break down into indolent ulcers. Sympathectomy is of great benefit in this state, for it heals the ulcers rapidly and abolishes the pain. In sixty-one traced cases out of a total of sixty-eight, the result has been good in fifty, fair in five, and failed in six.

Erythrocyanosis

Similar lesions occurring in the legs of young women are likewise due to poor blood supply, excessive fat, and cold. The ulcerated stage is Bazin's disease, which has frequently been misrepresented as a tuberculous lesion. As would be expected, the results of sympathectomy are almost identical with those in poliomyelitis. Out of seventy-three cases, sixty-five have been followed, and the result is good in fifty, fair in eight, and failed in seven, the failures being cases of long duration and very fat limbs.

Perniosis

Chilblains are allied to the above lesions, being local foci of superficial damage due to cold, with an inflammatory reaction. Very satisfactory results have followed sympathectomy in the cases severe enough to warrant operation. Of three upper and eleven lower limb cases all have remained cured.

Erythromelalgia

In this rare hyperæmic phenomenon, characterised by burning pain in a hot and red extremity, sympathectomy might reasonably be expected to make matters worse, but the fact is that the results are excellent. All seven cases thus treated have remained completely cured.

Hyperhydrosis

Occasionally sweating of the hands, feet, or face may be so severe as to interfere with work or cause great embarrassment. Sympathectomy is a certain cure in this condition, and in ten cases, six of them followed for many years, no return has occurred.

These results indicate that sympathectomy can save patients much in pain and misery when other treatment is ineffectual, and that the scope of the operation is considerable. You will agree, I think, that this series is a fine monument to the brilliant and persevering work of Professor Telford in this fascinating field.

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Results of Sympathectomy in the Upper Limb

By G. T. C. HAMILTON

An Address to the Ulster Medical Society, 13th February, 1947

THE sympathetic nerves have two main functions in the extremities. These are the control of the sweat glands and the regulation of blood-vessel calibre. Sympathetic nerve fibres reach the hand by passing down through the arm and forearm in the main somatic nerve trunks. At intervals along the course of these nerve trunks fibres are given off to supply the sweat glands of the region and the neighbouring blood vessels. These vasomotor fibres form plexuses on the surface of the blood vessels. A continuous stream of impulses passes down these fibres, so that normally there is a tonic constriction of blood-vessel walls. When the sympathetic connections to a part of the body are severed completely no sweating can take place and the blood vessels are no longer held in a state of constriction.

The object of sympathectomy is, in the vast majority of cases, to prevent harmful narrowing of blood vessels, which, if allowed to continue, would lead to impaired nutrition of the tissues and in the end to permanent damage. Only in a comparatively small number of cases is sympathectomy performed for other disorders such as causalgia or hyperhidrosis.

There have been three main phases in the evolution of operations for the sympathetic denervation of the hand. The first of these, mainly due to the work of Leriche,[1] was periarterial sympathectomy. This operation comprised stripping off the adventitia from a segment (usually one or two inches in length) of the main limb artery with consequent removal of this portion of the sympathetic plexus on its surface. In this way it was hoped to interrupt the sympathetic supply to the limb blood vessels. This operation did not produce very impressive results, because anatomically the sympathetic fibres to the hand vessels leave the somatic nerve trunks at a point far distal to the segment of the artery which was stripped. Thus this type of operation did not attack the relevant part of the sympathetic nervous system.

The next form of sympathetic denervation was the cervico-dorsal ganglionectomy.[2] In this operation the paravertebral ganglionic chain was exposed in the lower part of the neck, usually through an anterior incision, and the lower cervical and first dorsal ganglia removed. This operation gave excellent early results, apart from the inevitable occurrence of a Horner's syndrome, but when these cases were reviewed months or years afterwards many were found to be relapsing and quite a few were as bad as they had been before operation. An explanation for this may be that after ganglionectomy in the arm the excitor cells are destroyed, the postganglionic fibres degenerate, and the denervated blood vessels become hypersensitive to naturally circulating adrenaline.[3] It is interesting that clinically better

results have been claimed in the lower limb, where lumbar sympathectomy does not destroy many of the excitor cells to the foot. That is, lumbar sympathectomy is mainly a preganglionic operation.

To surmount this difficulty a new form of operation has been described in the past decade. This is a preganglionic sympathectomy. The technique has been described by Telford[4] of Manchester and Smithwick[5] of Boston, Massachusetts. In Smithwick's operation (fig. 1) a posterior approach is used. Access to the sympathetic chain is achieved by resecting the posterior end of the third rib and the adjacent part of the transverse process of the third dorsal vertebra. The second and third intercostal nerves are avulsed intradurally and their proximal inch removed. All connections of these nerves to the sympathetic chain are severed (fig. 1A). Finally, the chain itself is divided below the third dorsal ganglion, turned up, and stitched to the muscles of the back. Sometimes this turned-up portion of the chain is enclosed in a silk bag further to reduce any chance of regeneration (fig. 1B). As the lower cervical and first dorsal ganglia are left intact, no Horner's syndrome is produced, but there is usually some loss of sensation in the axilla due to the resection of the second and third intercostal nerves. At first the results of this operation seemed better than those of the earlier sympathetic denervations. Recently, however, surgeons have begun to doubt whether even this operation produces complete and permanent interruption of the sympathetic supply to the upper limb.

During the last few months, working in Edinburgh and Dublin, Professor Barcroft and I have had the opportunity of testing twenty-eight sympathectomized upper limbs. Their operations had all been of the Smithwick type. In twenty-seven the operation had been performed for severe attacks of the Raynaud phenomenon, the remaining limb had been sympathectomized because of causalgia. The cases tested in Edinburgh were under the care of Professor Learmonth and those in Dublin had been operated on by Mr. Fitzgerald.

Many methods of testing for the presence of sympathetic activity have been described.[6] Some of these are dependent on reflex sweat-gland activity, others on reflex vascular responses. We have found venous occlusion plethysmography the method of choice, as it measures the blood-flow through the sympathectomized area.

The principle of venous occlusion plethysmography is quite simple. The hand plethysmograph (fig. 2) consists of a metal cylinder closed at one end. A semi-rigid rubber diaphragm is fitted snugly round the wrist, care being taken that it is not tight enough to impede the circulation. To this diaphragm is stuck a thin rubber cuffet, so that it too encircles the wrist without compression. This cuffet is stuck to the wrist with rubber cement, producing a water-tight joint. The diaphragm is then bolted to the open end of the plethysmograph, so that the hand is inside. The plethysmograph is filled with water, which is kept at a temperature of 32°C. by means of heat from a Bunsen burner. It is most important to maintain this temperature, as it has been shown that the hand blood-flow varies with change of water temperature.[7] A small hollow rubber cuff, in point of fact a cut-down bicycle inner

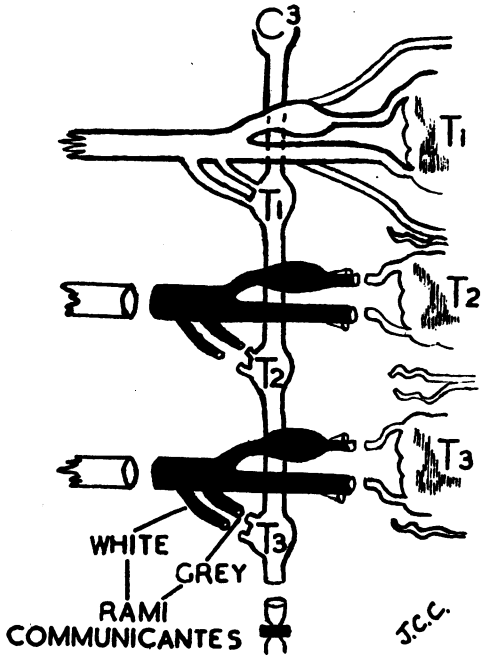


FIG. 1A.

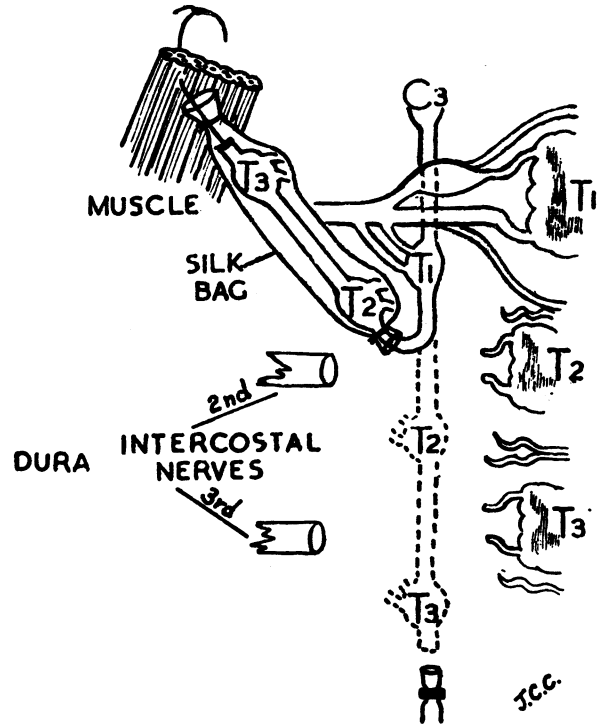


FIG. 1B.

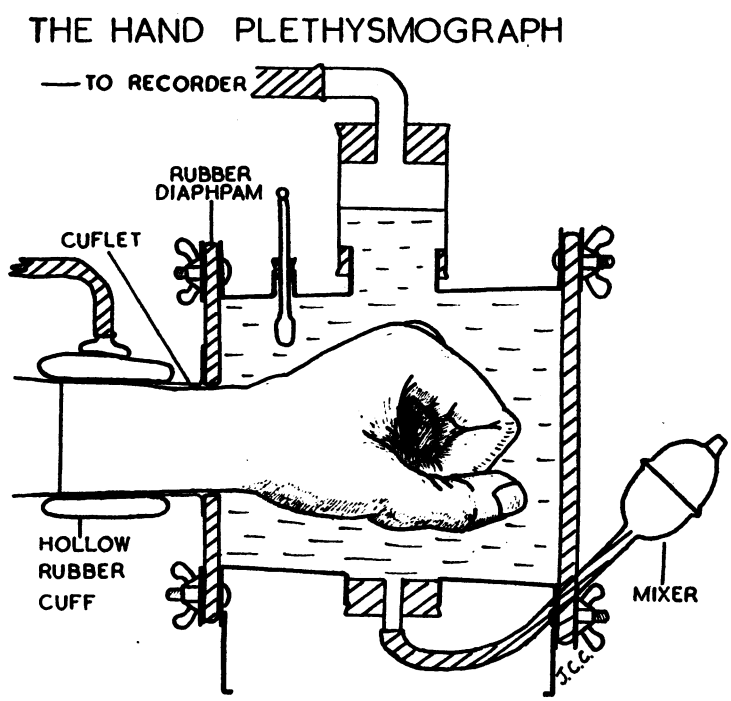


FIG. 2.

tube, is put round the wrist on top of the cuflet. It, too, though closely fitting, must not prevent arterial inflow or venous return from the hand. Using this apparatus, blood flows may be measured by rapidly blowing up the wrist cuff to a pressure just less than the diastolic blood pressure. The sudden inward pressure of the inflated cuff prevents venous return from the hand, but allows the arteries to continue to pump blood in without impediment. The hand therefore increases in volume, this increase being, for a short time, equal to the blood flow into the hand. The increase in volume is suitably recorded and from this the rate of blood flow in cubic centimetres per hundred cubic centimetres of hand per minute may be calculated

Two different tests were used. In the first of these, the heat test, blood flows were recorded for a control period to determine the basal level of flow. The feet were then placed in hot water (at 45°C.) and the patient covered with blankets to encourage reflex dilatation of the hand blood vessels. After about an hour of this indirect heating the feet were transferred to cold water (at 12 to 16°C.) for a short time, to attempt to produce reflex vasoconstriction. In normal hands reflex vasodilatation and vasoconstriction are present.[7] In hands in which these reactions were absent it was assumed that there was complete sympathetic denervation of the blood vessels.

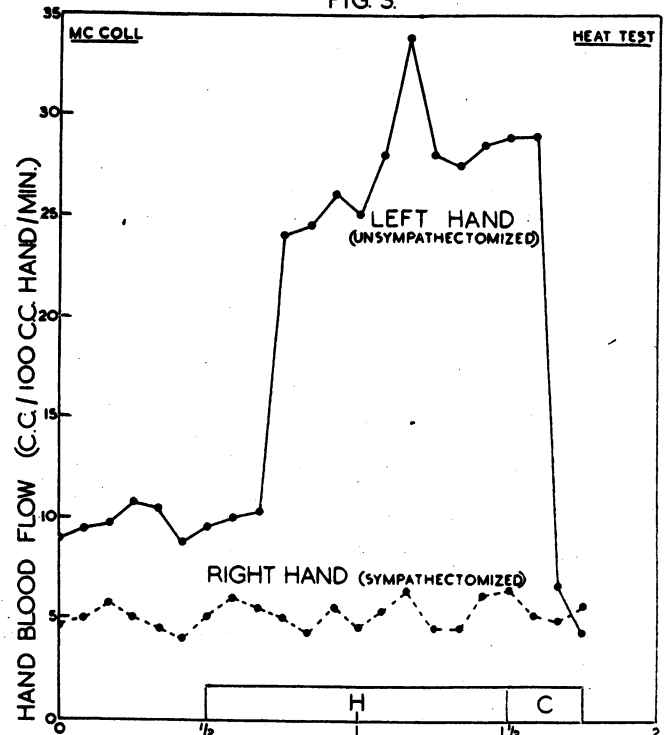
The other test, the nerve block test, comprised anæsthetization of the median, radial, and ulnar nerves in the arm with a four per cent. solution of Novocaine containing one part of adrenaline in fifty thousand parts of the solution. The radial nerve may be found at the junction of the upper and middle thirds of a line joining the insertion of the deltoid muscle and the lateral epicondyle of the humerus. The ulnar nerve is easily felt, as it runs in its groove on the medial epicondyle, while the median nerve is injected about an inch above the crease of the elbow where it lies just medial to the brachial artery. A very fine needle is used (at largest gauge 17) and a perfect block is almost certain if the tip of the needle is allowed to touch the nerve before any fluid is injected. This causes a well-marked, though by no means unbearable, feeling of pins and needles in the distribution of the nerve. It is wise to withdraw the needle slightly if any great resistance to the entry of the anæsthetic fluid is encountered, as, if injection is continued and the needle is buried in the nerve, disruption of fibres might occur with risk of some permanent loss of function. Blocking these three nerves produces complete motor, sensory, and sympathetic paralysis of the hand which lasts for at least an hour. This sympathetic paralysis causes in normal hands cessation of the tonic constriction of the blood vessels, and the blood flow through them increases greatly. Absence of vasodilatation when complete motor and sensory paralysis had occurred was taken as evidence of complete loss of sympathetic vascular control.

Results of the Blood Flow Tests

Fig. 3 shows the blood flows of a man who had had his right upper limb sympathectomized two-and-a-half years before testing. The upper line on this diagram represents the findings in the unsympathectomized hand. During the control period the blood flows remained constant. Within a short time after placing his feet in hot

COMPLETE SYMPATHECTOMIES.

FIG. 3.



H REPRESENTS TIME DURING WHICH FEET WERE IN HOT WATER (45°C)

C REPRESENTS TIME DURING WHICH FEET WERE IN COLD WATER 12-16°C

FIG. 4.

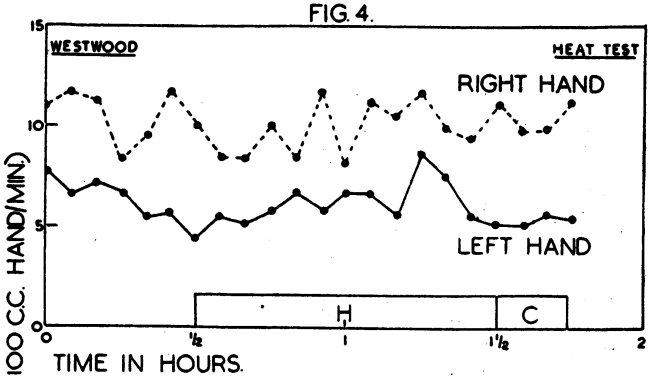
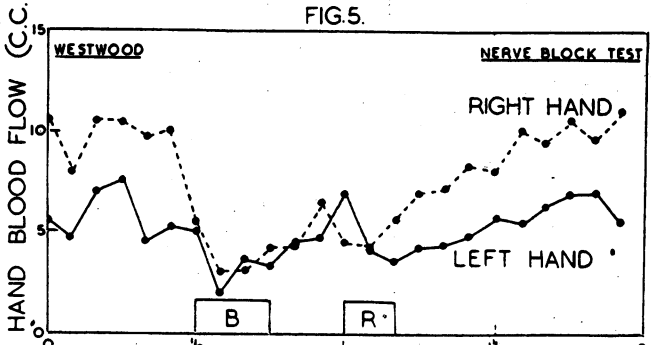


FIG. 5.



B TIME OF INJECTION OF MEDIAN RADIAL AND ULNAR NERVES.

R RE-INJECTION OF ANY NERVES NOT COMPLETELY ANAESTHETIZED.

water a large increase of blood flow occurred, which was maintained. When the feet were put in cold water there was a rapid vasoconstriction. The blood flow decreased to below its resting level within a few minutes. In the sympathectomized right hand (the lower curve in the diagram) the blood flow remained at a constant level throughout the period of the test. No change was produced by heating and then cooling the feet.

The blood flows of a subject who had had both upper limbs sympathectomized six months before the time of examination are shown in fig. 4. As in the sympathectomized hand of the previous case no change of blood-flow level occurred on putting the feet in hot water. No decrease in blood flow occurred on putting the feet into cold water.

Fig. 5 shows the blood flows of the same subjects as fig. 4, and here it may be seen that nerve blocks produced no increase in the value of the flows, though the blocks had completely paralysed the motor and sensory nerves to the hand. The fall in the blood-flow level which immediately followed nerve block was due to the adrenaline in the Novocaine solution which, on being absorbed into the blood stream, acts directly on the blood vessels, causing them to contract.

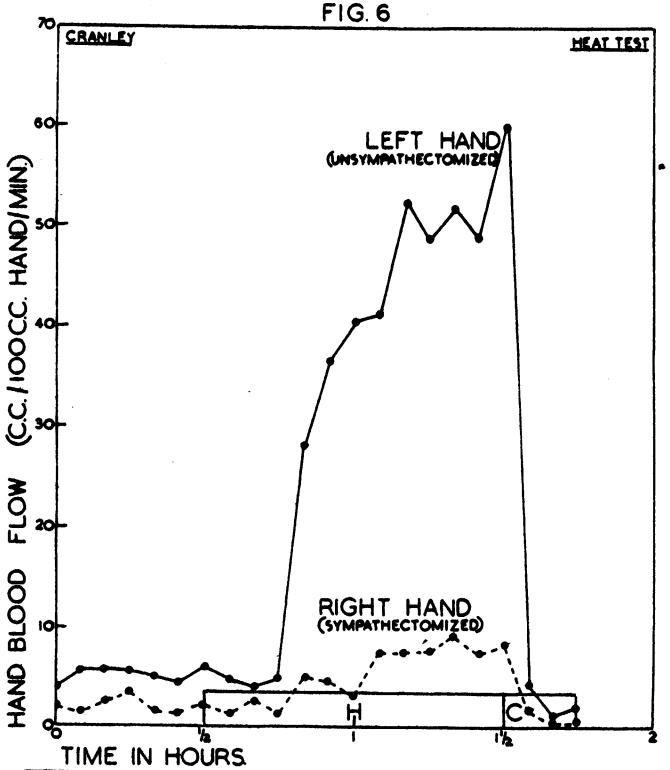
In all, sixteen out of twenty-eight sympathectomized limbs showed this type of response. No variation of blood-flow level was produced by indirect heating or cooling and no increase in the blood flow by nerve block. The blood vessels of these hands were therefore regarded as having been completely freed from central nervous control by operation. The time between operation and the carrying out of these tests varied from three weeks to five years.

The remaining sympathectomized limbs showed some degree of vasodilatation and vasoconstriction in the hands, as judged by the blood-flow curves. The findings in a typical unilaterally sympathectomized case are illustrated in fig. 6. A right-sided Smithwick sympathectomy had been performed three years previously. The upper curve shows the findings in the normal left hand. A great rise in blood flow occurred after putting the feet into hot water and an even more rapid fall, to below the basal level, ensued when the feet were transferred to cold water. In the sympathectomized hand, too, an increase in blood flow occurred to three times the preheating level on placing the feet in hot water, and a rapid fall to below the resting value followed when the feet were put into cold water. It is easily seen, however, that the degree of vasodilatation and vasoconstriction in this sympathectomized hand is very much less than in its normally innervated fellow.

Fig. 7 shows the blood flows of a hand sympathectomized fifteen months. In this hand also the blood flow begins to rise soon after the feet are put into hot water, and the final value of blood flow at the end of heating is greater than that which occurred in the previous case. As before, transferring the feet to cold water produced a marked falling off in the blood-flow level. Further proof that vasodilatation of nervous origin could occur in this hand was given by the response of the blood flows to anæsthetization of the nerves in the arm (fig. 8). This produced a rise above the basal level after the initial drop due to the adrenaline in the anæsthetic solution. Motor and sensory paralysis of the hand was complete.

INCOMPLETE SYMPATHECTOMIES

FIG. 6



H REPRESENTS TIME DURING WHICH FEET WERE IN HOT WATER (45°C).

C REPRESENTS TIME DURING WHICH FEET WERE IN COLD WATER (12°-18°C).

FIG. 7.

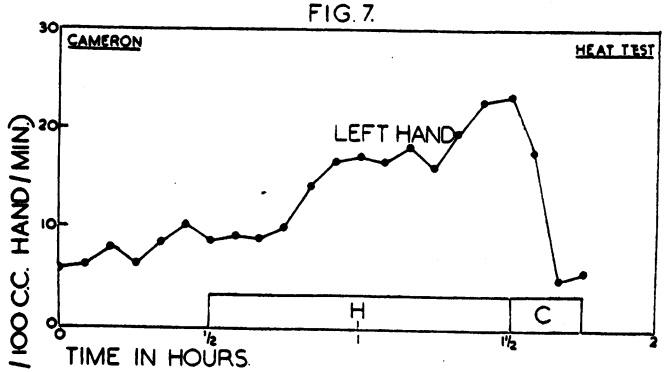
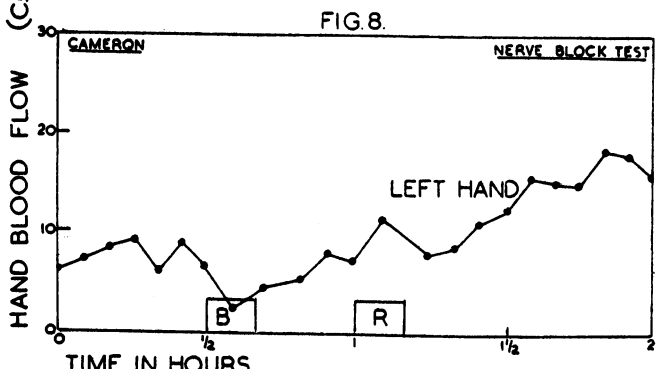


FIG. 8.



B TIME OF INJECTION OF MEDIAN RADIAL AND ULNAR NERVES

R RE-INJECTION OF ANY NERVES NOT COMPLETELY ANAESTHETIZED.

Twelve limbs, sympathectomized fifteen months to five years, showed this type of response. Indirect heating and nerve block produced vasodilatation and placing the feet in cold water caused vasoconstriction.

Using the blood-flow method, it was found that the results obtained by indirect heating always agreed with those produced by nerve block, and the heat test, which was more pleasant for the patients and more easily and quickly performed, was to be preferred as a routine post-operative method of investigation.

Sixteen of the twenty-eight sympathectomized limbs showed the complete absence of central nervous control from their hand blood vessels. The remaining twelve hands showed the presence of some vasomotor control at the time of testing. It must be emphasised, however, that in none of these was the amount of vasomotor control as great as that found in normal hands.

Though it is gratifying that, as judged by our methods of investigation, more than half of this series showed a perfect result, it is necessary to account for the twelve in which some vasomotor control was present. At least three explainations are possible.

Firstly, sympathetic denervation might not have been completely accomplished at the time of operation. The surgeons concerned agreed that this might explain a few, but certainly not all, of these partial failures.

A second possible explanation is that in a proportion of people an as yet anatomically undisclosed sympathetic pathway exists which is not interrupted by the Smithwick operation.

Thirdly, and the most likely of the three, that sympathetic pathways regenerate. This has been reported in man,[8] and there is also a great deal of evidence to support this view from animal experiments.[9]

We hope to re-examine these patients at intervals. If on reviewing them we find that the amount of vasomotor control in their hands shows an increase it will prove that vasomotor fibres are regenerating. On the other hand, if no change in the amount of blood-vessel control occurs, it will suggest that an anatomically incomplete sympathectomy had been performed.

A questionnaire was sent to all patients to find out if they were satisfied with the results of their operations. Their replies showed that in fifteen hands no vasospastic attacks had occurred after sympathectomy, though attacks had been frequent before operation. The hand which had been the site of causalgic pain was completely symptomless. Attacks of the Raynaud phenomenon of reduced severity and occurring at less frequent intervals were noted in nine hands. In one hand attacks of vasospasm persisted after operation, but though they were as frequent, they were much less severe. Only one patient considered that operation had not been worth while. She had obtained complete relief for three months, but after this her attacks had become as severe and as frequent as they had been before her operations. Her case was further complicated by the fact that at the time of questioning she was suffering from a severe degree of cardiac failure. In none of these patients had the attacks of vasospasm become more severe or of more frequent occurrence than they had been pre-operatively.

Thus these patients—and in this condition it is the opinion of the patient which is the criterion of success or failure—think operation has been well worth while.

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REVIEW

AN APPROACH TO SOCIAL MEDICINE. By John D. Kershaw, M.D., D.P.H. Baillière, Tindall & Cox. Pp. 329. 15s.

THIS book is not written wholly for the medical profession, but for all those persons who are vitally concerned in the life of society and who have an important share in determining the social conditions under which we all live. For this diverse audience the author has produced a simply worded attempt, not so much to teach social medicine, but to show its every-day presence in our lives and to encourage all those whose work lies in the realm of humanity to find a clear basis for their actions and deductions.

This book is comprehensive and covers all aspects of society, which are dealt with under the following headings :—The Anatomy of Society, the Physiology of Society, the Disorders of Society, Medicine in Society, Social Problems of Health, and the Philosophy of Health.

It is a very lucid, clearly thought out piece of writing, and while one regrets the stripping of all man's illusions and romances, one must admire the clear-sighted logic behind the arguments and the true picture remaining.

There is much to be learnt from this book, and an application of some of the ideas put forward would be of inestimable value to the welfare of all peoples.

Dr. Kershaw never descends to destructive criticism of present life, but he has a definite alternative ready to hand which is usually masterly in its simplicity. D. D. and J. C. J.

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The Problem of Endometriosis: A Review

By W. R. SLOAN, M.D., F.R.C.S.,ED. M.R.C.O.G.

No condition in the field of gynæcology exhibits such a variety of manifestations as does endometriosis. No other condition has in consequence been so prolific of speculation and theory to explain it.

The first description of endometriosis or adenomyoma as an entity is attributed to Rokitansky[1] in 1860. In 1870 Waldeyer[2] concluded that nearly all epithelial new growths of the ovary originate from a downward proliferation of the surface epithelium of the ovary, thus constituting invasions of the ovarian stroma by its own covering germinal epithelium. This theory was later to be adapted and developed to explain endometrial invasions of the ovary and developmentally kindred tissues. Von Recklinghausen[3] in 1896, when trying to explain the presence of endometrial tissue in the uterine wall, propounded the theory that when the Wolffian and Müllerian ducts cross in early life there may be an intermingling of these tissues at this site with at times a persistence of embryonic rests of Wolffian origin. This explanation failed entirely to explain why these so-called "rests" constantly develop a Müllerian rather than a Wolffian structure.

Russell[4] at Johns Hopkins in 1898 first described aberrant portions of endometrium in an ovary removed in the course of an operation on its fellow for cystic adenocarcinoma. After surveying the then available theories he came to the conclusion that these were aberrant portions of the Müllerian ducts due to an anomalous point of development in the germinal epithelium.

In 1908, Cullen[5] reporting in a masterly way on seventy-three cases of adenomyoma, was able to demonstrate continuity of the glandular elements with the endometrium in every one of fifty uncomplicated cases of diffuse adenomyoma of the uterus. He concluded that "all adenomyomata of the uterus in which the gland elements are similar to those of the uterine mucosa, and are surrounded by stroma characteristic of that surrounding the normal uterine glands, owe their glandular origin to the uterine mucosa or Müller's duct, no matter whether they be interstitial, subperitoneal, intraligamentary, whether solid or cystic." No one has disputed this since, though Cullen's suggestion that it is the diffuse myomatous growth which by making the interfascicular interstices larger provides the opportunity for endometrial invasion, is not accepted. By 1920 this worker[6] could report what he still chooses to call adenomyomata in no less than ten different places in the body, the more remote of these being in the rectovaginal septum, the ovary, the rectus muscle and the umbilicus. He offered no explanation of the mode of travel or transference of these varieties.

In 1921, Sampson[7, 8] provided a link between these different lesions and locations when he produced his revolutionary "spill and implantation" theory. He admitted that the easiest and most natural conception of the condition might well be that of an abnormal development of the germinal epithelium of the ovary, or of the developmentally displaced epithelium of the Müllerian duct, but gave no less than

sixteen good reasons for the validity of his own theory. This in brief is, that during menstruation desquamated fragments of endometrium wander through the fallopian tubes, and thus spilling into the peritoneal cavity become implanted on the ovary. There the endometrial tissue again exhibits its invasive tendencies, so well demonstrated in the case of so-called adenomyosis, forms blood cysts which later rupture and cause further scatter to the more remote sites in the pelvic peritoneum, where implantation or transplantation again takes place. In 1926[9] he was able to quote in support of this belief the experimental work of Jacobson[10] who successfully transplanted endometrial tissue into the peritoneum of rabbits.

Sampson's work provoked a revival of the metaplasia theory adumbrated, as we have already noted, by Waldeyer.[2] This property of metaplasia had already been extended to the peritoneum by Iwanoff[11] in 1898, and has been called the serosal theory. Novak[12] in a histological re-examination of many hundreds of fallopian tubes, found particles of uterine mucosa lying free in the lumen in only seven instances. In none of these had the patient been menstruating. In at least five of the seven, the portions of endometrium were so large that it would seem impossible for them to have entered through the tiny uterine orifice of the tubes, and as endometrial tissue was found in a number of the ovaries concerned, Novak believed that the fragments were travelling down the tube and not up. He challenged the idea that menstrual fluid regurgitates, at any rate with sufficient frequency to explain such a common condition as pelvic endometriosis. To his mind, the size of the uterine ostium, the prevailing ciliary current, the infrequency of reverse peristalsis in the tubes, and the physiological direction of travel of the ovum all argued against such a happening. Such a journey, moreover, requires several days for the ovum to complete, and so tissue travelling in the reverse direction is likely to take longer. This already dead or devitalized tissue is unlikely still to have the vitality to grow where it falls. Particularly is this so of the ovary, whose dense tunica albuginea seems an uninviting soil. In this connection the findings of Phillips and Huber[13] are of interest. They concentrated on the search for endometriosis of the tube. This they found frequently in the interstitial portion. Of twenty-three cases of abdomial endometriosis, nineteen showed endometrial extensions to the tubes, and of these fourteen were bilateral, and nine polypoidal in form. In almost all cases the fimbriated ends were open, but the interstitial portions closed. These authors say that Sampson's theory met with much opposition because it erroneously supposed that cast-off menstrual epithelium was the offender, whereas they believe that it is the living freshly built up mucosa which gets broken off at such sites as they describe and becomes transported and transplanted. Davis and Cron[14] and Rubin[15] with others have drawn attention to such possible causes of retograde transport and spill as operative manipulation, forcing through the tubes by the plunger effect of the dilators during the operation of curettage, the injection of air and CO_2 during tubal insufflation, and defective uterine drainage in the presence of retroversion.

The protagonists of the metaplasia theory however point out that all the genital epithelia are derived from the cœlomic epithelium of the urogenital folds, and so

are related to the peritoneum. Indeed, the endometrium and endosalpinx may be looked on as modified peritoneum, as is also the germinal epithelium of the ovary. The developmental potentialities of cœlomic epithelium, and in particular of the germinal epithelium, are not used up, and it is still capable, under the proper activating influence, of going on to further differentiation into endometrium or endosalpinx. We have now arrived at another phase of the metaplasia idea which is spoken of as the cœlomic theory.

Both schools recognised the necessity of some local circumstance or influence which favours the development of ectopic endometrium, whatever its origin. Sampson thought it might be due to some substance discharged from the end of the tube over the ovary and pelvic cul-de-sac. Novak and others postulated a hormonic factor and guessed that the high incidence in the ovary is due to the fact that it is the main producer of the hormones concerned, and hence they exert a more powerful influence upon local than distant tissues. Both again found themselves on common ground in 1930, when Sampson[16] published the results of his investigations of tubal stumps from one hundred patients who had had a previous salpingectomy or tubal sterilisation. The operation was bilateral in forty-seven cases giving one hundred and forty-seven stumps. Misplaced Müllerian mucosa was found in one hundred and twelve of these as against sixteen of two hundred normal cornua with intact tubes examined as control. He stated frankly that in these cases the tubal mucosa at times assumes the structure and function of uterine mucosa. He thus assented to the occurrence of metaplasia. In 1932 after a ten year study[17] of the fimbrial end of fallopian tubes, he found the mucosa-serosal junction an unstable affair. Here endometriosis arises by the tubal mucosa undergoing an invasive and metaplastic change to assume characters of endometrium and may spread over the surface or penetrate the ovary and cause endometrial cysts. In three patients operated on whilst menstruating, these conversion endometriomas showed typical menstrual reaction. Novak, who had earlier conceded that Sampson's implantation theory explained some cases of endometriosis, now found the latter admitting that some cases of endometriosis are due to direct metaplasia of tubal mucosa into endometrium, with subsequent invasion of the ovary, and could say that, "It seems possible that before many years have passed, Dr. Sampson and I might well be able to present a joint paper on the etiology of endometriosis."[18, 19]

The common belief in an exciting factor possibly of hormonic nature, finds support in the frequent co-existence of other pathological findings. Numerous workers have drawn attention to the almost constant association of fibroids, polypi, endometrial hypertrophy, and other conditions of a hypertrophic or neoplastic nature with endometriomata. Some, like Allen[20] or Jeffcoate and Potter[21] have drawn attention to the frequency of precedent menstrual disturbances as indicating ovarian dyscrasia. Witherspoon[22, 23] finds that when sixty-four per cent. of forty-four cases carefully studied show ovarian and uterine endometriosis associated with hyperplasia of the endometrium, this indicates more than a mere coincidence. Goodall[24] indeed regards hyperplasia of the endometrium as an integral part of the condition, and speaks of endometriosis of the endometrium. Meigs[25] concludes

that when thirty-six per cent of four hundred patients suffer, then the condition is not a true tumour, but represents disturbed physiology. The manifestations of endometriosis and the allied conditions just listed being mainly of a hypertrophic nature, and long known to be curable by castration, suspicion has fallen on the œstrogenic function of the ovary, and by most writers an excess of this hormone, absolute or relative, is regarded as the most likely common factor. The successful production of fibromyomata albeit atypical in guinea pigs by Nelson[26] and Lipschutz[27] using prolonged administration of œstrogens lends strong support to this conception. The latter, incidentally, also proved the antifibromatogenic and anti-œstrogenic effects of both testosterone and progesterone. What determines all the different manifestations discussed, and the variegated pattern of endometriosis itself, has been beyond the wit of man yet to suggest. It is, however, an established principle of endocrinology that endometrial and myometrial changes are invariably secondary to ovarian dysfunction and not vice versa. When we finally understand the normal hormone control of the healthy endometrium and why, for example, it reacts differently in different parts to the cyclic hormones of menstruation, we will doubtless have the key to these other problems.

This conception of endocrine influence has found a limited clinical use in the case of endometriosis. Miller[28] has used testosterone propionate pre-operatively over a period of three months to reduce the size of an endometrioma, and thus make a subsequent exclusion much simpler. Geist and Salmon[29] recommended its use more particularly in those cases in which operation had been refused or has been partial in order to conserve the reproductive function. Hirst[30] has used it in similar fashion.

A curious feature of endometriosis is that it tends to be a self-limiting disease. According to Goodall, spontaneous arrest takes place in about sixty per cent. of cases. Many cases go unrecognised even at operation because they are already healed, and many surgeons are not familiar with the evidence of the old lesion. Indeed, even the pathologist may fail to discern it due to the disappearance of the typical glandular elements. Sampson[8] attributes this to the destructive effect of recurrent menstrual hæmorrhage upon endometrial epithelium under confined conditions. Goodall[24] suggests that it is due to the spontaneous passing of the phase of hormonal dyscrasia. Similarly this writer suggests that when pregnancy occurs in the presence of endometriosis, this is likewise due to the removal of a biochemical barrier to conception set up by the hormonal imbalance.

The belief has prevailed since Sampson first gave expression to it that pregnancy has a favourable effect on endometriosis. This is extremely difficult of proof. Indeed, the evidence of the best documented case known to the writer runs counter to this belief.[31] It seems highly improbable that decidual reaction of itself, which is a constant finding in these lesions, would destroy ectopic endometrium any more than it does the endometrium proper. If then the occurrence of pregnancy does not signalize the passing of the hormonal dyscrasia, it would appear that the supposed benefits of conception are due either to the mere passage of time allowing a natural

tendency for cure to assert itself in the absence of the usual cyclic stimulation, or are bound up with the cognate problems of uterine enlargement and involution in pregnancy.

Whatever be the ultimate outcome of the search for an explanation of endometriosis, it can not be doubted that the conception which links together the endometrial hyperplasias with the various invasive and wandering propensities of the endometrium has the attraction of simplicity. Simplicity, however, can not be said to characterize the problems which await solution before we know the whole truth.

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Success and Faddery

By F. M. B. Allen, M.D., F.R.C.P.(Lond.)

Presidential Address to the Belfast Medical Students Association

It is an interesting occupation to view an audience of doctors, either from the platform or a balcony. They vary in their physique, their physiognomy, and their apparel. Some look like healthy gardeners, a few like successful tradesmen, some like professional gentlemen, and a small minority even resemble prosperous bookmakers.

Sometimes in contemplating a medical audience, I try to appreciate why one doctor is rated a success and another as being only of indifferent professional ability —the successful one may have been a moderate student, passing his exams indeed with some hesitations, reaching and conquering the final with an effort; whereas he who is regarded as only a mediocre doctor by most, and a good doctor by but a few, had a "brilliant medical career."

I do not know the answer, nor have I met an honest observer who can say in a few words why one has been favoured by success, whereas it seems to evade others. And, indeed, if an answer were forthcoming, it would be necessary to define "success."

Is success the accumulation of monetary wealth? Or should it be gauged by the magnificence of the doctor's residence and furniture and the possession of an expensive car; or by the extravagence of his hospitality? Or should it be measured by popular esteem? No, not by any or all of these, but by the personal satisfaction which one's conscience grants of work well done. The French have a saying—somewhat worldly, I admit—that the three essentials of success are:

"a little knowledge, much tact,
and a fair amount of advertisement."

But we remember that Dr. Johnson's opinion that the ultimate object of all ambition was "happiness at home."

Osler says:—"While living laborious days, happy in his work, happy in the growing recognition which he is receiving from his colleagues, no shadow of doubt haunts the mind of the young physician, other than the fear of failure; but I warn him to cherish the days of his freedom, the days when he can follow his bent, untrammelled, undisturbed and not as yet in the coils of the octopus. In a play by Oscar Wilde, one of his characters remarks, 'there are only two great tragedies in life, not getting what you want and getting it!' and I have known physicians whose treadmill life illustrated the bitterness of this and whose great success at sixty did not bring the comfort they had anticipated at forty. The mournful echo of the words of the preacher rings in their ears, words which a physician quoted 'better is a handful of quietness, than both hands full with travail and vexation of spirit.'"

My Miscellany is going to lead me through a series of thoughts without any logical sequence and by ways that have mostly been trodden before.

Life has been compared with a race since Biblical times—"The race is neither to the swift, nor the battle to the strong; time and chance cometh to all." It is an apt comparison, particularly for the competitive life in our profession with its host of competitors, its handicaps, its hurdles, and its strenuous course. The scope and amount of medical work are always increasing, and it has been said—let me quote it for your comfort!—"That though Democracy may starve the clergy and the practitioners of the Arts, it will always demand doctors." (Dean Inge). In other words, do not be depressed by the number of doctors around you—there is a prize for everyone who merits it. Some of you will start out joyfully, as did Christian and Hopeful, and for many days will journey safely towards the Delectable Mountains, dreaming of them and not thinking of disaster until you find yourselves in the strong captivity of Doubt and under the grinding tyranny of Despair. You may have been over-confident. Osler advises you to "begin again and more cautiously." He says "no student wholly escapes from these perils and trials; be not disheartened, expect them. Let each hour of the day have its allotted duty, and cultivate the power of concentration which grows with its exercise, so that the attention neither flags nor wavers, but settles with tenacity on the subject before you."

There is an important consideration which warrants your attention as students —namely, the necessity for a true sense of vocation. I cannot imagine anything that will lead more surely to failure than taking up the profession of medicine if one's temperament is unsuitable, or if one's inclinations and ambitions are attached elsewhere. Do not be attracted to our ranks because someone has acclaimed the "nobility" of doctors or surgeons; the profession may be made a noble one by each and all of us practising it and doing good to our fellowmen—but we are not greater saints, neither are we greater philanthropists, than those carrying out their daily work in other walks of life. Robert Hutchison has said that he would: "commend it on the mundane grounds that medicine is an interesting, intriguing, and even an amusing occupation in which, although, with all its labours and languors you may often know fatigue. You will at least escape boredom; that it gives opportunity for the exercise of all your powers, physical, mental, and moral, and that it offers an admirable field for the study of human nature in the raw."

Who knows what the future holds for our profession in face of the impending legislative changes; but I feel assured that a doctor will always make a living: his skill once acquired has a very wide market, for disease is the same all over the globe. Making a fortune is an entirely different matter. Very few men in any learned profession make a fortune, and if your ambition lies in this direction, get rid of the illusion at once and direct your talents elsewhere! Sir Andrew Clarke said (after forty years of hard work) that he had striven for ten years for bread, ten years for bread and butter, and twenty years for cakes and ale. Perhaps the new medical service may render the first ten years unnecessary; but I doubt if many will enjoy the "cakes and ale" stage. Remember, however, that: "The doctor, like water, is one of the few indispensibles of life. He launches us into

the world. Upon our voyage therethrough he is periodically summoned on board to assist us in that most delicate operation known as 'executing repairs while under steam,' and when the end comes at last, and the failing machinery refuses any longer to obey the calls from the bridge, it is he who takes the wheel and pilots us with tenderness and skill to our last anchorage. That seems to me a rather fine privilege" (Ian Hay).

In your student or post-graduate career you will realize quite early how untrue it is to say that all men are born equal. Some may have indifferent health, others lack of intelligence, inborn laziness, or shyness, and some may feel poverty a handicap. Most of these may be overcome, and although poverty may be (and often has proved) a spur, the rich parent may provide many facilities but not the incentive created by poverty.

A well-known physician, Sir Robert Hutchison, when asked—supposing he were a good fairy—what gifts would he bestow on anyone setting out on a medical career, gave a short list which I commend to your attention, because I regard them as being all essential in greater or lesser degree in that pursuit of success to which I have again returned. He said his first gift would be good health, because medicine is a dangerous profession and a sick doctor is a tragedy. Not the vulgar good health of the athlete who regards physical fitness as his goal, but rather the wiry constitution which is able to resist fatigue and infection. There are obvious and many ways in which health can be spoiled and ruined—but it is not for me to point to the obvious pitfalls of youthful indiscretions.

Then there is luckiness. I am a firm believer in the part luck (or good fortune) plays in happiness and success. If you chance to have a good background in your home, your parents and your friends; to find in your examinations questions to which you happen to know the answers; to obtain an appointment which has just become vacant; to meet an agreeable partner (in practice or in love)—then indeed have you been gifted. Too often I think a plan of life is made by the student or young doctor much too early in his career. This, if followed too rigidly, is a mistake, except in so far as it includes a resolve to work hard and to exercise patience. Flexibility of mind as well as of body should be cultivated. Position and timing in life and in work are as important as in games. You will all learn in due course how many of your teachers and retired "elder statesmen" found their course diverted by some unforeseen event—sometimes a disappointment, at other times an unexpected opening meant a complete alteration of plan with a more successful outcome. An open and receptive mind and patience are essential attributes until one's course seems set.

This fairy must also endow the student or doctor with brains. There is a happy medium between the "super" and the brainless. The best student may be a consistent prizewinner and excel in examinations; but this is not a guarantee of success as a doctor. Indeed it is sometimes dangerous to be "too clever." The cynic will go to the other extreme and give unjustifiable encouragement to the dull and stupid with the statement that the student who just scrapes through his examinations (with some or many rebuffs by the examiners) often makes a successful doctor.

This is not so. The most experienced of our medical philosophers and guides hold that the student who does well at examinations does best in after-life. However, diligence, persistence, and doggedness often do make up to the average student what he lacks in brilliance of intellect.

Everyone is agreed that equanimity (the fourth gift) is a desirable, if not essential, quality of mind for the doctor. You should read Osler's inimitable "Aequanimitas." It is the faculty of facing sudden events and disconcerting emergencies with calmness and of preserving you from the wearing effect of all the worries and anxieties inseparable from medical practice. Time develops the desirable state, but do not let it be replaced by, or mistaken for, indifference. Those of you who possess true sincerity and sympathy and a sense of justice will go far with your patients. I do not mean those exaggerated mannerisms described as perfect "bedside manners"—or exaggerations of the habit. The patient, especially a sick child and its mother, is the supreme test of genuine sympathy and sincerity. There is, however, another wide field for the exercise of these qualities—amongst your professional brethren and those lay persons who for one reason or another are associated with your activities. Although you will find yourself in professional rivalry with other doctors, be slow to take an unfair advantage of them, and close your ears when you hear something to their discredit; you may find yourself worsted in the exercise of low cunning, and the bearer of unfavourable criticism may have yourself as his next victim.

There is magic in having a sense of humour. It is invaluable to help you to bear with serenity the changing temperament of your patient and the apparently unreasonable attitude of relatives; and to treat with tolerance and some amusement the eccentricities of your colleagues. It will often let you see yourself in a different light and may even make you laugh at yourself; you must be prepared to enjoy a joke against yourself, to appreciate a reversal of wit. You will certainly be saved from the besetting sin of pomposity, for it will save you from taking yourself too seriously. Develop it, but let me remind you that it cannot be cultivated in solitude —it thrives in company which is intellectual, social, and athletic. It is fit and proper that you should create the opportunity to break away from your professional work with some regularity and indulge in some interest apart from medical "shop." And if you perforce find yourself a patient, you must see the humour of many of our traditional practices and the whimsies of doctors when viewed from the bed. Robert Lynd describes: "The humiliation of helplessness is at first rather overwhelming to anyone to whom the life of a patient is a novelty; one is reduced to the condition of a newborn baby, even as regards washing, without the newborn baby's beautiful unconsciousness of its plight."

This list of gifts cannot be closed without mentioning a sense of beauty as highly desirable. There is so much in medical life that is ugly—distressing diseases of cancer and ulcers, the social sordiness of the slums, the hardships of the poor and the disabled, the struggle of the widow with an adverse world, and the loneliness of the aged and infirm. To cultivate and exercise one's senses in fresh fields is necessary as a compensating and steadying influence. Whether it be in music, in

literature, in a garden, in poetry, or in games and physical exercise, you should cultivate a hobby which will distract your mind from continuous contact with your work and provide you with a broader outlook and vision which will add to your personal happiness as well as your professional success. As Lord Horder says: "What does he know of Medicine, who only Medicine knows."

Some of you may already have set your hearts on some specialism, even in your early student life. The drama of the operating theatre or the manipulation of the bacteriologist's tubes may appeal to you as your life's work; but I would suggest to you that the whole patient must be studied, not the height of a column of mercury in a syphmomanometer or of blood in a sedimentation tube. The danger of specialisation is that the whole attention of the specialist is directed to the narrow field of his own speciality in which he becomes absorbed in details, assisted by complex instruments, and so he cuts adrift from his colleagues and pursues a voyage of his own. Walshe said in his own pungent fashion: "The doctrines of those who see their own speciality everywhere in medicine, who have their own touchstone by which the phenomena of illness are to be assessed. They measure every man's corn by their own bushel, and are obsessed by this or that cult of ideas. They make up those cohorts of hobby-horse riders who cavort noisily to and fro across the fields of medicine, throwing up little but dust into one's eyes."

In passing, I would have you note that the study and practice of child health and disease in children is not a speciality. It is the practice of medicine in a certain age-group. The pædiatrician is a general physician first and all the time, and it happens that it is among children he lives his professional life. Pædiatrics attracts a lot of interest nowadays, not because of any sentimental attachment to children, but because it is realised how much ill-health and disease arise in early life. Many of the morbid processes of the adult have their seeds in childhood, and many of the diseases can be avoided by proper preventive measures. And further, if any other reasons were necessary, is the acknowledged fact that a very large proportion of general practice is amongst the children.

After this mild sermonising as to how to achieve success—or some of the factors involved in its attainment, let me now turn to some of the less desirable methods by which some reach the goal or at least gain notoriety. By the practice of fads and the following of fashions many doctors take the opportunity of the flood-tide of popular beliefs, and gain a position—and a successful one too—which would not otherwise have been theirs. Remember—

> "There is a tide in the affairs of men,
> which taken at the flood leads on to fortune."

How many surgeons have flourished by following indiscriminately the fashion of removing the tonsils or appendix, resecting the colon, suspending the uterus, and fixing the proptosed kidney, colon, or stomach? There are "fashions" in medicine just as there are in clothes, the feminine hat, or the male trousers. Psychoneurosis has replaced neurasthenia, glucose has supplanted Eau de Cologne in the sick-room, digoxin has relegated powdered digitalis to the pharmacist's storeroom,

and liquid paraffin holds sway where senna pods or liquorice once ruled in the nursery.

A fashion, in its essence, is characteristically transient. Last year's hat will not serve at next year's weddings, and probably last year's fashion for the repair of a hernia will not satisfy next year's popular surgeon. Fads are less desirable than fashions, because they are the products of individuals; whereas a "fashion might be regarded as an epidemic fad." It is fortunate that fads are usually spread only by persons of some importance; also the faddist must be of a forceful character, preaching his doctrine in season and out of it; and he must keep up the reiteration of his belief on the principle that "what I say three times is true."

There are congenital faddists—those "born with a kink." These are credulous individuals who ever fail to be sceptical and are without humour, judgment, and common sense. Macaulay said of the faddist that he is "utterly lacking in the faculty by which a demonstrated truth is distinguished from a plausible supposition."

Others achieve "faddery" by specialism in one branch of medicine or surgery. There is the tuberculosis expert who regards every lung as "suspicious," the hæmatologist who must know the red-cell count of every patient; the V.D. specialist who can only see his clinical problem through a "syphilitic fog"—Oliver Wendell Holmes said of a famous French syphilologist that he would submit Diana to treatment with the mineral specifics and order a course of blue ointment (or N.A.B.) for the Vestal Virgins. Fads are often practised as the result of boredom with things as they are or by the restless desire for something novel—just as in politics. And just as cranks try to be too good and become vegetarians and the like, so some doctors, by endeavouring to be too clever or scientific, become faddists.

The advertising chemist is responsible for a certain number of medical fads. With the resumption of postal advertising the doctor will have thrust upon him information on the virtues of charcoal as a means of combatting auto-intoxication, intestinal flatulence, and much else—and by the end of a month he will have been informed of at least ten elegant preparations for dispensing it. Purgatives, aperients, laxatives, cholagogues, hormones, extracts, vitamins will follow in rapid succession, until the wise physician will turn with relief to the well-tried and authorised preparations of the pharmacopœia and the materia medica lecture-room. It would be better for more of us to follow Pope and—

"Be not the first by whom the new is tried,
Nor yet the last to lay the old aside."

There are fashions which have had their day. I know of at least nineteen preparations recommended for bed-wetting, and undoubtedly each one, as it was introduced, effected cures; but alas, the success could not be maintained, and new idol after new idol succeeded to the throne! It reminds one of Trousseau's advice to a patient: "Take this while it is still curing."

It is essential, therefore, that we should exercise our critical faculties, practise humour, adopt a sane view of the new and the novel, avoid the snares and pitfalls of the priesthood of fads and fashion-following; remembering all the time that

Jenner, Semmelweiss, Lister, and many others were originally regarded as cranks.

Before being committed to a new venture it is wise to pause and think—to use the critical faculties with which we have been endowed—and to utilise the knowledge we possess particularly of history (medical) and pathology. Minot said :—"Biography and history, including that concerning medicine, serve for orientation and perspective, and is stimulating, along many lines. There is always something corresponding to our own lives to be found in history. Whether one reads of Sylvius and learns how he first introduced bedside teaching, or about the life of a statesman or any other human being, one will become a better student of man for the experience."

As regards pathology, this school is fortunate in having one of the finest systems of teaching available anywhere. The student who fails to grasp the opportunities available at Queen's is unworthy to be accepted in the Faculty of Medicine.

Do not argue with the crank or the faddist. A sense of humour is a much better weapon to defeat him, and ridicule helps to destroy him. But we must be sure of our facts. Accurate observations are essential in every walk of life, but in none more vital than in medicine. It is better not to discuss a problem at all than to be "an inexhaustible source of inaccurate information." Remember that "the knowledge which a man can use is the only real knowledge, the only knowledge which has life and growth in it and converts itself into practical power. The rest hangs like dust about the brain or dries like rain-drops off the stones" (Froude).

Recently the tercentenary of the first Astronomer Royal—John Flamsteed—was celebrated. It is said of him that he was largely self-taught, and entered Greenwich Observatory on its foundation in 1675. He found that there was no satisfactory method of finding the longitude of a ship at sea. Such a calculation could only be made when precise information as to the position of fixed stars and tables of the moon's movements were available. It entailed the preparation of a catalogue of the fixed stars and the systematic observation of the sun, the moon, and the planets so that tables could be prepared from which their positions could be computed with accuracy. This was indeed a Herculean task, too great for one man, and a garbled inaccurate volume of his observations was published without his consent. His insistence upon accuracy was outraged, and caused him to acquire as many as he could of the four hundred printed copies, which he publicly burned as "a sacrifice to heavenly truth." His is the story of unflagging industry and scrupulous care—just as it is in the world of medicine, of those men and women who have added greatly to our knowledge of disease and its treatment.

I have mentioned that the future of medical services in Northern Ireland has not yet been publicly declared. It will doubtless, in the main, follow the scheme in England. While there is much to criticise and condemn in the proposals, there is something to admire. I hope some plan will be evolved whereby the general practitioner will be re-established as the family doctor and be the "guide, philosopher, and friend" of his patients. I abhor the idea of doctors who have undergone a strenuous six years of medical education—at considerable expense—becoming nothing more than "signposts" directing their patients to the cardiologist, neurolo-

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gist, radiologist, or psychiatrist. The true function of the family doctor is to treat the sick, and when specialist help is necessary in diagnosis or treatment, he should be in a position to know where and when he can obtain the best advice; and in addition, I can see the family doctor taking an increasingly important part in preventive medicine, in practising the acknowledged methods of preventing disease and in working in association with local authority organisations.

There is no better training for this than in pædiatrics. Because in this field the beginnings of disease can be seen and studied; real preventive work can be undertaken; and, more important still, the pædiatrician becomes an expert observer. So much depends upon the eye and the hand, and so many of the special investigations are either very difficult or even impossible to carry out, that the doctor dealing with infants and children becomes specially competent. But he must be accurate in his observations, and if I can commend one thing especially to you which will contribute to your success, it is the cultivation of the habit of precise and accurate observations and recording of the facts available. Thus will you be in a position to make a diagnosis, and once you know what is wrong with your patient the treatment is accessible to you and you can estimate the duration of the illness and the prospect of your patient's recovery. And thereby you will have answered the three questions which every patient consciously or unconsciously asks you: "What is wrong with me? How long will I be ill? Am I going to recover?"

I introduced Osler in my early remarks, and I cannot do better than use his words to close: "To you, the silent workers of the ranks, in villages and country districts, in the slums of our large cities, in the factory towns, in the homes of the rich and in the hovels of the poor, to you is given the harder task of illustrating with your lives the Hippocratic standards of learning, of sagacity, of humanity, and of probity. Of learning, that you may apply in your practice the best that is known in our art, and that with its increase in your knowledge there may be an increase in that priceless endowment of sagacity, so that to all, everywhere, skilled succour may come in the hour of need. Of a humanity that will show in your daily life tenderness and consideration to the weak, infinite pity to the suffering, and broad charity to all. Of a probity that will make you under all circumstances true to yourselves, true to your high calling, and true to your fellow-man."

I gratefully acknowledge the use I have made of the writings of Sir Robert Hutchison in the preparation of this address. I have always appreciated his friendship and have admired his philosophy and humour. To the others from whom I have quoted so freely I also express my indebtedness.

The Adrenal of the Newborn

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THE involutionary changes occurring in the suprarenal cortex during the neonatal period and the gradual development of the adult cortical architecture were first described in 1911 by Thomas, Kern, Elliott, and Armour. Other longer series of suprarenals have been studied (Lewis and Pappenheimer (1916), Benner (1940), Blackman (1946)), and it was with a view to discovering if the observations, sometimes diverse, of these and other workers, were borne out by an examination of the material at the disposal of this Institute, that the present study was undertaken.

At birth, the adrenal medulla is small, and the cortex with the exception of a peripheral layer, corresponding to the adult zona glomerulosa, is composed of large polyhedral cells with eosinophilic cytoplasm and distinct circular nuclei showing a granular arrangement of chromatin. These cells are closely packed together, their arrangement showing no definite pattern. They have been given a variety of names, fœtal cortex, fœtal reticular zone, androgenic zone, and X-zone; and for the sake of brevity the last mentioned name will be used for descriptive purposes.

The adrenals of one hundred and sixty infants were studied (the age distribution is tabulated in the accompanying table), main attention being focussed on those dying within the neonatal period. With the exception of the five anencephalic monsters, the infants were unselected, the causes of death being varied, asphyxia predominating in those dying within the first twenty-four hours, while the majority of the remaining neonatal deaths were attributable to sepsis, frequently bronchopneumonia.

Number of adrenals examined		160
Age Distribution:		
Still births	19	
Infants dying within 24 hours	28	
Infants dying 2-7 days inclusive	38	Neonatal deaths 116
Infants dying 8-14 days inclusive	34	
Infants dying 15-28 days inclusive	16	
Infants dying 5-12 weeks	20	
Anencephalic still births	5	

Blocks from the adrenals were fixed in Zenker's solution, and stained with hæmatoxylin and eosin. The average width of the true cortex was measured by projecting the image on to a scale. No satisfactory method was devised for measuring the degree of degenerative changes in the cells of the X-zone, so this had to be estimated subjectively. It was rapidly realised that the width of the true cortex and the degree of X-zone involution were not directly proportional, particularly in the youngest age groups studied.

A brief description of the histological changes occurring during involution will

be given before considering the changes seen in this series. At birth, there is frequently congestion of the X-zone adjacent to the medulla and there may be small extravasations of blood; degenerative changes start in this area, affecting first individual cells. The cytoplasm becomes pale and granular, the cell outline is lost, the nucleus appears to undergo karyolysis, and finally isolated cells drop out. While this is occurring a connective tissue network, surrounding the degenerating cells, comes into prominence. This process spreads to the periphery until the previously compact mass of polyhedral cells is replaced by connective tissue supporting degenerating cells in its meshes, and in the majority of cases the X-zone ceases to exist as a zone by the third week. During this period the zona fasiculata has developed inside the zona glomerulosa and is gradually growing in until it reaches the connective tissue of the involuted X-zone. Changes now occur more slowly, the isolated X-zone cells taking several weeks, sometimes months, to disappear, the connective tissue band, however, remaining as a few strands of fibrous tissue. The medulla increases in size and the three adult cortical layers can be distinguished.

The small group of stillbirths will be considered first; the majority showed congestion of the inner X-zone, with a few degenerative changes in individual cells, and a few showed commencing growth of the zona fasiculata. There was no variation with the degree of maturity of the infant or with sex.

In the group dying within twenty-four hours, there were eight females and twenty males. Of these twenty-two were not more than thirty-eight weeks estimated maturity or weighed less than five and a half pounds. The typical histological appearances resembled those of the previous group. There was much individual variation to which no cause could be assigned, premature infants showing as wide a variation in cortical width as the mature, though an impression was gained that the onset of necrosis was established more rapidly in the former. Five cases in the group were infected, all showing pneumonia. Of these, four showed cortices of average width and one of more than average width. There were no differences attributable to sex.

Twelve of the infants dying from the second to the seventh day inclusive were recorded as premature. Cortical changes were seen to be proceeding with rapidity, and by the seventh day the zona fasiculata was well developed in most cases, and degenerative changes had involved the entire X-zone with the exception of a narrow peripheral band. There was wide variation in cortical width, and in two cases degeneration had involved the whole X-zone by the seventh day. One twenty-eight weeks infant dying on the second day showed an extensive degree of degeneration combined with a greater development of cortex than seen in others of the same age. A child dying on the fourth day with bronchopneumonia showed changes in advance of the group, but there was nothing in the history or pathological findings to distinguish this infant from the others.

In 44 per cent. of the group, eight to fourteen days old, the X-zone had ceased to exist as a zone, being represented by a connective tissue network containing degenerating cells. In general, the changes were progressive throughout the group. Degeneration appeared retarded in two infants, one showing changes compatible

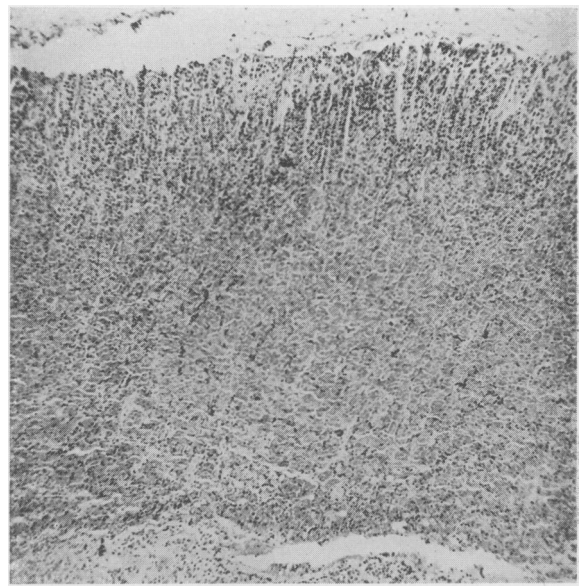

Plate 1 (x60)

Suprarenal. Three day old infant showing narrow true cortex (A) and broad X-zone (B).

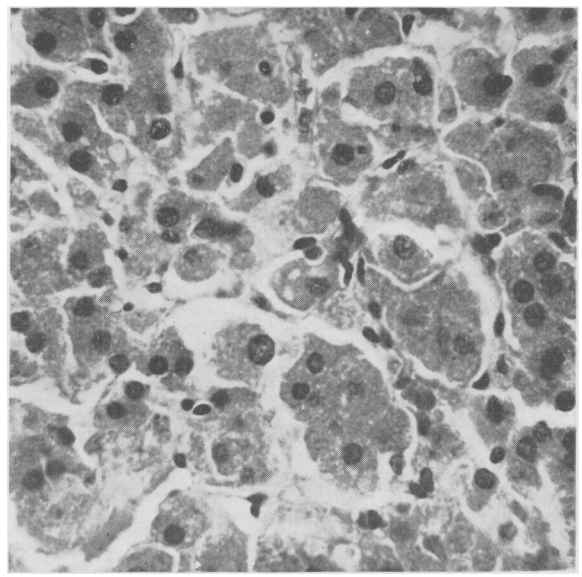

Plate 2 (x450)

Suprarenal. One day old infant showing the granular polyhedral cells which compose the X-zone.

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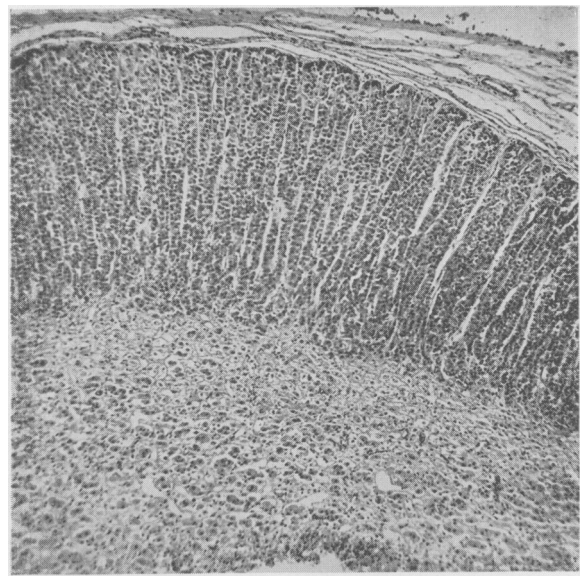

Plate 3 (x60)

Suprarenal. One month old infant showing growth of the true cortex (above) and degenerating X-zone (below).

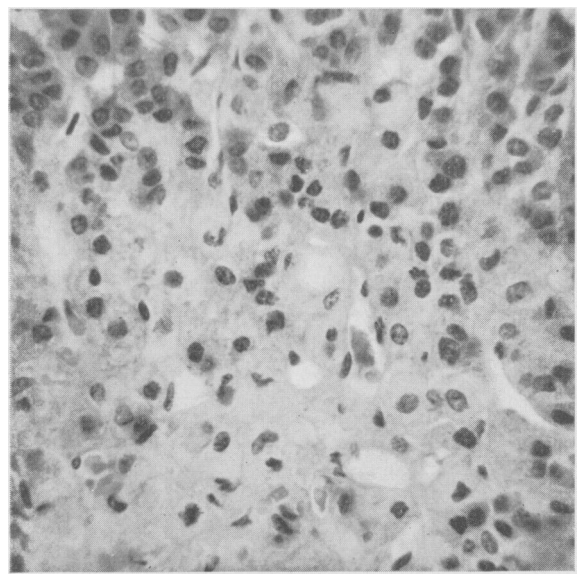

Plate 4 (x450)

Suprarenal. Infant—one month old—showing connective tissue network containing degenerating X-zone cells (below) being invaded by the columns of the proliferating zone fasiculata (above).

with a three day old infant. Both these patients had bilateral pneumonia, with empyema and abscess formation respectively. Twins dying at ten days showed essentially the same picture, although a patent interventricular septum was demonstrated in one, while the other had severe jaundice with intracanalicular bile thrombi, pelvic megacolon and localised peritonitis.

Involution continued fairly uniformly in those dying between fifteen and twenty-eight days, only one infant showing a definite X-zone after sixteen days. This child, who lived a month, showed a degree of involution compatible with an eight day old infant, but there was nothing remarkable in this infant's history and at post-mortem it showed laryngitis and bronchopneumonia.

Finally the cases dying between one and three months were examined. Here again there was individual variation. Two infants still possessed a definite X-zone (although showing necrosis). One was alleged to have been jaundiced from birth and showed hæmosiderosis of the liver and spleen and bronchopneumonia, while the other showed septic bronchopneumonia with abscess formation. Three cases showed a more adult configuration of the gland with the X-zone condensed to a narrow band of fibrous tissue; these cases all showed malnutrition.

Having described the observations made on these cases, it is of interest to see whether these bear out those of previous series. In general there is agreement regarding the process of involution in its broad outlines, and the period at which the changes occur; although the degree of individual variation to which no causative factor can be assigned, must be stressed. It is agreed that prematurity has no effect on the involutionary process, the condition of the X-zone appearing to depend on the duration of extra uterine existence, but syphilis, pneumonia, congenital cardiac abnormalities and anencephaly have all been implicated as causing variations in the normal process.

Syphilis is alleged to retard the disappearance of the X-zone. In this series there were five babies in whom the pathological changes of congenital syphilis were demonstrated at post-mortem; one a stillbirth, and three dying in the group from four to twelve weeks, showed changes consistent with their age group, while the other, who lived nine days, showed changes rather in advance of its age group. It is impossible to be dogmatic where only five cases have been studied, although the original observation was made by Lewis and Pappenheimer on a smaller group of cases, yet it can be definitely stated that in this material no retardation of the disappearance of the X-zone due to syphilis was observed.

Pneumonia is stated to cause an increase in size of the true cortex. In this series it was difficult to confirm this point, as the majority of babies died with evidence of bronchopneumonia. Where there were non-pneumonic babies for comparison the true cortex of the former appeared to be of average or over average width. In a few cases where the true cortex of the pneumonic baby was of less than average width, empyema or abscess formation was present as a complicating factor.

Children with congenital cardiac malformations are said to have delayed post-natal involution as a result of low oxygen tension in the child's blood—no evidence for this was found in this series where five cases with major abnormalities were

examined, nor was any retardation of involution seen in any other condition characterised by dyspnœa and cyanosis.

Adrenal hypoplasia in anencephalic monsters was first observed by Morgagni in 1723; and Elliott and Armour (1911) in describing a case of "hemicephaly" demonstrated that this hypoplasia was due to the absence of fœtal cortex (X-zone) and that the adrenals (in a monster of five days old) resembled miniature adrenals of a child of one year old. Angevine (1938) has made a study of eighteen of these monsters and found the suprarenals to be all of adult type, and following Meyer's (1912) observations that the five months anencephalic fœtus shows a normal X-zone, it was assumed that the involution, which normally occurs post-partum, had occurred during the second half of intra-uterine life.

Five stillborn anencephalic infants were studied, of which two were full term, and a third weighing 3lb. 4½oz. was estimated at thirty-six weeks maturity (one of triplets). In three cases the adrenals were small, in one the right adrenal was large and the left small, but in none of these cases was there failure to demonstrate the X-zone. Two cases, one of which was full term, showed a broad X-zone and a true cortex indistinguishable from that of the average stillborn infant. In two other cases the growth of the zona fasiculata was more advanced than that of the average stillborn infant, but there was a distinct narrow band of X-zone present showing congestion with slight degenerative changes in the central cells. The final case, a full-term female, in addition to advanced development of the true cortex, showed degenerative changes in the narrow band of X-zone, comparable to those of an eight day infant. The loose connective tissue framework had been formed and cells were dropping out and showing degenerative changes.

Thus in only one case out of five was there evidence that degenerative changes had commenced prior to birth and the duration of involution in this case had probably not exceeded eight days, if the process is comparable to that occurring in the average infant. The theory that involution occurs in the second half of pregnancy to produce an adult suprarenal gland at birth in the anencephalic monster was not borne out in this series.

The function of the X-zone and the significance of the rapid involution during the early neonatal period remain unexplained—various theories have been advanced, none of which is entirely satisfactory. An androgenic function has been assigned to this zone (Grollman (1936) Vines (1938)) and where persisting cellular elements hypertrophy in adult life the adreno-genital syndrome is said to result. This has been denied by Blackman, who finds in two infantile pseudohermaphrodites an X-zone undergoing normal involution. Howard (1927) has demonstrated a zone in the mouse adrenal, which develops after birth and is definitely linked up with sexual function; which she considers homologous to the human X-zone. Others have associated X-zone involution with the physiological switch-over to an independent existence; thus alterations in oxygen tension, changes in heat production and an increased basal metabolic rate have all been implicated. Blackman claims to recognise the developing adult reticular zone by the seventh day in the outer layer of the X-zone, and considers the latter is merely the fœtal reticular zone from which

the adult will differentiate. No attempt can be made to dogmatise as regards X-zone function from this series of adrenals, but there are several observations that might have a bearing on this important subject. In only one case in one hundred and sixty (an anencephalic fœtus) was there strong evidence that involution had been initiated before birth, in other stillbirths degenerative changes were minimal and might not be part of the involutionary process, as there appeared to be a post-natal lag period of two to three days before degeneration occurred to any marked degree. This coupled with the fact that the maturity of the infant does not appear to affect the rate of involution of the X-zone, would suggest that the process is initiated by some stimulus of extra-uterine existence or the withdrawal of some stimulus of intra-uterine existence and the finding of a definite, if somewhat reduced X-zone, in the suprarenal of the anencephalic fœtus, would bring these monsters into line with the normal infant. The degree of individual variation for which no cause could be assigned and the persistence of the X-zone found in three infants between the ages of one and three months, might suggest that the infant was unaffected by variations in the rate of involution of its fœtal cortex. It is possible that the demonstration of the function of the X-zone might throw light on some of the physiological problems of the fœtus during and immediately following its parasitic existence, and it is felt that if an endocrine function can be assigned to this zone at all, it might be associated with the delicate balance between fœtal and maternal hormones during pregnancy.

Summary

1. Observations are recorded on the involution of the adrenal X-zone in one hundred and sixty infants under three months of age.
2. No variations in involution due to syphilis or congenital heart disease were found
3. The presence of an X-zone was demonstrated in five anencephalic monsters.
4. The theories as regards the function of this zone are briefly outlined.

I wish to thank Professor J. H. Biggart for much help in the preparation of this paper, and Mr. D. Mehaffey, A.R.P.S., to whom I am indebted for the photography. (See plates in middle of Journal)

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Giant Follicular Lymphoblastoma (Brill-Symmers' Disease)

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DISEASE processes affecting the reticuloendothelial system fall into three main groups :

1. *Reactive.*—The changes found in the marrow, spleen, and lymphoid tissue are produced in response to infection, acute or chronic.

2. *Hyperplastic.*—The causative factor is unknown. This group includes the leukæmias, Hodgkin's disease, and giant follicular lymphoblastoma.

3. *Neoplastic.*—The commonest are reticulum cell sarcoma and lymphosarcoma.

Around some of these conditions, in particular Hodgkin's disease and lymphosarcoma, there has grown a voluminous literature.

Giant follicular lymphoblastoma, although not uncommon, has received scant attention.

The condition is of relatively recent recognition. Brill (1925) described two cases. Symmers (1938) in an exhaustive account recorded twenty-five cases. Between these years some forty-three cases appeared in the literature.

Giant follicular lymphoblastoma is almost invariably mistaken by the clinician for Hodgkin's disease, with which it has many features in common. Both are characterised by localised or generalised enlargement of the lymph glands. Splenomegaly may occur in either. Systemic manifestations such as fever and wasting, however, point to Hodgkin's disease rather than giant follicular lymphoblastoma.

Pathologically the diseases are easily distinguished. In Hodgkin's disease the histological picture is complex, while in Brill-Symmers' disease the picture is comparatively simple, consisting, as it does, of hyperplasia of the lymph follicles, and of an increase in their number. The distinction is of importance from the prognostic and therapeutic aspects, since giant follicular lymphoblastoma in its early stages is a reversible hyperplasia and readily amenable to treatment by deep X-ray therapy in comparatively small doses.

Examination of the biopsy and post-mortem material in the Institute of Pathology reveals that seven cases of this disease occurred during the ten-year period 1937-46.

The pathological features of these cases will be described and the clinical history will be given in such detail as the records permit.

CASE 1

H. K., male, aged 21. Surgical Extern, R.V.H., 6/4/40.

Complaint.—"Glands" in the neck for fourteen years. No change in size noted until two weeks before the date of examination, when a swelling appeared beneath the left side of the jaw.

Examination.—Enlarged lymph gland under the left side of the jaw. Many other glands are palpable in both sides of the neck. The glands are freely mobile. Throat —right tonsil enlarged. No abnormality detected in the chest or abdomen.

Investigation.—Cervical gland biopsy.

Histological Examination.—The striking feature is a numerical and dimensional increase in the follicles of the gland. Some of these follicles almost completely fill the low power of the microscopic field. The enlargement of the follicle is produced by a hyperplasia of the germinal centre. The cells composing the germinal centres have the characteristics of lymphoblasts, i.e. cells with scanty cytoplasm, large deeply staining nucleus with distinct nuclear membrane and nuclear chromatin arranged in coarse dots. In some of the nuclei a prominent nucleolus is evident. Mitotic figures are not infrequent. Most of the germinal centres are surrounded by a narrow limiting zone composed of normal mature lymphocytes. In parts, the cells of the hyperplastic germinal centres have grown through the boundary zone of lymphocytes. There is, however, no extension through the capsule.

Comment.—This patient received no treatment and is at present well—seven years after diagnosis and twenty-one years after the onset of the disease.

CASE 2

E. S., female, aged 25. Surgical Ward, R.V.H., 31/8/45.

Complaint.—Swelling in the left groin of eleven months' duration. One week before admission the swelling increased in size and became painful.

Examination.—A tumour is present in the left inguinal region. (The presence or absence of enlargement of the remaining superficial glands or of the spleen is not recorded.)

Operation, 31/8/45.—A tumour was removed from the left inguinal region. It was found to be composed of a mass of discrete rubbery glands resembling Hodgkin's disease.

Biopsy Report.—The gland shows a multiplication of follicles, each of which is hyperplastic. The cells composing the follicles are primitive lymphoblasts. The appearances are consistent with a diagnosis of Brill-Symmers' giant follicular lymphoblastoma.

X-Ray Chest.—Enlarged glands both sides of chest not characteristic of any single lesion.

The patient was discharged from hospital on 14/8/45, without further treatment. A report from the patient's doctor in February, 1947, stated that since the operation she had remained well.

CASE 3

E. McC., female, aged 55. Admitted to a Medical Ward, R.V.H., 21/5/46.

History.—Noticed enlarged glands in the neck and groins in 1944. In September, 1945, she developed right-sided pleurisy. Following this she became weak and breathless and suffered from pain beneath the sterum.

Examination.—The patient is a frail elderly woman. Enlarged glands are palpable in both axillæ. Dilated superficial veins are apparent over the chest.

Lungs.—There is dulness on percussion and absence of breath-sounds at both bases.

No abnormality is found in the cardiovascular system.

The abdomen is distended; free fluid is present.

The spleen is just palpable.

Biopsy of Cervical Gland.—The gland showed a massive enlargement of the follicles. The follicles could be seen on naked-eye examination of the section, and some were of such a size as to fill almost completely the low power field of the microscope. The enlargement of the follicles resulted from appearance of huge germinal centres. The cells composing these had the characteristics of lymphoblasts. In addition to an increase in dimension of the cortical follicles, the gland showed a numerical increase in the follicles and the presence of follicles in the medulla, the latter apparently arising from the development of germinal centres in the medullary pseudo-follicles. The huge germinal centres were surrounded by a narrow zone composed of compactly arranged lymphocytes. In one area the boundary zone of the mature lymphocytes was absent from parts of the enlarged germinal centres. From these cells of the lymphoblastic type could be seen spreading from the follicles through the capsule of the gland and into the pericapsular tissue, where the appearance was that of a lymphosarcoma.

X-Ray Chest, 25/8/46.—Bilateral pleural effusion.

Blood Examination, 7/10/46.—R.B.C., 3,830,000; W.B.C., 3,120; Hb., 60 per cent. Film—marked microcytosis. *Differential Count.*—P. neutrophil, 60 per cent.; lymphocytes, 30 per cent.; monocytes, 1.5 per cent.; eosinophils, .5 per cent.

Repeated chest aspirations revealed a blood-stained sterile fluid.

Death occurred on 7/11/46.

Post-Mortem.—The pleural and peritoneal cavities were filled with a hæmorrhagic fluid. The lungs showed pressure collapse. The spleen was enlarged to twice its normal size. The cut surface showed a marked congestion and prominent malpighian bodies. The abdominal aorta from the level of the diaphragm to its bifurcation was surrounded by a mass of firm white tumour tissue. Tumour tissue had in places invaded and destroyed the overlying peritoneum. The right broad ligament and the right ovary were involved in tumour growth. Microscopically the tumour tissue was composed of cells with a large nucleus and scanty cytoplasm. The nucleus stained deeply and had a distinct nuclear membrane. The nuclear chromatin was arranged in coarse dots. In some nucleoli were prominent. Mitotic figures were frequent. The cells were of identical appearance with the lymphoblast seen in the germinal centre of the lymph follicle. In addition to the lymphoblast, the tumour tissue showed variable numbers of cells presenting the appearance of mature lymphocytes.

Microscopically the malpighian bodies in the spleen presented no abnormality. The pulp, however, showed an increase in cellularity due to presence of cells similar to those of the tumour tissue.

Foci of tumour cells were seen in the liver and kidneys.

Comment.—From the history it is apparent that sarcomatous change had occur-

red within a year of the appearance of the first evidence of Brill-Symmers' disease. At post-mortem the histological picture was that of a lymphosarcoma. No evidence was found of the pre-existing giant follicular lymphoblastoma. It is apparent that in the absence of biopsy some time prior to death, the origin of a lymphosarcoma from a giant follicular lymphoblastoma may not infrequently go unrecognised.

CASE 4

H. McK., female, aged 75. Admitted to a Surgical Ward, R.V.H., 4/11/46.

Complaint.—Swelling in the groin of three months' duration. The swelling is gradually getting larger. It is not painful.

Examination.—There is a firm rounded swelling in the right groin below Poupart's ligament.

On general examination there are a few crepitations at the bases of both lungs, but no other abnormality.

Operation, 5/11/46.—A swelling the size of a tangerine orange was removed from Scarpa's triangle on the right side. It was superficial to the deep fascia and shelled out easily and had no deep connections. On section it appeared to be a lipoma or soft fibroma.

Biopsy Report.—The tumour consists of enlarged lymph nodes which show an increase in the number of follicles. The germinal centres of the follicles are hyperactive. The appearance is that of a Brill-Symmers' giant follicular lymphoblastoma, but in many areas there is sarcomatous degeneration.

The patient was discharged from Hospital on 15/11/46. She reported on 17/2/47 that apart from slight swelling of the right foot and ankle she was symptomless.

Comment.—While the follow-up period—three months—is too short to rule out the possibility of recurrence, it may well be that early surgical removal has effectively eradicated the neoplasm.

CASE 5

G. L., aged 4½. Children's Hospital. Admitted 13/11/40.

Complaint.—Mother noticed a lump on the right side of the neck one month before admission. No increase in the size of the lump was noticed. A few days prior to admission stertorous breathing appeared.

Examination.—A swelling the size of a golf ball is present in the right supraclavicular region. The swelling is composed of glands which are separate, not attached to skin or deeper structures. Smaller glands are present in both sides of the neck. A gland the size of a walnut is palpable in the left axilla. Inspiratory stridor was seen, but no abnormality found on examination.

The spleen was not enlarged.

Blood Investigation.—R.B.C., 3,870,000; W.B.C., 5,000; Hb. 80 per cent. *Differential White Cell Count.*—P. neutrophil, 71 per cent.; monocytes, 5 per cent.; lymphocytes 24 per cent. Mantoux—1/10,000 neg. 1/5,000 neg. Biopsy of a cervical gland was performed on 14/11/46.

Histological Report.—The gland is composed of cells larger than lymphocytes and with nuclei almost entirely filling the cell. They are arranged in giant follicles,

but the intervening tissue and the capsule and pericapsular tissue is also infiltrated by similar cells. The appearance is that of a Brill-Symmers' giant follicular lymphoblastoma with sarcomatous degeneration.

The patient was discharged from hospital on 18/11/40 and died four months after discharge.

Comment.—The total duration of the illness was in this case less than six months. It must be presumed that sarcomatous change occurred soon after the appearance of the disease.

The leukopenia apparent in this case is not an unusual feature of the disease (Symmers, 1938).

CASE 6

D. J., female, aged 51. Admitted to a Medical Ward, 7/8/42.

History.—12th July, 1942, developed sore throat, cough, and night sweats. 19th July, 1942, became suddenly breathless. Breathlessness persisted in spite of aspiration of fluid from the chest.

Examination.—The patient is a well-nourished middle-aged female. There is no enlargement of the superficial glands. There are signs of a massive left-sided pleural effusion. B.P. 155/110. No other abnormality is found on general examination. X-ray of chest confirmed the presence of a massive left-sided pleural effusion.

Repeated thoracic paracentesis was performed. On each occasion a chylous fluid was obtained. On examination the fluid was sterile and of a high fat content.

In spite of repeated chest aspirations, breathlessness increased and death occurred on 29th September, 1942.

Post-Mortem.—A neoplasm was seen to involve the mediastinal and para-aortic lymph glands. The neoplasm had occluded the thoracic duct. There was a bilateral chylothorax and pressure collapse of the left lung.

The spleen was slightly enlarged and on section showed prominent malpighian bodies.

Microscopic examination of the mediastinal tumour showed a pleomorphic cellular picture. The predominating cell had the characteristics of a lymphoblast—scanty cytoplasm, large nucleus with distinct nuclear membrane and prominent nucleolus. Mature lymphocytes were also evident and cells whose appearance indicated a transitional stage between the lymphoblast and the mature lymphocyte.

A striking feature on microscopic examination of the spleen was enlargement of the malpighian bodies. Some were of such a size as to almost completely fill the low power field of the microscope. The enlarged follicles were composed of cells with the characteristics of lymphoblasts.

The malpighian bodies in the spleen were, therefore, of similar structure to the massive follicles seen in the glands in the other cases.

Comment.—The spleen in this instance provided the only evidence that the neoplasm had arisen from Brill-Symmers' disease.

CASE 7

A. S., male, aged 69. Admitted R.V.H., 24/6/46.

This patient was admitted to a Surgical Ward for the removal of a tumour from his right axilla. This on pathological examination proved to be a simple squamous papilloma.

General examination revealed an enlarged lymph gland in the left axilla but no other abnormality.

The gland was removed and submitted for pathological examination.

Histology.—The gland is the seat of a lymphosarcoma which has almost completely destroyed the normal architecture. There is invasion of the capsule and spread of tumour cells into the pericapsular tissue. Numerous giant follicles composed of lymphoblasts are seen indicating the origin of the tumour from a preceding giant follicular lymphadenopathy. There is no connection between this tumour and the squamous papilloma removed from the right axilla.

The patient was discharged from hospital on 18/7/46 and unfortunately cannot be traced.

Comment.—In this case the discovery of the early stage of transformation of a Brill-Symmers' disease to a lymphosarcoma was entirely fortuitous.

From the histological picture in this case it is apparent that neoplastic transformation may quickly obscure the evidence of a pre-existing giant follicular lymphadenopathy.

Discussion

The cases recorded indicate the main characteristics of the disease process. The condition is a hyperplasia of the lymphoid tissue allied to Hodgkin's disease. The hyperplasia characteristic of Hodgkin's disease results in the production of many different types of cell—reticulum cells, giant cells, fibroblasts, cells of the lymphocytic series, and myeloid cells, many of which may be eosinophils.

Giant follicular lymphoblastoma differs from Hodgkin's disease in that the hyperplasia is confined to one cell element of the reticulo-endothelial system—the lymphoblast of the germinal follicle of the lymphoid tissue. New germinal centres appear in the pseudo-follicles of the medulla of the lymph glands. The result of these changes is a numerical and dimensional increase in the follicles.

Follicular hyperplasia may simultaneously affect the lymph glands, the malpighian bodies of the spleen, the tonsils, and the lymphoid tissue of the gastro-intestinal tract. Alternatively the hyperplastic process may remain confined to the lymphoid tissue of one area.

The cervical glands constitute the tissue most commonly affected in localised Brill-Symmers' disease. The condition may, however, be confined to the spleen or again the only manifestation of the disease may appear in the appendix. Symmers (1944) has described nine appendices characterised by marked hyperplasia of the lymph follicles without clinical evidence of lymphoid disease elsewhere.

Clinically, apart from those cases in which the changes are confined to the appendix, the condition resembles Hodgkin's disease. The patient presents himself with a localised or generalised enlargement of the lymph glands. The spleen may or may not be palpable. Enlargement of the deep glands may interfere with venous return and so produce serous effusions. Constitutional disturbance is not a feature of the

malady. There is no characteristic blood picture although a hypochromic anæmia, a moderate leucopenia, or slight eosinophilia may occur.

Unfortunately this benign hyperplasia often undergoes malignant degeneration and the affected tissue is then rapidly invaded and replaced by a lymphosarcoma. It is impossible to state at what stage in the disease such sarcomatous change may occur. In some it is present when the patient first consults the practitioner, in others it may never occur (Case 1). Robb Smith (1938) was of opinion that the average period of survival after diagnosis was five years.

The intimate relationship with the other hyperplastic conditions and with the neoplasms of the reticulo-endothelial system and hence the prognostic difficulties are indicated by an analysis of twenty-five cases collected by Symmers (1938). This shows—

1. Uncomplicated giant follicular lymphoblastoma - - - - - - - 7
2. Follicular lymphoblastoma with lymphosarcomatous degeneration 7
3. Follicular lymphoblastoma associated with Hodgkin's disease - - 7
4. Follicular lymphoblastoma associated with lymphatic leukæmia - - 4

The etiology of giant follicular lymphoblastoma is no more certain than that of other hyperplastic conditions of the reticulo-endothelial system. Since the cervical glands compose the lymphoid area most constantly involved, Symmers suggests that it is inflammatory or toxic in origin. It is true that follicular hyperplasia of a minor degree may be seen in the lymph glands draining a septic focus. An association of Brill-Symmers' disease with Hodgkin's disease is noted in the series of cases described by Symmers and recorded above. Many, although on doubtful evidence, regard Hodgkin's disease as an infective process and in this connection it is noteworthy that Longcope regarded follicular hyperplasia as the earliest histological change in the development of this disease. If then, the inflammatory theory be tenable, Brill-Symmers' disease might be regarded as a stage intermediate between simple reactive inflammatory hyperplasia and the pleomorphic fatal hyperplasia characteristic of Hodgkin's disease. However against an inflammatory origin is the fact that no specific organism has been isolated and further that involvement of the sinuses of the lymph glands, a feature characteristic of lymph glands involved in an inflammatory process, is not found in giant follicular lymphoblastoma. At the moment, therefore, the lesion remains as a hyperplasia of unknown etiology. The history of the recorded cases suggests that it is a pre-sarcomatous proliferation.

The relative incidence in relation to the more common diseases of the reticulo-endothelial system recognised at biopsy and post-mortem in the Institute of Pathology during the ten-year period 1937-46, is shown in the following table :

	Biopsy	P.M.	Total
Reticulum cell sarcoma - - -	35	14	49
Hodgkin's - - - - -	26	5	31
Lymphosarcoma - - - -	16	—	16
Brill-Symmers' disease with sarcomatous degeneration - - - -	4	1	5
Uncomplicated Brill-Symmers' disease -	2	—	2

From this emerges the interesting facts that giant follicular lymphoblastoma is little less than half as common as the generally recognised lymphosarcoma and that 27 per cent. of lymphosarcomata arise from a preceding follicular lymphoblastoma.

It is probable that a not inconsiderable number of cases of this disease go unrecognised since early sarcomatous change may completely obscure the hyperplastic process.

From the point of view of therapy two points are of importance :

1. Sarcomatous change may occur while the condition is still localised to one group of glands.

2. Uncomplicated giant follicular lymphoblastoma is usually amenable to mild X-ray therapy.

The high incidence of sarcomatous degeneration in this series contrasted with that of other published cases suggests that during the past ten years some cases of uncomplicated Brill-Symmers' disease have gone unrecognised. Absolute diagnosis can only be established by biopsy and histological examination of the glands.

In order that sarcomatous degeneration in this disease may be prevented or delayed, the following measures are suggested :

1. Patients showing localised or generalised lymphadenopathy of doubtful etiology should have an early biopsy.

2. Giant follicular lymphoblastoma if localised should be treated by removal of the affected glands.

3. The condition if generalised, should be treated by deep X-ray therapy.

Summary

Seven cases of Brill-Symmers' disease are reported.

The incidence and pathological characteristics are recorded.

Though essentially benign, the condition is prone to neoplastic transformation. Measures are suggested which may be of value in preventing this change.

I wish to thank Professor J. H. Biggart for help in the preparation of this article. Mr. D. Mehaffey, A.R.P.S., was responsible for the photography. (See plates in middle of Journal.)

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Giant Follicular Lymphoblastoma

(Brill-Symmers' Disease)

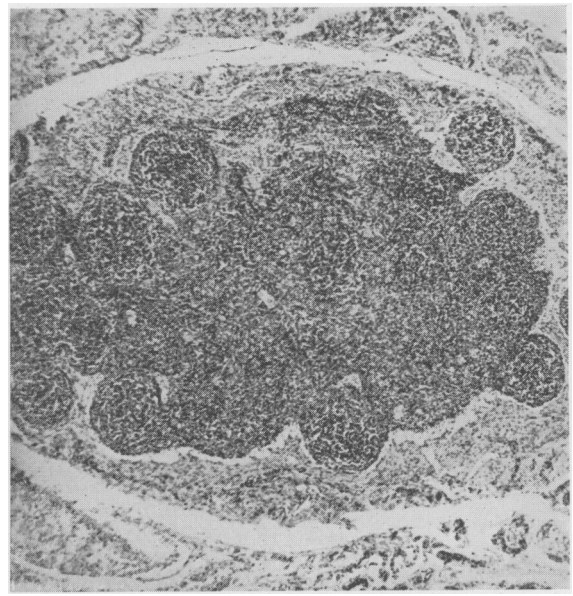

Plate 1 (x50)

Lymph gland showing normal follicular structure. The follicles are confined to the periphery of the gland.

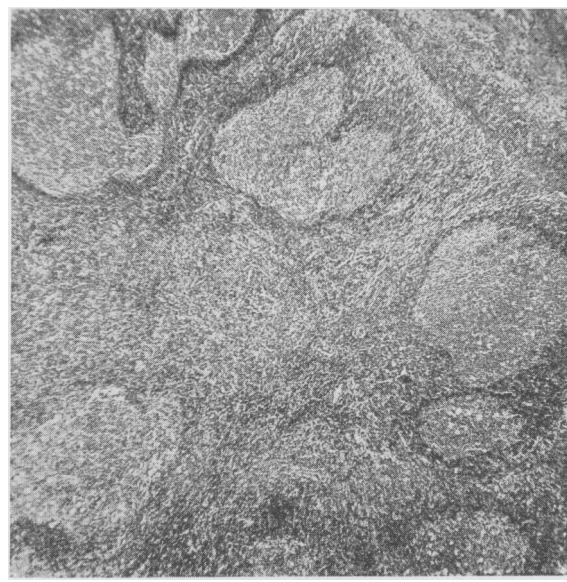

Plate 2 (x50)

Lymph gland—Brill-Symmers' disease—showing a numerical and dimensional increase in the follicles. Each follicle is composed of poorly staining lymphoblasts surrounded by a narrow capsule of more deeply staining lymphocytes.

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Giant Follicular Lymphoblastoma

(Brill-Symmers' Disease)

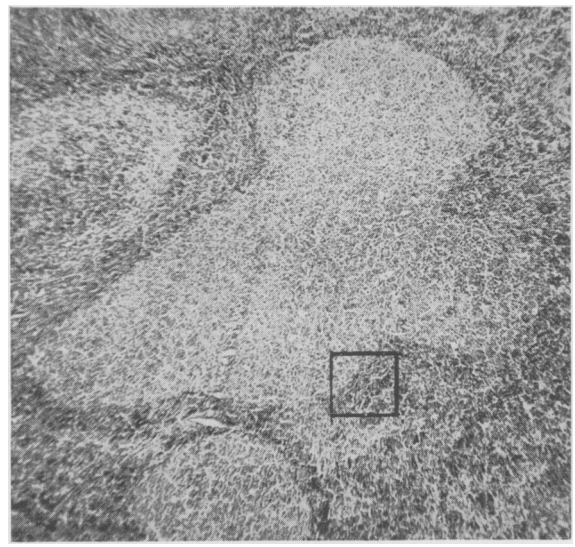

Plate 3 (x100)

Lymph gland—Brill-Symmers' disease—showing a giant irregular follicle.

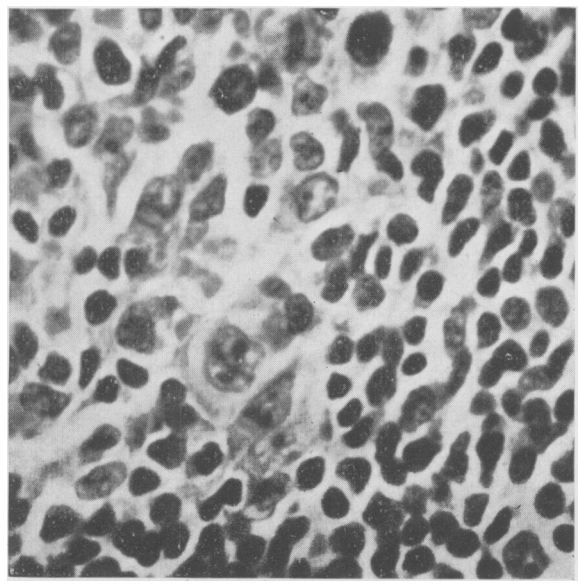

Plate 4 (x1000)

High power. The edge of a follicle seen in Plate 3. Above are seen the lymphoblasts of the hyperplastic follicle; below, the mature lymphocytes composing the capsule of the follicle.

Giant Follicular Lymphoblastoma

(Brill-Symmers' Disease)

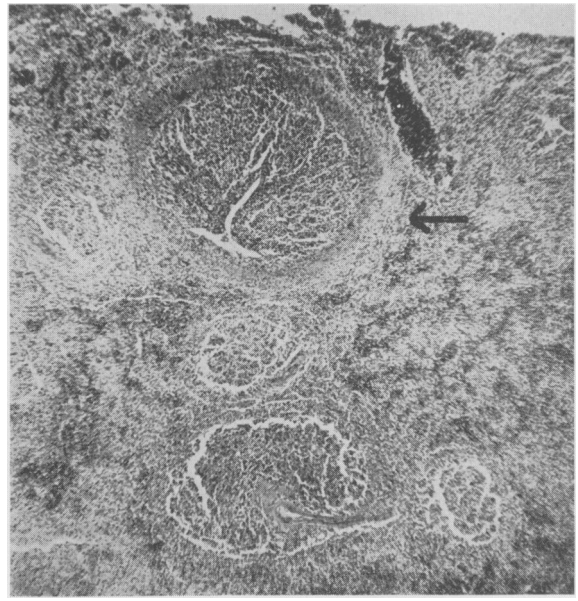

Plate 5 (x50)

Spleen—Brill-Symmers' disease—(Case 6). There is a marked hyperplasia of the malpighian bodies. Invasion of a vein by neoplastic tissue is indicated.

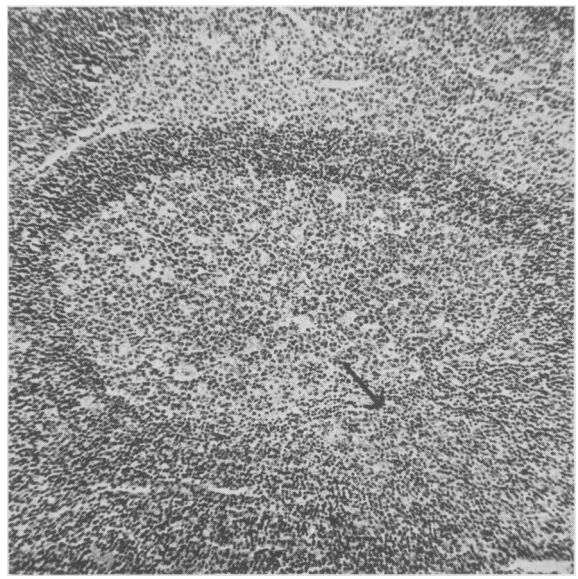

Plate 6 (x50)

Lymph gland showing Brill-Symmers' disease with early sarcomatous change. The proliferating lymphoblasts of the follicle are breaking through the lymphocytic capsule.

Giant Follicular Lymphoblastoma

(Brill-Symmers' Disease)

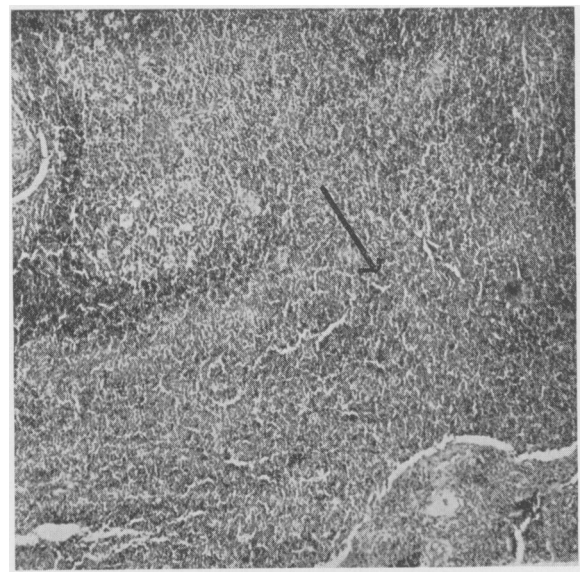

Plate 7 (x100)

Lymph gland—Brill-Symmers' disease—with sarcomatous transformation. The proliferating lymphoblasts of the follicle have completely broken through the lymphocytic capsule and are seen in the medulla of the gland growing as a lymphosarcoma.

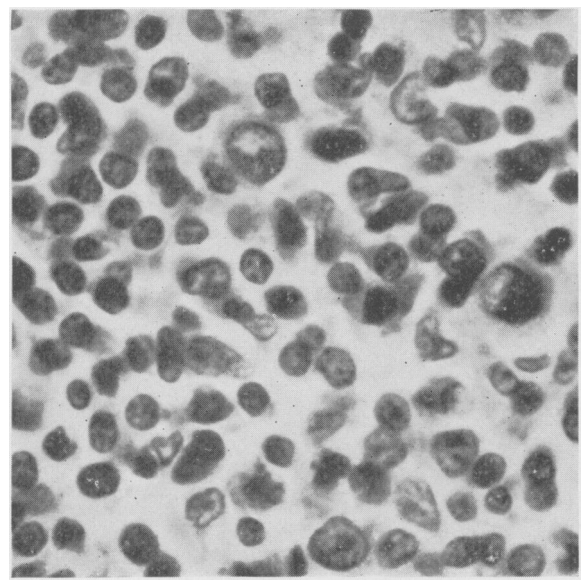

Plate 8 (x1000)

High power showing the plemorphic lymphosarcoma following Brill-Symmers' disease. Many of the cells are lymphoblasts similar to those in the hyperplastic follicle (Plate 4). Mature lymphocytes, and cells whose appearance indicates a transitional stage, are also seen.

Some Aspects of the Pathogenesis of Cardiac Tuberculosis

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TUBERCULOSIS of the heart is not a common condition. It is very often an autopsy finding, which clinically was of little or no importance, being but a part of a generalised tuberculous infection. Sixteen examples of cardiac tuberculosis were found among the records of 3,500 cases post-mortemed in the Institute of Pathology in the last ten years, an incidence of only 4.6 per 1,000. Of these sixteen cases there was direct evidence for regarding the condition as tuberculous in origin in ten only, but it is possible to bring forward strong circumstantial evidence that the cause of the pathological changes found in the other six cases was originated by infection with the tubercle bacillus.

The following is a brief summary of the pathological features of these sixteen cases :

CASE 1 : Male, aged 23 years; generalised miliary tuberculosis with tubercles in the myocardium; endocardium and pericardium not affected; tuberculosis of the right epididymis with surgical removal two years previously; acute fibro-caseous tuberculosis of the right seminal vesicle; ante-mortem thrombi in the periprostatic, right internal and common iliac veins; infarction of the lung.

CASE 2 : Female, aged 50 years; generalised miliary tuberculosis with tubercles in the myocardium; endocardium and pericardium not affected; fibro-caseous tuberculosis of the upper lobe of the left lung; early tuberculous meningitis; also acute non-specific right sided mastoiditis, ethmoidal and sphenoidal sinusitis.

CASE 3 : Female, aged 15 years; generalised miliary tuberculosis with myocardial and subendocardial tubercles; pericardium not affected; fibro-caseous tuberculosis of the lower lobe of the right lung with tuberculous hilar adenitis; tuberculous meningitis; localised tuberculous peritonitis.

CASE 4 : Male, aged 22 years; generalised miliary tuberculosis with myocardial and subendocardial tubercles; pericardium healthy; right sided renal phthisis with tuberculosis of ureter, bladder, prostate and seminal vesicle; non-bacterial thrombotic endocarditis of the mitral valve superimposed on healed rheumatic endocarditis.

CASE 5 : Female, aged 45 years; solitary tuberculoma in the myocardium; endocardium and pericardium healthy; no other tuberculous lesions found in any part of the body; diabetes and hyperglycæmic coma. (Partial post-mortem examination only performed.)

CASE 6 : Female, aged 6 years; generalised miliary tuberculosis with subendocardial and myocardial tubercles; endocardial tuberculosis; large caseating areas in myocardium, extending through the endocardium and discharging caseous material into the heart cavity, and in direct communication with caseating areas

in the pericardium; acute sero-fibrinous pericarditis; large active tuberculous focus in apex of left lung; tuberculosis of the mediastinal glands; tuberculous ascites with enlarged peritoneal glands; chronic venous congestion of liver secondary to cardiac tamponade. (See plate 1.)

CASE 7: Female, aged 50 years; generalised miliary tuberculosis; early localised fibrinous pericarditis in relationship to a caseous hilar lymph node; normal endocardium and myocardium; extensive tuberculous lesion right upper lobe with slight fibrosis but no cavitation; tuberculous broncho-pneumonia; both calcified and caseous hilar lymph nodes, with direct extension to the pericardium.

CASE 8: Female, aged 63 years; acute fibrinous and organising tuberculous pericarditis; normal endocardium; focal areas of myocardial fibrosis but otherwise no lesion demonstrated in the heart muscle; caseous lymph node at the root of the aorta; auricular fibrillation with bundle branch block and chronic venous congestion; generalised arterio-sclerosis; old scarring in lungs. (See plate 2.)

CASE 9: Male, aged 60 years; fibrinous and organising pericarditis; normal endocardium and myocardium; bilateral apical fibrous scars in lungs; caseous tracheo-bronchial lymph glands; chronic venous congestion; thrombosis of prostatic veins; infarction of lung.

CASE 10: Male, aged 20 years; acute sero-fibrinous pericarditis; normal endocardium and myocardium; tuberculous abscess in lung; bilateral pleurisy; chronic peritonitis; cardiac cirrhosis.

CASE 11: Female, aged 22 years; generalised miliary tuberculosis; chronic adhesive pericarditis; normal endocardium and myocardium; primary tuberculous complex in lower lobe of right lung; tuberculosis of right inferior group of tracheo-bronchial lymph glands; bilateral pleural effusions; extensive fibro-caseous tuberculosis of the retro-pancreatic lymph glands; tuberculous peritonitis.

CASE 12: Male, aged 29 years; generalised miliary tuberculosis; chronic tuberculous pericarditis with adherent pericardium; normal endocardium and myocardium; primary tuberculosis of right upper lobe with involvement of the bronchi and extension to the left lung; tuberculous pneumonia; tuberculous ulceration of left main bronchus; tuberculous pleurisy with effusion; tuberculous peritonitis with ascites.

CASE 13: Male, aged 33 years; chronic adhesive pericarditis; endocardium and myocardium not affected by tuberculosis but both show evidence of previous rheumatic infection; tuberculosis with caseation in left upper lobe of lung; tuberculous pleurisy; calcified hilar lymph glands; tuberculosis with destruction of both adrenals and development of Addison's disease.

CASE 14: Male, age not known (carried in dead); chronic adhesive pericarditis; normal endocardium and myocardium; chronic fibroid phthisis with cavitation of both lungs; terminal hæmorrhage from ruptured blood vessel in cavity of left lung.

CASE 15: Female, aged 38 years; adhesive and obliterative pericarditis with patches of calcification; normal endocardium and myocardium; old left sided pleurisy.

CASE 16: Female, aged 30 years; calcified pericarditis; normal endocardium and

myocardium; old standing tuberculosis with caseation in hilar lymph glands; Pick's disease; thickened and fibrosed pleura with patchy calcification; non-specific inflammatory reaction in lung, possibly, but not definitely, tuberculous; death followed post-operative mediastinal hæmorrhage.

Of the sixteen cases the pericardium was affected in eleven, and these eleven cases include all six cases in which direct proof of cardiac tuberculosis was not obtained. Even assuming that all eleven cases were, in fact, tuberculous, this gives an incidence of only 3.1 per 1,000 in the records of this department for tuberculous pericarditis.

This incidence is very much smaller than that recorded in the literature. Osler in 1893 was able to review seventeen cases which he had seen personally, and wrote: "Tuberculosis follows hard upon rheumatic fever as a cause of pericarditis—in 1,000 autopsies there were 275 cases with tuberculous lesions, in 7 of which the pericardium was involved." Norris (1911) found 1,780 cases of tuberculosis in 7,219 autopsies, and 82 of them had tuberculous pericarditis; and Kornblum, Bellet, and Ostrum (1933) state that the incidence in general autopsies of tuberculous pericarditis is approximately 1 per cent., and that tuberculous involvement of the pericardium occurs in about 4 per cent. of autopsies on patients with pulmonary tuberculosis.

Tuberculosis of the Endocardium

Tuberculosis of the endocardium must be regarded as a condition of little practical importance, since when it does occur it is invariably but part of a very serious and often generalised form of tuberculosis such as that of the miliary type. Here tubercles may be found within the musculature usually of the ventricle, or just underneath the endocardium, tubercle bacilli having been carried to these sites by the blood of the coronary arteries. Occasionally a subendocardial tubercle may rupture into the cavity of the heart, and this serves to hasten the inevitable end-result. Rarely a fulminating tuberculous pericarditis may spread by direct extension into the myocardium and rupture through the endocardium into the heart cavity. Tuberculosis of the endocardium, or of the valves, akin to acute or subacute bacterial endocarditis, is an extraordinarily rare condition.

Baker (1935), in an exhaustive survey of the literature, found about thirty cases reported, but concluded that only four of them could be regarded as having established their claim to be tuberculous endocarditis, and he regards but one of these thirty cases as being the only fully established case of tuberculous endocarditis analogous to rheumatic or bacterial endocarditis. Since then Davie (1936) has reported two cases of what appear to be true tuberculous endocarditis, and Bevans and Wilkins (1942) reported a further case. This rare condition, interesting especially because of its rarity, should alone be termed "tuberculous endocarditis," the other more frequent finding being designated "endocardial tuberculosis." Davie put forward a new hypothesis to account for the rarity of tuberculous endocarditis. His theory assumed the existence of a tuberculous allergic endocarditis similar in type to rheumatic endocarditis, and he postulated the rare coincidence of a tuberculous bacillæmia during the phase of the allergic endocarditis to explain the

accepted form of tuberculous bacterial endocarditis. So he brought the latter condition "into line ætiologically with subacute bacterial endocarditis."

One still wonders, however, why a tuberculous bacteræmia should spare the valve which has been affected by rheumatism when the relatively non-pathogenic streptococcus viridans can so often multiply there and cause disaster.

To complete this brief discussion of tuberculous endocarditis, it should also be pointed out "that there is no evidence that *chronic* valvular disease can originate either directly from tuberculous inflammation or indirectly from the toxic effect of tuberculosis elsewhere in the body" (White 1946).

Cases 3, 4, and 6 are examples of subendocardial tubercle formation occurring as part of a miliary tuberculosis. Case 6 also shows the spread of myocardial tuberculosis to the endocardium and the rupture of a caseating focus into the heart cavity. In this case tubercle bacilli were demonstrated by Ziehl-Neelson staining in the material about to be discharged into the blood stream.

Tuberculosis of the Myocardium

Tuberculosis of the myocardium is usually unsuspected during life. Occasionally, however, a small tubercle may involve the auriculo-ventricular conduction system and lead to heart block; or an aneurysm of the heart wall may occur, rupture, and lead to sudden death (White 1946). This condition is also rare. Raviart (1906) in a series of 7,683 cases of tuberculosis found myocardial tuberculosis only 49 times (or 0.63 per cent.). In our series there were 6 cases among the 3,500 post-mortem reports examined, which is an incidence in general pathology of only 1.7 per 1,000 cases.

Cases 1, 2, 3, 4, and 6 all showed tuberculous infection of the myocardium and all had associated generalised miliary tuberculosis. Case 5 is an example of solitary myocardial tuberculoma found at post-mortem. This case showed no other active tuberculous lesions, although old pleural adhesions were found; unfortunately, however, only a partial post-mortem examination was carried out. In this particular case the tuberculoma had not interfered with the patient's condition and was quite unsuspected. Death occurred in diabetic coma. Case 6, which, incidentally, illustrates almost all the findings of acute cardiac tuberculosis, was also an example of how a very active pericardial tuberculosis can spread directly into the heart muscle: in this case there were undoubtedly many extensions of caseous material into the blood stream and some at least, if not all, occurred after the onset of the pericarditis.

Tuberculosis of the Pericardium

Tuberculosis of the pericardium, though not a common disease, is nevertheless an important one. The pericardium may be infected in one of three ways:

1. Via the blood stream.
2. Via the lymphatics.
3. By direct extension.

Osler (1893) wrote: "Tuberculous pericarditis is due in the majority of cases to infection of the membrane by caseous mediastinal lymph nodes. The disease may

be confined to the glands and to the pericardium." This view is widely accepted by all authorities on the subject, but it is only within recent years that the real reason for the close association between pericarditis and hilar lymph adenitis has been appreciated. This followed the work of Rich and others. True, in miliary tuberculosis, small tubercles may form on any serous membrane, including the pericardium, but a tuberculous effusion or a tuberculous pericarditis, in the usual conception of the term, does not usually develop. The pathogenesis of tuberculosis of all serous cavities is similar. Effusion will only develop in the presence of either a massive dose of organisms, hypersensitivity, or both. In the discussion on this subject, Rich (1944) states: "As in the case of the meninges, tubercle bacilli do not escape freely from the blood stream into the serous cavities. The writer has not encountered in the literature an instance of tuberculous effusion occurring as a prompt and direct result of the intravascular injection of tubercle bacilli into experimental animals, nor in his own experience has he ever seen that event happen in any of the many normal and hypersensitive animals, that have been subjected to intravenous or intra-arterial injections of large numbers of tubercle bacilli." And again: "In miliary tuberculosis in human beings, likewise, miliary tubercles develop on serous surfaces, but abundant effusions into the cavities do not occur."

Experimentally it has been found by many workers, that an abundant effusion will occur if tubercle bacilli are injected in large numbers directly into the pleural or peritoneal cavities of hypersensitive animals, but hypersensitivity is necessary, or effusion will not occur. It can be assumed that the same reasoning holds true for pericardial effusions, and this argument agrees well with the already established fact that tuberculous hilar lymph glands, healed or active, are invariably found at autopsy and that direct extension or lymphatic spread from these glands had occurred. It must be pointed out, however, that although large numbers of tubercle bacilli require to be injected into the serous cavities of even hypersensitive animals to produce effusions, "this does not mean that a proportionally large number must be discharged into the cavity in the human being, for the degree of inflammatory exudation depends upon the balance between the number of bacilli and the degree of hypersensitivity, and the human being can develop a decidedly higher degree of hypersensitivity than laboratory animals" (Rich, 1944). Indeed in the human it is very probable that a tuberculous effusion can develop following the discharge into a serous cavity of tuberculoprotein and disintegrated dead bacilli, no actual living organisms being required.

Actually a tuberculous hilar lymph node could affect the pericardium by any one of three different methods. Firstly, the gland could rupture through the pericardium and discharge caseating material into the sac. Such cases have been described. Secondly, there could be a lymphatic spread from the gland to the parietal pericardium and Hannesson (1941) states that this is the most likely method of spread in most instances, but to assume this is to postulate that a retrograde extension occurs and this is never a very attractive hypothesis. Thirdly, the tuberculous material could pass directly from the gland to the pericardium. Harvey and Whitehill (1937) were able to demonstrate this mode of extension in three cases and this

would seem to be the usual way by which the condition is brought about. In Case 7 the pericarditis was localised to that part of the parietal layer in contact with a caseating lymph gland.

It should be pointed out that the demonstration of a tuberculous gland, especially when it is not in contact with the pericardium, does not necessarily mean that this gland infected the sac, since it may be one of the group of glands draining the pericardium and so infected by the serositis rather than being the cause of the serositis. In this way, many so-called retrograde lymphatic spreads may conceivably be explained.

From this general discussion of the pathogenesis of tuberculous pericarditis, the various types met with in practice will be described briefly.

These can be divided into four groups :

1. That associated with generalised miliary tuberculosis.
2. That associated with generalised serous membrane tuberculosis.
3. That due to extension from neighbouring structures.
4. That developing independently.

That associated with Generalised Miliary Tuberculosis :

The first group has already been dealt with. In this series there were no true examples of this particular type. Case 6, although showing pericarditis and miliary tuberculosis, must be regarded as being of the third type, and, as has been mentioned previously, in this case it is very probable that the miliary tuberculosis followed the pericarditis and not vice versa.

That associated with Generalised Serous Membrane Tuberculosis :

The second group includes many cases of so-called polyserositis or Concato's disease. Under this generic term is included a well defined group of cases with chronic inflammatory thickening of the serous membranes, often associated with recurrent serous effusions. Burrell, Hare, and Ross (1929) believe that chronic tuberculosis of the great serous sacs progressing to the production of polyserositis is a condition associated with a high degree of immunity to the infection, and that in more chronic cases the infective element is slowly submerged as the clinical picture becomes one of mechanical obstruction to the heart and circulation. It is in this way that Pick's disease may be produced.

That this condition is usually due to tuberculosis is not accepted by all. But it is not difficult to imagine how this could be produced by infection with the tubercle bacillus and it does seem that tuberculosis is, at any rate, a common cause for the condition. Case 11, for example, showed chronic adhesive pericarditis, bilateral pleural effusions and peritonitis, in other words, inflammation of the three serous membranes. If in this case the tuberculous foci in the lung and glands had been healed and not evident, the patient would have presented the picture of a polyserositis. The serous membranes may be extensively affected with minimal tuberculosis elsewhere. Case 9 is an example with healed pulmonary tuberculosis, caseous tracheo-bronchial glands, and a fibrinous but organising pericarditis, this patient dying from a pulmonary infarction associated with thrombosis of the pro-

static veins; and it is easy to see how the allergic reaction, which occurs in any serositis, may be maintained or heal with gross fibrosis and thickening, when the focus, which was the cause of that serositis, becomes quiescent and at autopsy is found only as a small area of scar tissue, the ætiology no longer obvious. It is easy to see, too, how the pleura and pericardium could be implicated by the same group of caseous lymphatic glands which later might heal. The end result of this pathology is the syndrome called polyserositis.

That other disease processes apart from tuberculosis may cause this syndrome cannot, of course, be denied.

That due to Extension from Neighbouring Structures :

The third group, where extension occurs from neighbouring structures, is the largest group and includes most cases of acute fibrinous and sero-fibrinous pericarditis. Cases 6, 7, 8, 9, and possibly 10 are examples of this group. In Case 7 a direct extension was demonstrated histologically between the caseating gland and the pericardium.

In the early stages of this process the membranes are only a little thickened and often tubercles can be seen just underneath the endothelial layer. In other instances the contiguous surfaces of the pericardium are covered with yellow caseous material and in certain cases collections of thick cheesy pus may be found between the two layers. It is obvious how in these cases the tuberculous process might involve the myocardium directly as has been mentioned previously.

With the advent of hypersensitivity, effusion occurs. Osler (1893) describes this effusion as being of four main types :

1. A simple plastic exudate is formed, similar to that of rheumatic pericarditis, with little serous effusion or thickening of the membrane. Histologically, however, one finds tubercle formation in the disorganised pericardium.

2. An extensive sero-fibrinous exudate is found and here the membranes may be greatly thickened.

3. Hæmorrhagic effusions may develop. The colour of these may be bright red but more commonly is of a reddish-brown or chocolate colour.

4. The effusion may be purulent. And, to quote Osler, "This, too, apparently from the onset and not following paracentesis. The exudation may be enormous and has been diagnosed as left sided empyema."

These effusions may be of very great size indeed, but since the effusion is slow in development and so unlike rheumatic pericarditic effusion, it is relatively well tolerated by the patient (White 1946). Incidentally, White mentions that "A pericardial friction rub may be heard over the præcordium even in the presence of a large effusion" and Harvey and Whitehill (1937) found a friction rub in 30 per cent. of twenty cases with large effusions (over 300 c.c.). They state : "Consequently a large effusion does not prevent the appearance of a friction rub." In Case 6 a præcordial friction rub was recorded as having been heard. It is very difficult indeed to imagine how this rub could possibly be produced.

The patient may die in this stage of the disease, but in many cases, probably the

majority, the condition settles and healing takes place. The end result of healed acute tuberculous pericarditis is the important clinical variety.

With healing, the pericardial cavity may be partially or completely obliterated, so-called adhesive pericarditis, and occasionally the adhesions may extend to and involve other structures producing the condition known as chronic adhesive mediastinitis or mediastino-pericarditis. A similar condition can be produced by rheumatic fever, which is, in fact, the commonest cause of this particular pathological change. Unless these adhesions hamper the heart's contractions, the condition is usually unsuspected. Blalock and Burwell (1941) state: "Even generalised union of the epicardium and the pericardium, if non-constricting, may produce no significant disturbances of cardiac function. It is believed that most cases (of mediastino-pericarditis) follow rheumatic fever."

The more important complication following acute tuberculous pericarditis is the condition known as chronic constrictive pericarditis. In this condition the thickened fibrotic pericardial surfaces are firmly adherent and enclose the heart in a sac of scar tissue, which, like all other scar tissue, contracts with age. It is a slowly progressive condition, taking many years to develop and so often met with in elderly patients. It has been recorded in octogenarians (Osler 1893), and Blalock and Levy (1938) gave as the average age of 42 cases, 40.3 years; they had one example in a patient over 70 years of age, three in patients over 60, and nine in patients over 50. In this connection, Graham, Singer, and Ballon (1935) state that in the aged, tuberculosis is the most common cause of pericarditis.

Constrictive pericarditis produces a characteristic clinical picture of which there are two varieties, one in which the superior vena cava is obstructed ("superior mediastinal pressure syndrome") and the other and more common condition where the inferior vena cava and often the hepatic veins are constricted ("inferior mediastinal pressure syndrome"). The patho-physiological aspects of the condition are well dealt with by Blalock and Burwell (1941). According to these authors most of the symptoms and signs are dependent on two changes. (1) Diminution in the amount of blood pumped by the heart per minute and an inability to increase the output per beat. This diminution leads to weakness, fatigue, tachycardia, low pulse pressure and a limited tolerance for exercise. (2) Increase in the venous pressure. This increase is also apparent in the pulmonary circulation but "various findings indicate that the congestion is more severe in the systemic than in the pulmonary area." The increase in venous pressure leads to venous distension, to engorgement of the liver, to the formation of peripheral œdema, to epistaxis, and to the transudation of fluid into the pleural and peritoneal cavities.

It is thus apparent that the alterations in constrictive pericarditis include changes in the venous pressure which are similar to those of congestive heart failure and changes in the cardiac output and blood pressure reminiscent of those changes which occur in patients suffering from surgical shock. To quote Blalock and Burwell (1941), "However, in the latter condition, the veins are usually collapsed in sharp contrast to the distended veins seen in constrictive pericarditis."

White (1946) writes that it is the hepatic vein obstruction secondary to the con-

striction of the heart itself, with or without an additional factor of local blocking, that leads to hepatic congestion, enlargement, and eventually cirrhosis in the inferior mediastinal pressure syndrome. It is this particular end-result that is called Pick's disease, and at post-mortem examination the so-called "sugar icing of the liver" is found due to the chronic peritonitis which is produced. Pick's disease may or may not be associated with polyserositis, although, of course, it is possible that Pick's disease may follow polyserositis.

The striking condition of pericarditis calculosa is sometimes seen when calcium is deposited in the greatly thickened and fibrotic pericardium of a chronic pericarditis. Occasionally the plaques of calcium are small and of no real importance except that they show up well on radiograms of the chest. At other times, however, the heart may be completely encased in a thick deposit of calcium, the condition picturesquely called "armoured heart" or "marble heart."

This condition has always aroused a considerable amount of interest or curiosity. One notes that marble heart disease appears to have been recognised by the American author Hawthorne as long ago as 1818. The condition is described in a story by this author entitled "Ethan Brand." Ethan Brand is related to have committed suicide by plunging into the burning lime kiln which in former days he had attended. Hawthorne concluded his story as follows : "The marble was all burnt into perfect snow-white lime. But on its surface, in the midst of a circle, snow-white too and thoroughly converted into lime, lay a human skeleton in the attitude of a person who, after long toil, lies down to long repose. Within the ribs, strange to say, was the shape of a human heart." This story in more detail is recorded by Hewitt (1932).

In the present series there were two cases of pericarditis calculosa. Case 15 had small plaques of calcium in the pericardium which was associated with an adhesive obliterative pericarditis and an old unilateral pleurisy. No active tuberculous infection was found. The condition of the pericardium in Case 16 was more striking and the whole heart was encased in calcium. Here there was an old caseous hilar lymph gland and healed pleurisy with some non-specific but probably tuberculous chronic inflammatory changes in the lung. No evidence of rheumatic infection was found in either case and the evidence, admittedly circumstantial, was that the cause of both cases was tuberculosis.

The ætiology of most cases of constrictive pericarditis is, in fact, still in debate. Since at post-mortem one finds only scar tissue, and the damage done by this scar tissue, it is exceedingly doubtful if positive proof of an ætiological factor can ever be forthcoming in every case. One has to rely entirely on indirect evidence. In our sixteen cases of tuberculosis of the heart there are included six cases of chronic pericarditis. Two of these cases with calcification of the pericardium have just been discussed. All the other cases had associated active tuberculous infection in some other part of the body. Case 11 had tuberculosis of the lung, tracheo-bronchial glands, both pleural membranes, peritoneal lymph glands, and peritoneum. Case 12 had tuberculosis of the lungs, bronchi, pleura, and peritoneum. Case 13 had tuberculosis of the lungs, pleural cavities, and both adrenal glands with resultant Addison's disease. It should be pointed out that this case also showed evidence of

previous rheumatic infection which may well have been the cause of the pericarditis, but the evidence seems to indicate that it actually was a tuberculous pericarditis. And Case 14 had chronic fibroid phthisis with cavitation of both lungs.

No one denies that tuberculosis can and does produce constrictive pericarditis in many cases. But in just what percentage of cases of this syndrome can the tubercle bacilli be implicated? That is the question which cannot be satisfactorily answered.

This problem is discussed at length by Blalock and Levy (1938). To put the problem in its proper perspective, the following authors are quoted :

Wells (1902) : "Many cases of adherent pericardium are probably of tuberculous origin although not showing any anatomic characteristics of tuberculosis. However, it is to be understood that this is not the only cause."

Lilienthal (1925) : "Few, if any, of the calcifications of the pericardium are of tuberculous origin."

Sprague, Birch, and White (1932) : "Tuberculosis of the insidious type is the most probable cause of the constrictive pericarditis of Pick."

White (1935) reported fifteen cases of constrictive pericarditis and wrote the following : "The ætiology of chronic pericardial disease can be assigned as follows : Tuberculosis in two (questionable in two others), pneumonia with polyserositis (including both pleuritis and pericarditis) in two, sepsis in one, rheumatism in none, uncertain or unknown in ten (in five of which there was a definite history of acute pericarditis)."

And finally, Blalock and Levy (1938) write : "Of the nineteen patients with undoubted constrictive pericarditis which have been studied—eleven were found to be tuberculous in origin and five others were believed to be" and "It is likely that this disease (i.e. tuberculosis) accounts for the majority of cases of chronic constrictive pericarditis." Regarding the possibility of the condition being of rheumatic origin, they state : "Our experience and particularly that of White in Boston, makes one wonder seriously if rheumatic infection ever results in marked constrictive pericarditis." The strongest evidence that rheumatism can not be regarded as a cause of constrictive percarditis would appear to come from White (1935), who states : "A series of 1,000 children with rheumatic infection studied—and followed over a period of ten years, has shown in not a single instance any evidence of chronic constrictive pericarditis, even though the heart was often seriously involved in other respects, and even though acute pericarditis had been noted in many cases during their acute rheumatic infection."

Thus it would appear that at any rate rheumatic fever cannot be incriminated as a cause of this syndrome.

That Developing Independently :

There remains one other variety of tuberculosis of the heart, namely, that condition which is said to develop independently. Briefly this is a condition which ". . . presents the bread and butter appearance. No other active foci of tuberculosis are found in the body" (Thompson, 1933). In this rather rare variety the peri-

carditis is supposed to be either the only or the oldest tuberculous lesion and the condition is called "primary tuberculosis of the pericardium." It occurs in elderly patients and the tuberculous nature of the condition is usually unsuspected clinically. Thompson notes the following points and gives as his opinion, that it should be possible to recognise clinically that it is, in fact, a form of tuberculosis.

1. The average age is over 60 years.

2. The onset is insidious in patients without previous history of cardiac symptoms or evidence of previous rheumatic disease, syphilis or arterio-sclerotic heart disease.

3. There is unexplained fever in all cases.

4. There is a rapidly progressing increase in symptoms of cardiac insufficiency, proceeding relentlessly to a fatal termination within a very few months of the appearance of the first symptom. "It is precisely this rapidly fatal evolution and this striking failure to respond to treatment that identified this disease."

Some authors consider that in this condition tuberculous infection occurs only in the pericardium and not in other tissues, unless it so happens that spread from pericardium to other parts of the body takes place. This view seems most unreasonable and it would appear much more likely that the true primary tuberculous focus, for example in lungs and mediastinal glands, had healed and was no longer demonstrable clinically or at post-mortem examination. The term "anatomically primary cases," which is often applied to this group is therefore not a good one. The fact remains, however, that the pericarditis may be the only active tuberculous focus found and when this is so, the condition may be called primary tuberculosis of the pericardium. In Cases 8 and 9, the pericarditis was the dominating feature and although both patients had caseous lymph nodes they could probably be included in this group. One patient was aged 60 and the other 63 years.

Summary

1. Cardiac tuberculosis is quite a rare condition. Only sixteen cases were found among the records of 3,500 cases post-mortemed in the last ten years in the Institute of Pathology.

2. Tuberculous endocarditis is extremely rare and it would appear that only four cases have ever been recorded. Endocardial tuberculosis, however, is quite frequently found as part of a general miliary tuberculosis or as an extension inwards of a tuberculous pericarditis.

3. Tuberculosis of the myocardium may be part of a general miliary tuberculosis or it may be the result of spread from a very active tuberculous pericarditis.

4. The usually accepted picture of tuberculous pericarditis with effusion will only be found if hypersensitivity to the tubercle bacillus is associated.

5. It would appear that :

(*a*) Chronic adhesive pericarditis, where the two layers of pericardium are partially or completely fused together, is often due to tuberculosis.

(*b*) Chronic mediastino-pericarditis, where the two layers of pericardium as well as being glued together are strongly attached to other mediastinal structures with consequent hampering of the heart's action as it attempts to contract, is seldom due to tuberculosis.

(*c*) Polyserositis, which may be followed by constrictive pericarditis, is very often due to tuberculosis.

(*d*) Constrictive pericarditis may present as either a superior or an inferior mediastinal pressure syndrome and is most commonly due to tuberculosis.

(*e*) Calcified pericardium is a subvariety of constrictive pericarditis and so is also most commonly due to tuberculosis.

(*f*) Rheumatic fever seldom, if ever, causes constrictive pericarditis.

6. The important literature on the subject is briefly reviewed.

Thanks are due to Professor J. H. Biggart for his help in the preparation of this paper and to Mr. D. Mehaffey, A.R.P.S., to whom I am indebted for the photography.

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REVIEW

SUICIDE AND THE MEANING OF LIFE. By Margarethe von Andics. William Hodge & Co. Pp. 219. 8s. 6d.

Perhaps the best features of this book are its arresting title and the foreword by Professor Sir Cyril Burt. Dr. von Andics has analysed the case-histories of one hundred persons who have been seen in the Potzel Clinic in Vienna or its branches, most of whom came from the poorer classes of society. All had failed—obviously—in their attempts to commit suicide, and in some cases these do not seem to have been very determined attempts. As might be expected, they had become weary of life for such causes as maladjustment to their environments. Forty-three per cent. were between the ages of 20 and 40, and forty-three per cent. were males. Only eleven of seventy-eight cases were regarded as of normal or supra-normal sexuality. The author does not give any very clear idea of "the meaning of life," thus leaving the impression that her book title is barmecidal.

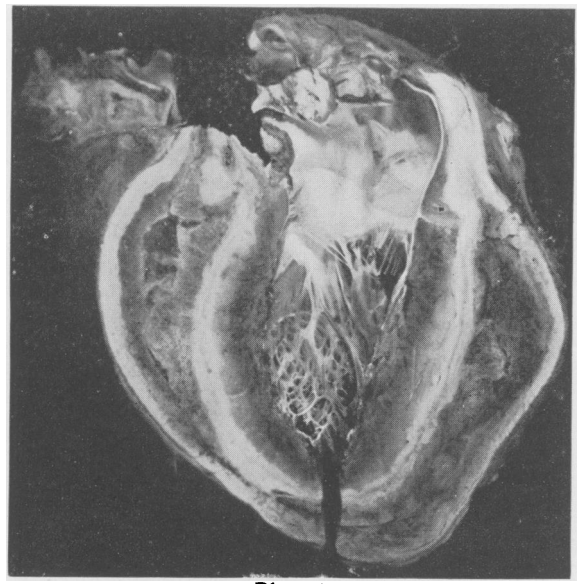

Plate 1

(Case 6, female child aged 6 years)
Acute sero-fibrinous tuberculous pericarditis with extension into the myocardium.

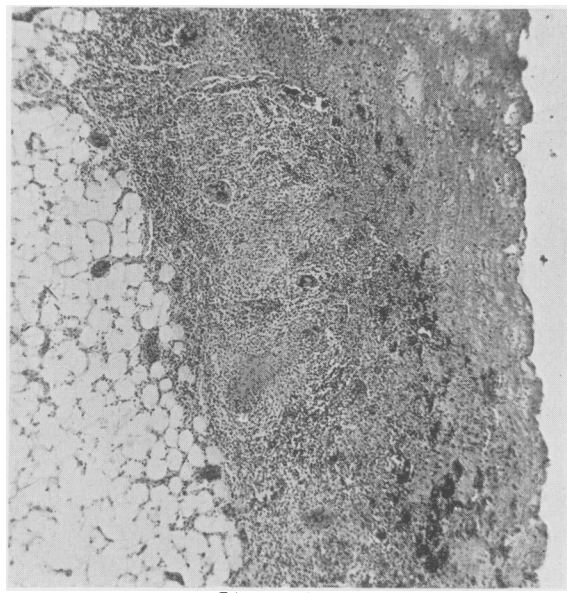

Plate 2 (x50)

(Case 8, female subject aged 63 years)
Section through pericardium showing tuberculous pericarditis.

(*c*) Polyserositis, which may be followed by constrictive pericarditis, is very often due to tuberculosis.

(*d*) Constrictive pericarditis may present as either a superior or an inferior mediastinal pressure syndrome and is most commonly due to tuberculosis.

(*e*) Calcified pericardium is a subvariety of constrictive pericarditis and so is also most commonly due to tuberculosis.

(*f*) Rheumatic fever seldom, if ever, causes constrictive pericarditis.

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REVIEW

SUICIDE AND THE MEANING OF LIFE. By Margarethe von Andics. William Hodge & Co. Pp. 219. 8s. 6d.

Perhaps the best features of this book are its arresting title and the foreword by Professor Sir Cyril Burt. Dr. von Andics has analysed the case-histories of one hundred persons who have been seen in the Potzel Clinic in Vienna or its branches, most of whom came from the poorer classes of society. All had failed—obviously—in their attempts to commit suicide, and in some cases these do not seem to have been very determined attempts. As might be expected, they had become weary of life for such causes as maladjustment to their environments. Forty-three per cent. were between the ages of 20 and 40, and forty-three per cent. were males. Only eleven of seventy-eight cases were regarded as of normal or supra-normal sexuality. The author does not give any very clear idea of "the meaning of life," thus leaving the impression that her book title is barmecidal.

Simmonds' Disease

Report of a Case

by J. Martin Beare, M.D.

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Paulesco in 1907 drew attention to a syndrome which developed in animals following removal of the anterior lobe of the pituitary gland. Acquainted with this experimental work, Simmonds in 1914 was able to correlate ante-mortem and post-mortem findings in a woman who died with undue emaciation and premature ageing, and who at autopsy was found to have destruction of her anterior pituitary. It is obvious that the clinical syndrome was known before these papers of Paulesco and Simmonds appeared, but its relationship to destruction of the anterior pituitary was not recognised until Simmonds wrote his now classical paper and applied Paulesco's experimental work to human medicine.

Silver (1933) has defined the syndrome as "a clinical state, most common in women, characterised by progressive extreme emaciation, premature ageing, wrinkling of the facial skin, loss of pubic and axillary hair, dental caries and loss of libido and sexual function, accompanied by depression of the basal metabolic rate. Untreated it is a progressively fatal disease, usually terminating suddenly with a short period of coma." While this definition undoubtedly covers many of the cases, it certainly does not apply to them all. As is becoming more generally appreciated, emaciation is not a *sine qua non* for the diagnosis of Simmonds' disease. If we apply a pathological definition to the syndrome, it is likely that the true clinical picture will become much clearer and more cases will be recognised.

Briefly then, Simmonds' disease is better considered as a condition resulting from the destruction, partial or complete, of the anterior lobe of the pituitary gland. The actual cause of the destructive process is of secondary importance to a proper understanding of the condition. As Sheehan (1939) says: "It must therefore be emphasised that the one primary requirement of the syndrome is that there shall have been some gross destructive lesion in the anterior pituitary." The fact that a fairly large amount of anterior pituitary tissue must be lost before recognisable symptoms can occur was first pointed out by Simmonds (1918). The symptoms themselves can involve any system of the body, they are of very varied incidence, and practically any one of them may or may not occur without any satisfactory explanation of its presence or absence. Furthermore, they do not show any regularity of association (Sheehan, 1939).

The following is a report of a case of Simmonds' disease in a male, verified at post-mortem examination, and in whom emaciation was notable for its absence, despite the fact that the patient had had the condition for at least six, and possibly sixteen, years.

Report of Case

The patient was a male aged 48 years. He was married and had two children, one born in 1925, the other in 1927. His wife and both children are alive and quite

normal in every way : they have not suffered from any serious or significant illness. The patient's blood relatives did not suffer from any mental or endocrine abnormality.

In 1931 the patient, according to his wife's story, disappeared from home for a period of five months. Up to that time he had led a perfectly normal life. He had been employed as a night watchman. His wife has stated that up to that time too their sexual relationships had been quite normal.

In December, 1931, he was admitted to the Belfast City Hospital with a mild infection of his conjunctivæ. His wife was notified, and on his discharge within a few days he went back to live with her. His behaviour was not, however, normal; he had definite persecutory ideas and thought that his wife and one of his children were trying to kill him. His mental condition deteriorated rapidly, and he was admitted to the Belfast Mental Hospital in April, 1932. He was described then as being a rather small but well nourished man; he was certainly not obese. His hair was dark and he had a normal male distribution of body hair. On his head he had a thick crop of dark hair. His expression was "depressed," but otherwise there was no abnormality in his appearance. On physical examination all systems were found to be normal. He said that he had stopped work nine months previously because of his "nerves." He was dull and quiet and did not talk freely. He thought he was being followed everywhere, his food was being poisoned, and that he had some "dirty and bad" disease. He blamed all this on his wife and one of his children. He attributed his immediate breakdown in mental health to the loneliness of his work as a night watchman.

During the next seven years he remained in the Mental Hospital. At times he was dull and stupid, at other times he was restless and excited. His mental condition did not improve in any way; if anything, he seemed to deteriorate. His physical condition remained, however, good until March, 1939, when he had a severe attack of bronchopneumonia. With the onset of this acute illness he became quite mute. Within two months he had completely recovered from this physical illness but was still mute. He was very dull and resistive. He then developed a conjunctivitis and a furunculosis of his pinna. He recovered from this within a few days and apparently had no complications, intracranially or otherwise : at any rate there is no evidence that he had any more serious trouble. Six months later his mental condition had improved considerably. He was still mute, but he was described at this time as "bright and active, working industriously, and always clean and tidy." Some time later, in October, 1941, he had become sufficiently improved to be discharged from hospital under the care of his wife and sister.

On discharge from hospital his wife stated that apart from being rather pale and very thin he looked quite normal. He had a normal distribution of body hair and he had not started to lose his scalp hair. He was rather quiet and dull. He expressed no desire to lead any kind of sex life again.

Within a year his whole appearance had noticeably changed. He no longer had to shave once a day but found that once a week was sufficient. And, as his wife

said, "It was vanity which made him shave as often as that!" He began to get fat and to lose his scalp hair. He often had headache, and very frequently vomited in the mornings. He was unable to do any kind of work, being very easily tired and always lethargic. He did not like cold weather; in fact, he apparently always wore a heavy overcoat, even on the warmest day in summer. He was said to turn a yellow or green colour at times; this lasted a few hours, then his usual pallor returned. This green colour must have been very noticeable, since some of his neighbours volunteered the information when they were asked to recall and describe the appearance of the patient.

More or less in this state, he existed until his final illness. On 9th March, 1947, he was admitted to the Belfast City Hospital in coma. On examination he was found to be a "stout man of medium height." He had very little scalp or body hair. He was very pale and his skin was dry and cold. His pulse was not palpable and his heart sounds very faint. His respiratory and alimentary systems were normal on examination and his tongue was dry and clean. His pupils were found to be equal, central and dilated; they did not react to light. All deep reflexes were absent and his limbs were quite flaccid.

He died within a few hours and before any other investigations or a more complete examination could be carried out.

Post-Mortem Examination

The following were the essential findings of the post-mortem examination. Negative findings, except where significant, are omitted.

The body was that of a rather short, "plumpish" man, who looked rather older than his forty-eight years. He was extremely pale. There was complete lack of body hair and almost complete lack of scalp hair. His skin was dry and rather coarse. There was some œdema of his ankles. Neither testicle was in the scrotum. As found later, the left one was absent or replaced by a small amount of unrecognised fibrous tissue and the right testicle was in the inguinal canal.

Body Cavities.—All contained a moderate amount of œdema fluid. There were dense adhesions in the pleural cavities.

Heart.—This was rather small in size, weighing 270 grm., but there was some hypertrophy of the musculature of the right ventricle (6 mm. thick). The left ventricle was 1 cm. thick. On histological examination there was marked vacuolation of individual muscle cells and considerable œdema of the myocardium. In view of this it may be concluded that the heart was actually very much reduced in size, in spite of the hypertrophy of the right side.

Lungs.—The pleura showed evidence of previous inflammation, being thickened and fibrotic. There was considerable emphysema confirmed on histological examination. There was also some cubical metaplasia of alveolar walls and squamous metaplasia of the lining epithelium of the bronchi. There was some œdema of the bases of the lungs.

Liver.—This viscus was only slightly reduced in size, weighing 1,260 grm. The

hepatic cells showed vacuolation of their cytoplasm. There was a marked degree of brown atrophy around the portal tracts.

Spleen.—This was very small, weighing only 110 grm., yet histologically there was marked congestion of the splenic pulp.

Kidneys.—These were somewhat reduced in weight, being about 100 grm. each. Histologically there was a marked degree of vacuolation of the cells of the tubules, especially of the lower parts of the nephron. Over all, one had the impression of atrophy of the organ.

Pancreas.—Again there was no very definite abnormality, only an impression of general atrophy.

Adrenals.—Both glands were rather small. On microscopic examination the capsule was found thickened with fibrous tissue. The cortex was markedly reduced in size, being about one-third of the normal minimal width. The zona glomerulosa was only slightly narrower than normal, but the cells of this layer contained a large amount of lipoid material. The zona fasiculata was noticeably reduced in width, but the zona reticularis was almost entirely, and in places completely, absent.

Thyroid.—All acini were rather small, and there was a very definite atrophy of the gland. There was no marked lymphocytic infiltration, a finding which has been described in many cases of Simmonds' disease.

Bone Marrow.—A specimen of bone marrow from the vertebral column showed abnormal but incomplete fatty replacement of the marrow. Again the picture of atrophy was apparent.

Testes.—The spermatogenic tissue has been completely replaced by a very homogenous hyaline type of tissue, and no normal sperm-producing cells were seen. Of great interest was the absence of the interstitial cells of Leydig. In other words, complete atrophy of the whole of the testis was present. This finding was of special interest, in view of the fact that in 1925 and 1927 the patient apparently became the father of two children. The fact that the left testicle was absent and the right incompletely descended must be taken as coincidental, and the extensive atrophy of both the spermatogenic and endocrinal cells of the right gland be assumed to be due to deficiency of anterior pituitary secretions.

Pituitary.—At post-mortem the gland was noticed to be very small. The posterior clinoid processes extended abnormally far forward as though "collapsed" over the shrunken gland. On microscopical examination the anterior lobe was found to be almost completely replaced by fibrous tissue. Serial sections of the gland were made in the search for more anterior lobe cells, but no more were found. Those few which remained were, for the most part, chromophobe cells. In one area a small nest of lymphocytes was detected, but nothing to indicate a possible etiological factor. Evidence of tuberculous or syphilitic destruction of the gland was searched for in vain. The posterior lobe, on the contrary, remained almost completely intact, apart from a certain fibrous tissue encirclement with patchy fibrosis of its anterior margin. This, of course, is also against a destruction by any form of granulomatous tissue.

This selective destruction of anterior lobe would seem to indicate a vascular etiology akin to the end result of the post-partum destruction, so important in females. However, the etiological agent in this particular case remains obscure.

Brain.—There was evidence of some degree of cerebral œdema, with flattening of the convolutions and slight cerebellar coning. A section through the hypothalmus showed a little subependymal gliosis. There was a fairly definite dropping out of cells in the nucleus supraopticus and a well marked pallidal siderosis.

Aorta.—There was a moderate degree of atheromatous degeneration, but no other lesion noted. There was no evidence of syphilis.

Skin.—A section of skin from the abdominal wall showed a definite atrophy and replacement by adipose tissue of some of the sweat glands, a finding which is in keeping with the clinical condition of the skin.

Summary

Simmonds' disease.
Fibrosis of anterior lobe of pituitary.
Atrophy of all viscera (microsplanchnia).
Cryptorchidism and hypogonadism.
Pulmonary emphysema and right heart hypertrophy.
The immediate cause of death was probably a severe attack of hypoglycæmia.

Commentary

It will be seen, therefore, that although the fundamental finding of anterior pituitary destruction was present in this case, and that therefore the case was one of Simmonds' disease, emaciation was absent. However, the case fits into the so-called "pituitary myxœdema, or Simmonds' disease masquerading as myxœdema" (Means *et al,* 1940). The fact that emaciation is not found in all cases of Simmonds' disease was, apparently, first pointed out by Sheehan (1939). He wrote: "This type of Simmonds' disease is relatively common, but the cases frequently remain undiagnosed . . . The confusion appears to rise from the misconception that patients with Simmonds' disease usually show cachexia."

There are four main types of Simmonds' disease (Sheehan, 1939; Cameron, 1945).

1. *The typical post-partum case of Simmonds' disease.*—Here there is absence of lactation and sometimes hypoglycæmia following a complicated delivery usually in a multipara. The uterus becomes superinvoluted and the external genitalia atrophic. Menstruation fails to return and libido is absent. There is a gradual loss of body hair. Mental apathy and extreme sensitivity to cold develop. The patient may look myxœdematous or prematurely senile. The weight is usually little altered unless there is great anorexia. The blood pressure is low. The basal metabolic rate is about 25 per cent. There is a hypochromic anæmia sometimes with a definite eosinophil leucocytosis similar to that occasionally seen in myxœdema. The blood cholesterol may be a little raised and the blood sugar rather low. After ten, twenty, or thirty years the patient may become typically myxœdematous or may develop

mental changes with anorexia and some loss of weight. At this stage the anæmia may become hyperchromic, the basal metabolic rate may fall to 35 per cent, but the blood pressure is usually normal. Finally the patient goes into coma and dies usually as a result of hypoglycæmia.

It will be seen that this description of Simmonds' disease given by Sheehan (1939) and representing "the typical post-partum case" differs in a great many respects from the generally imagined clinical picture of the condition.

2. *Pituitary Myxœdema.*—Here the patient exhibits typical myxœdema. A differential diagnosis from primary thyroid insufficiency is of great importance, because administration of thyroid in the usual dosage may precipate acute failure of the adrenal cortex, and death result. There are now quite a number of reports in the literature of such cases. A case was described in detail by Castleman and Hertz (1939). Their patient was a woman of 48 years. She was said to be moderately obese, and this obesity was of no special type, being fairly generalised. The onset of her ill health was ten years previously following pregnancy. The authors noted as a striking feature "the preservation of such excellent nutrition despite chronic failing health over a period of ten years." This case was diagnosed clinically as one of myxœdema. She was given thyroid, and, as the authors state, "It was . . . quite likely that our patient died of adrenal insufficiency after the attempt to relieve her thyroid deficiency." It would appear as if the deficiency of thyroid hormone compensates to some extent for the deficiency of adrenal secretions. The whole organism is made to work at a lower speed. Any attempt to increase the rate of working of the organism, by administering a single hormone such as thyroid, makes manifest a gross deficiency of other hormones. Castleman and Hertz suggest that a differential diagnosis may be made if the possibility is always borne in mind in cases of myxœdema in which earmarks of other endocrine deficiencies are present, such as onset of early amenorrhœa (instead of the more usual metrorrhagia), or signs or symptoms of adrenal insufficiency. To this might be added radiography of the pituitary fossa for signs of destruction to the clinoid processes or abnormal calcification in a tumour, etc., and other signs of a pituitary tumour should also, of course, be sought. Castleman and Hertz were able to find six other similar cases in the literature, and Biggart (1941) reported two cases which presented as myxœdema and were found at post-mortem to be examples of Simmonds' disease.

3. *Pituitary Addison's Disease.*—This is a most interesting sub-group of Simmonds' disease. The name is applied to those cases which show predominantly the asthenia typical of destruction of the adrenal cortex. They may show all the symptoms and signs of Addison's disease with one important exception, namely Addisonian pigmentation, which is rarely seen (Sheehan, 1939). Of course, in this respect, the presence of other endocrine abnormalities may point to the correct diagnosis. A typical case has been reported by Moss (1942).

4. *Mild Simmonds' Disease.*—Since all grades of damage to the pituitary are possible, all grades of severity of clinical symptoms should be possible. Sheehan states that in these cases there is nearly always a pronounced, and often a complete,

recovery if patients with a small post-partum necrosis become pregnant again. However, it must be pointed out that conditions which have led to the complicated delivery in the first instance are liable to recur on a subsequent occasion with disastrous results. The improvement in the patient's condition is attributed to the physiological hypertrophy of the remaining pituitary tissue which normally occurs during pregnancy, but in these circumstances subsequent regression to the previous (reduced) volume does not occur.

Mental Symptoms.—The interpretation of the mental changes found in Simmonds' disease is not at all straightforward. This aspect of the condition has been reviewed by Wadsworth and McKeon (1941). They state that there does not appear to be a uniform mental symptomatology. They attribute apathy, somnolence, depression, and slowing of mental processes to the pituitary disease itself, and state that transient attacks of excited, restless behaviour accompanied by delusions or vivid hallucinations are very likely due to states of severe hypoglycæmia. It would appear that these abnormal states can be dramatically relieved by intravenous administration of dextrose. A case was reported by these authors which showed manic-depressive psychosis with associated Simmonds' disease due to post-partum necrosis of the pituitary. In view of the fact that the patient gave a history of two rather vague periods of depression, one following the death of her father and the other the death of her mother, Wadsworth and McKeon were inclined to regard this previous history as indicative that the mental abnormality in their patient was not due to pituitary destruction. Nevertheless, it was only after the complicated delivery that really severe mental symptoms ensued, and the fact that anyone should feel depressed following the death of their parents, especially since no other periods of depression were noted prior to the occurrence of the organic lesion in the pituitary gland, is surely not enough evidence on which to make a diagnosis of double pathology.

In the discussion on this aspect of their case these authors noted that Grinker (1939) had pointed out that the symptom complex in manic-depressive psychosis is identical with the variations of mood accompanying hypothalmic lesions. Electrical stimulation of the anterior hypothalamus produces restlessness, excitement, euphoria, and mania; stimulation of the posterior portion causes sleepiness and unconsciousness. Against this hypothesis in the fact that, with present histological technique, no constant organic lesion has been found in straightforward cases of manic-depressive psychosis occurring in man. Wadsworth and McKeon's case showed histological damage to the hypothalamus. They found degenerative changes in the supraoptic and paraventricular nuclei, which they considered were secondary to the pathological changes in the anterior lobe of the pituitary. They also found in the brain multiple petechial hæmorrhages and some subependymal gliosis, which they thought might be due to hypoglycæmia. As remarked previously, they concluded that they were dealing with double pathology. Nevertheless, the findings in our case are so similar (an illness like manic-depressive psychosis which in our case antedates the physical changes of Simmonds' disease, associated with the pathological changes of sclerosis of anterior pituitary with degenerative changes in the

nucleus supraopticus) to those of Wadsworth and McKeon, that one wonders whether or not the mental changes in our case were the first outward signs of the destructive process which had occurred in the base of the skull and which finally ended in such gross physical abnormalities. If this opinion is not acceptable then, like Wadsworth and McKeon, one must conclude that our patient had two pathological lesions, both of an exactly similar type to their case.

Mental changes occur in about 50 per cent. of all cases of Simmonds' disease, and they are often of the manic-depressive type. In view of this it is difficult not to accept the idea that in our patient mental symptoms preceded physical signs by a period of about ten years.

Admittedly this possibility would be a completely new idea in the symptomatology of the condition and difficult for many people to accept. But since this type of insanity does seem to be related to the hypothalamus, since hypothalmic changes were found in these patients and since the hypothalamus and pituitary gland are so intimately related anatomically and physiologically, the possibility of this organic basis for the mental symptoms cannot easily be excluded.

Etiology.—In an extensive review of the literature, Calder (1932) noted that almost half the cases described had shown as an essential finding a destruction of glandular elements with replacement by scar tissue—"the almost universal result of healed injury." Obviously many pathological processes are capable of bringing about destruction of the pituitary gland. In our case we found only the non-specific scar tissue of any healed injury. The fact that it was limited to the anterior lobe would seem to implicate the vascular system. Perhaps it was a thrombosis or an embolus, perhaps infected, perhaps not. To speculate further regarding the etiological agent which was at work in our patient many years ago, would be futile.

Even the exact mechanism at work in post-partum necrosis is by no means clear. Sheehan (1937) concluded that the lesion is the result of the effects of shock due to hæmorrhage. Most of his cases had a labour complicated by retained placenta, and he postulated that the resulting low pressure allows thrombosis to occur in the engorged sinusoids of the pregnancy gland. Biggart (1941) is not convinced that the mechanism is so straightforward. Many patients die within a week after loss of blood and degrees of shock quite comparable in their severity to those seen in complicated deliveries, yet necrosis of the pituitary has not been seen in such patients. It may be noted too, that even in severe shock an attempt is made to maintain the blood supply to the vital centres, and it would seem that the pituitary would benefit from its juxtaposition to the central nervous system. If the blood supply is so poor as to permit intravascular clotting, this is therefore most likely to occur in other organs. Biggart pointed out that perhaps the placenta may play a more important role than had so far been assigned to it. Large doses of hormones can produce necrosis experimentally in animals, and it is possible that pituitary necrosis may have an endocrine origin. The retained placenta, once the fœtus has become separated, may discharge the contained hormones into the circulation, and these in turn may act upon the anterior pituitary. Such an explanation certainly allows us to understand more easily the limitation of the complication to pregnancy.

Whatever our ideas on the mechanism at work, it is clear that more investigation is required before the condition is fully understood.

I wish to thank Professor J. H. Biggart for his advice, help, and criticism in the preparation of these notes; Dr. N. C. Graham and Dr. T. H. Crozier for giving me access to the clinical notes of the patient; and Dr. D. Gardiner for help in compiling notes relating to the patient's psychological condition. I am indebted to Mr. D. Mehaffey, A.R.P.S., for the photography. (See plates in middle of Journal)

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REVIEW

INTRODUCTION TO CLINICAL NEUROLOGY. By Gordon Holmes, M.D., F.R.S. Edinburgh: E. & S. Livingstone Ltd., 1946. 12s. 6d.

It is fortunate for those interested in clinical neurology that Dr. Gordon Holmes has published in book form what he has taught for many years at the National Hospital.

Dr. Holmes' name is a household word with all neurologists, but especially those who have heard him teach or discuss cases. He writes with the same clarity and criticism as he teaches and he very often stimulates the pupil's mind to probe neurological conditions still further and from other angles. This book is not one descriptive of disease, its diagnosis and treatment, so much as symptomatology and its interpretation. Subjects are dealt with rather than diseases. For example, there is a chapter on "Muscle Tone and Co-ordination of Movement." There is one on "Examination of Sensation." A third is entitled "Reflexes," and so on. Diseases affecting the central nervous system are, of course, not forgotten. There is an excellent chapter devoted to "Convulsions and Other Involuntary Movements," while through each chapter clinical conditions are being constantly mentioned to illustrate the subject being discussed.

Pathology is not attempted, except in a short chapter, which shows the ways in which the central nervous system generally may be affected.

Mention must be made of the diagrams, which are original and clear and are a great help to the student.

The book is intended to be an "introduction," but with such a wealth of material available in such a small space, this book will be read and re-read by teacher and student alike. H. H. S.

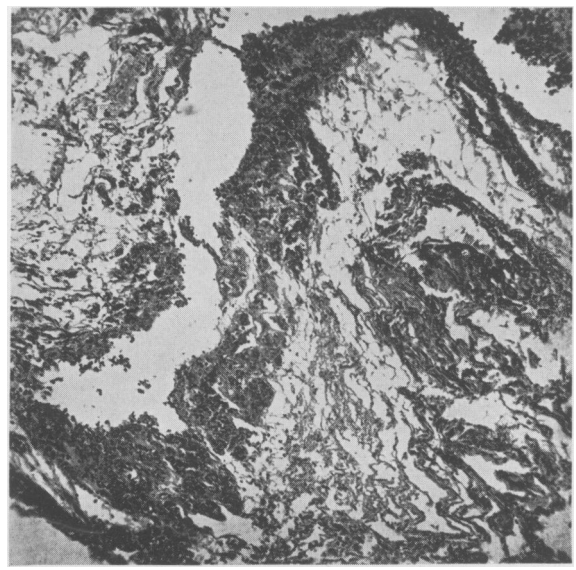

Plate 1 (x60)—Pituitary

Section through anterior lobe to show almost complete replacement by fibrous tissue. Only a few chromophobe cells remain. No eosinophil or basophil cells were detected.

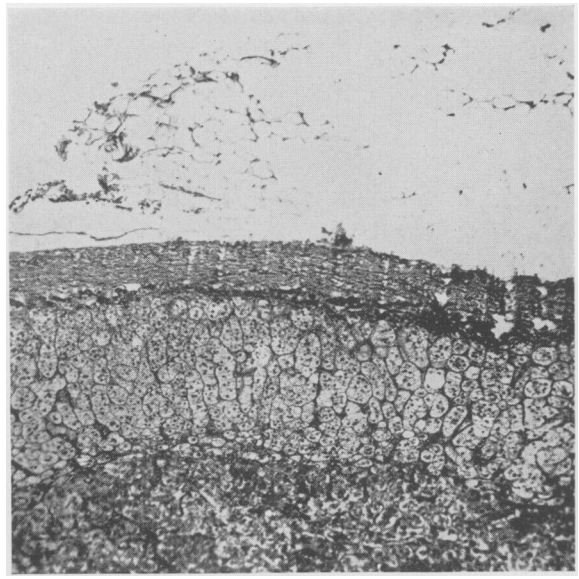

Plate 2 (x60)—Adrenal

Section through cortex to show reduction in width owing to almost complete absence of zona reticularis and great diminution in zona fasiculata. The cells of the zona glomerulosa contain an excess amount of lipoid material. The capsule of the gland is markedly thickened.

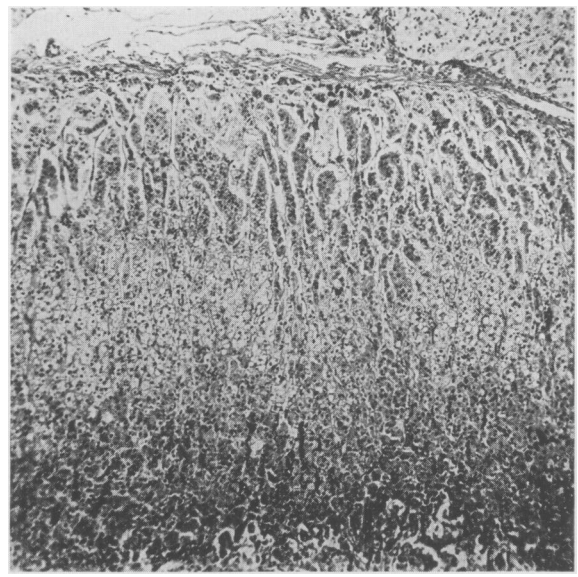

Plate 3 (x60)—Normal Adrenal

Section photographed at same magnification as Plate 2 for comparison.

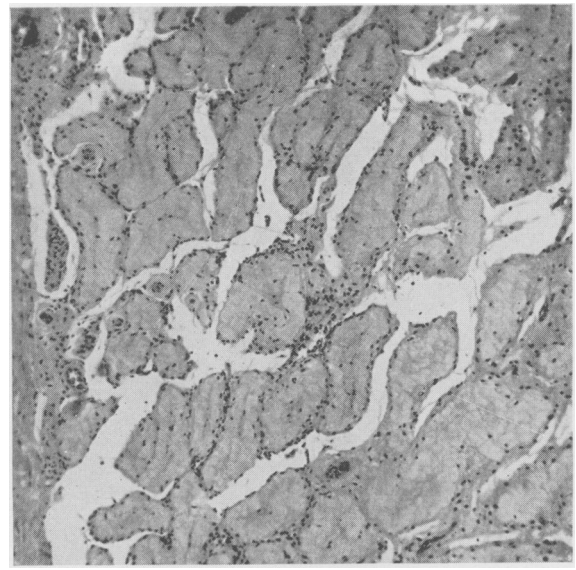

Plate 4 (x60)—Testis

Showing marked atrophy of spermatogenic tissue and replacement by a hyaline type of tissue. Note also absence of interstitial cells of Leydig.

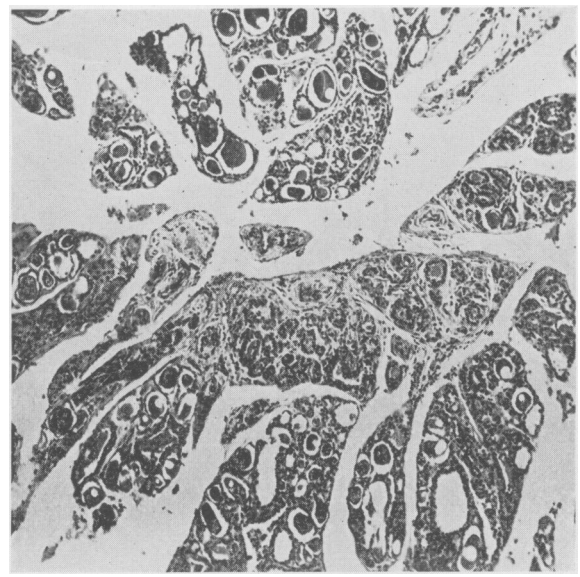

Plate 5 (x70)—Thyroid

Section to show the very marked atrophy of the gland.

Whatever our ideas on the mechanism at work, it is clear that more investigation is required before the condition is fully understood.

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INTRODUCTION TO CLINICAL NEUROLOGY. By Gordon Holmes, M.D., F.R.S. Edinburgh: E. & S. Livingstone Ltd., 1946. 12s. 6d.

It is fortunate for those interested in clinical neurology that Dr. Gordon Holmes has published in book form what he has taught for many years at the National Hospital.

Dr. Holmes' name is a household word with all neurologists, but especially those who have heard him teach or discuss cases. He writes with the same clarity and criticism as he teaches and he very often stimulates the pupil's mind to probe neurological conditions still further and from other angles. This book is not one descriptive of disease, its diagnosis and treatment, so much as symptomatology and its interpretation. Subjects are dealt with rather than diseases. For example, there is a chapter on "Muscle Tone and Co-ordination of Movement." There is one on "Examination of Sensation." A third is entitled "Reflexes," and so on. Diseases affecting the central nervous system are, of course, not forgotten. There is an excellent chapter devoted to "Convulsions and Other Involuntary Movements," while through each chapter clinical conditions are being constantly mentioned to illustrate the subject being discussed.

Pathology is not attempted, except in a short chapter, which shows the ways in which the central nervous system generally may be affected.

Mention must be made of the diagrams, which are original and clear and are a great help to the student.

The book is intended to be an "introduction," but with such a wealth of material available in such a small space, this book will be read and re-read by teacher and student alike. H. H. S.

Studies from the Institute of Pathology, No. 14

A. 5691

A CASE OF MALIGNANT HYPERTENSION

Clinical History

The patient was a male aged 50 years. He was quite well till ten weeks prior to admission to hospital, when he began to complain of breathlessness on exertion, abdominal pain, swelling of the feet and ankles, and loss of weight. The abdominal pain was in the left hypochondrium, was dull in character with sharp twinges, and was not related to food or exercise.

On admission to hospital the patient was seen to be a moderately well nourished but anæmic male subject. His pulse was regular, and heart sounds were normal. The blood pressure was 200/150, and on X-ray of the chest, the heart was enlarged and of the aortic type. Albumen was present in the urine, the specific gravity of which was 1,025. The Wassermann reaction was negative.

During his stay in hospital his symptoms became worse. The day before his death he had a sudden and severe hæmatemesis followed by melæna. He died ten days after admission.

Post-Mortem

The body is that of a poorly nourished adult male subject. Rigor mortis is present. There is no jaundice or enlargement of the superficial lymph nodes. The lower extremities are oedematous.

Body Cavities.—The pleural and pericardial sacs are normal. About half a pint of blood-stained fluid is present in the peritoneal cavity.

Heart.—Weight 600 gm. The epicardial surface is smooth and glistening. There is no abnormality of the right auricle apart from dilatation. The tricuspid valve admits four fingers. The wall of the right ventricle is 10 mm. thick, showing a marked degree of hypertrophy. The left auricle is normal. The mitral valve admits three fingers and there is no thickening of the cusps. The left ventricular cavity is dilated and its muscle hypertrophied measuring 24 mm. in diameter. The endocardium is everywhere translucent, except for some thickening on the proximal side of the aortic valve. The ascending aorta shows marked scarring with pearly grey and yellow plaques present in the intima, and a great increase of fibrous tissue in the adventitia. The process which appears syphilitic does not, however, involve the cusps of the aortic valve nor the orifices of the coronary arteries.

Lungs.—These are voluminous and feel air-containing. Emphysematous bullæ are present along the anterior margins, and at the apices. On section, there is a generalised coarsening of the alveolar pattern. There is a terminal bronchitis, but no pneumonia or œdema.

Liver.—Weight 1,800 gm. The capsule is smooth. On section, the lobular pattern is distinct and, apart from terminal congestion, no lesions are seen.

Spleen.—Weight 100 gm. The capsule is wrinkled. On section, the pulp is bright red and firm in consistency. The Malpighian bodies and trabeculæ are clearly visible.

Pancreas.—The gland is normal.

Kidneys.—These are reduced in size. The capsule strips with difficulty, revealing a brownish finely granular external surface. On section, the cortex is reduced in width, and presents a rather blotchy appearance, areas of congestion and pallor disturbing the normal cortical striations. A few small hæmorrhages are present in the pelves.

Adrenals.—Their size is normal and the cortex is well filled with yellow lipoid.

Genital Organs.—These are normal.

Stomach.—There is a mild degree of mucosal congestion, but no evidence of ulceration.

Small Intestine.—Several areas of perforation varying in size from 5 mm. to 20 mm. are present in the jejunum. The intestine in this region is deeply congested, its wall œdematous, and the lumen as far as the ileo-cæcal valve filled with blood. On removal of the blood clot, the mucosa of the jejunum is found to be ulcerated in many areas. The ulcers are irregular in outline, with ragged overhanging edges, and extend deeply into the muscle coat, several having perforated.

Microscopical Examination

Heart.—There is hypertrophy of the muscle fibres of the left ventricle. Small areas of fibrosis are seen in the myocardium, and a few fibrillar paravascular scars are also present. The coronary arteries and mitral valve are normal.

Lungs.—In all sections examined there is emphysematous change with well developed fibrous thickening of the broken alveolar walls. There is patchy bronchiolitis.

Liver.—The lobular pattern is normal. There is congestion and œdema around the central veins. The hepatic arterioles in the portal tracts are thickened, and one vessel shows fibrinoid necrosis of its wall.

Spleen.—The pulp is deeply congested and in a few areas foci of large cells with basophilic cytoplasm are present. Similar cells line some of the trabeculæ.

Pancreas.—The acinar tissue is normal. The pancreatic arterioles show marked hyalinisation and occasional necrosis of their walls.

Kidneys.—The capsule is thickened by dense fibrous tissue. There are many cortical scars present, infiltrated by dense numbers of lymphocytes. The glomeruli in the areas of scarring are hyalinised and the afferent arterioles tortuous and much thickened. In less affected areas the glomeruli show all stages of atrophy varying from peri-capsular fibrosis to thickening of the basement membrane of the glomerular capillaries, with or without partial replacement of the tuft by fibrous tissue. As well as being hyalinised, the afferent arterioles are occasionally necrotic, the media

assuming a structureless eosinophilic appearance. The vascular necrosis extends into the hilum of the glomerulus and is sometimes associated with complete necrosis of the tuft and adhesion to Bowman's capsule with early crescent formation (plate 1). Blood is observed in some of the tubules. The interlobar arteries show well marked intimal musculo-elastic hyperplasia.

Adrenals.—The intra-capsular arterioles are hyalinised. A few are necrotic.

Aorta.—The adventitia is thickened by fibrous tissue in which the vasa vasorum show endarteritis and perivascular cuffing with lymphocytes and plasma cells. Medial scarring is also present, and the intima is thickened by plaques of fibrous tissue.

Small Intestine (Jejunum).—The mucosa is infiltrated by chronic inflammatory cells, and in the areas of ulceration the epithelium is completely destroyed. The inflammatory change extends through varying thicknesses of the bowel wall and is sometimes accompanied by fibrosis. Many macrophages filled with hæmosiderin are present in the submucosa. The arterioles in this layer are the seat of a necrotizing arteritis, showing destruction of their walls with or without thrombosis (plate 2). Several vessels in the muscle and subserosal layer are also necrotic (plate 3). The affected arterioles show a complete absence of any perivascular inflammatory infiltration.

The other organs show no lesion of note.

Anatomical Diagnosis

Essential hypertension with terminal malignant phase.
Hypertrophy left ventricle.
Arteriolosclerosis and arteriolonecrosis kidneys, adrenals, pancreas, liver.
Arteriolonecrosis mesenteric vessels with jejunal hæmorrhage, ulceration, and perforation.
Pulmonary emphysema.
Hypertrophy right ventricle.
Syphilitic aortitis.

Commentary

Malignant hypertension develops as a terminal episode in about ten per cent. of cases of benign hypertension. The cause of death in such cases is usually renal insufficiency, and the patient presents in rapid succession all the signs of progressive renal failure.

In this case, however, there were no such symptoms, and even at post-mortem the appearance of the kidneys was not characteristic of the malignant phase, nor did there seem to be any association between the renal lesions and the ulceration of the small intestine.

On histological examination, there were in the kidneys the usual changes of essential hypertension, with arteriolosclerosis and arterial musculo-elastic hyperplasia. In addition, a few arterioles had undergone fibrinoid necrosis and the related glomeruli showed acute degenerative changes with patchy necrosis and leakage of

blood into the tubules. The appearance suggested a very early stage in the development of malignant hypertension with minimal renal vascular involvement, and was in accordance with the absence of clinical signs of incipient renal failure.

The cause of the intestinal lesion was quite evident on histological examination. Involvement of the arterioles in this site by a fulminant necrotizing arteriolitis explained the entire pathological picture. Deposits of hæmosiderin were abundant in the submucosa, indicating repeated hæmorrhages from previously damaged blood vessels. Necrosis of the overlying epithelial layer resulted in sloughing and ulceration, a process which in some areas had not only involved the mucosa superficially, but extended right through the muscle coat, with subsequent perforation and leakage of blood into the peritoneal cavity. It might be suggested that the vascular necrosis was secondary to the ulcerative lesions of the mucosa, but in other regions of the small intestine and deep within the muscle coat, and even on the serosal surface, necrotic arterioles were observed.

Polyarteritis nodosa should also be considered in the differential diagnosis in this case, but in view of the lesions in the kidney, admittedly not gross, but quite typical of malignant hypertension, and the absence of any perivascular inflammatory reaction around the necrotic vessels, even when thrombosed or showing signs of healing, this may be discarded as a possibility.

Intestinal ulceration of uræmic origin has of course been described frequently in association with renal failure developing during the course of a malignant hypertensive phase, but it is usually found in the colon, rarely in the small intestine, nor is it accompanied by a local vascular lesion.

This case, therefore, illustrates an unusual complication of malignant hypertension. In our post-mortem material one other similar case report is available. A child of twelve, suffering from chronic pyelonephritis with hypertension, at post-mortem was found to have arteriolonecrosis of renal and mesenteric vessels, the latter lesion being accompanied by multiple ulcers of the terminal ileum (plate 4).

It is not intended to enter upon a discussion of the possible mechanism responsible for the development of arteriolar necrosis in malignant hypertension. Vasospasm, toxic factors, and inherent weakness of the arterioles have all been suggested. The rapidity with which the blood pressure rises is probably the most important single factor. However, we can not hope to understand fully the pathogenesis of malignant hypertension till the whole problem of essential hypertension has been further elucidated.

In summary, therefore, a case of malignant hypertension is presented in which death was due to necrosis of the mesenteric vessels leading to jejunal hæmorrhage, ulceration, and perforation.

F. McK.

I am indebted to Dr. F. M. B. Allen for allowing access to the clinical notes of this case. Mr. D. Mehaffey, A.R.P.S., was responsible for the photography.

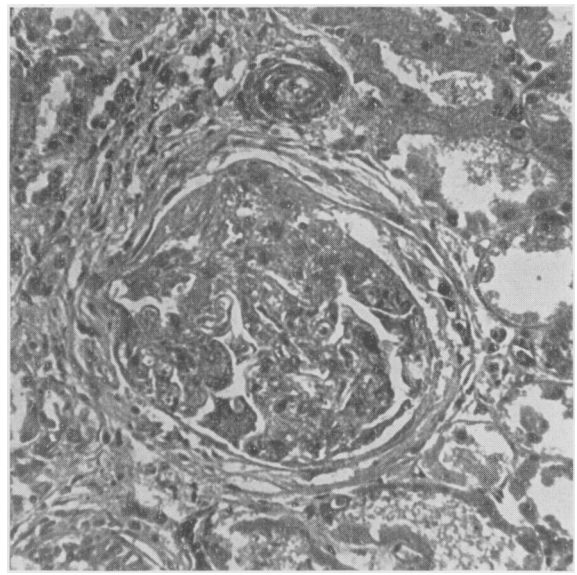

Plate 1—Kidney

Necrosis of afferent arteriole and glomerulus. Note early crescent formation.

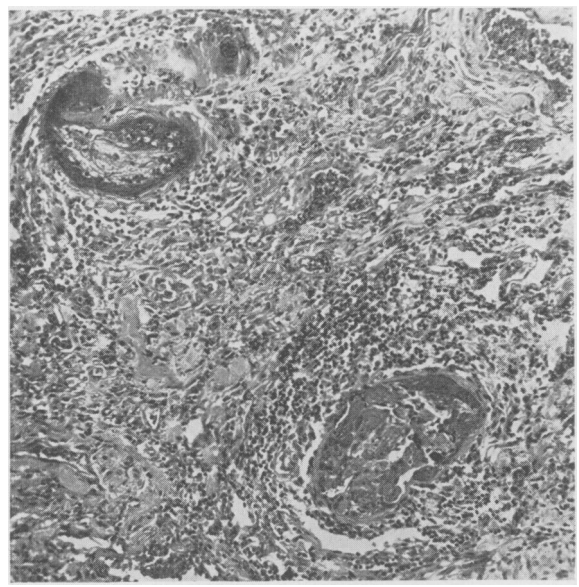

Plate 2—Jejunum

Two arterioles in the submucosa showing fibrinoid necrosis and thrombosis.

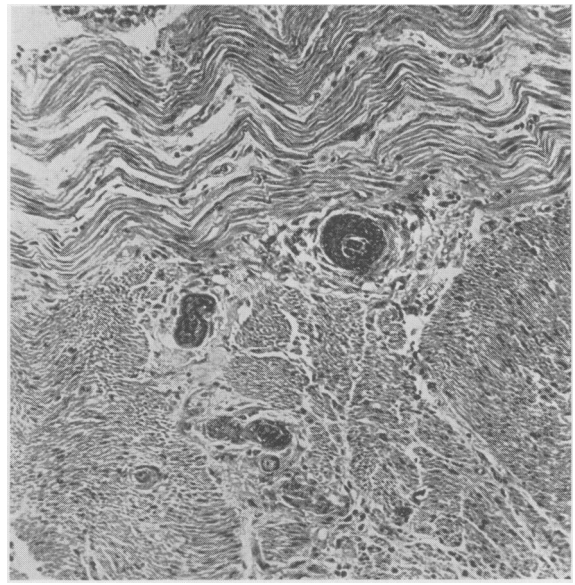

Plate 3—Jejunum
Several arterioles in the muscle coat showing fibrinoid necrosis.

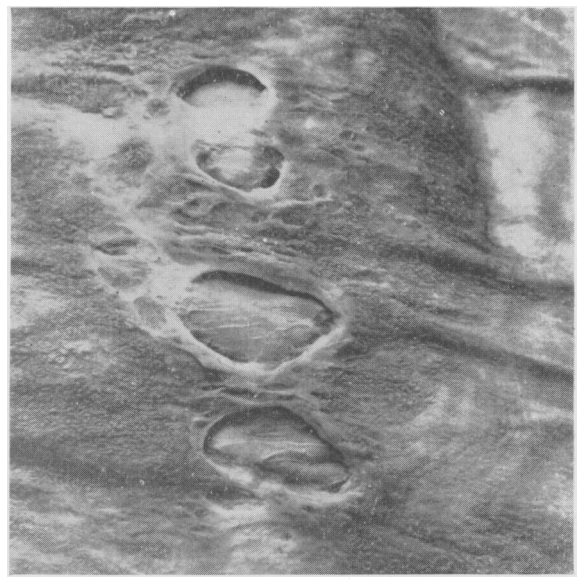

Plate 4—Ileum
Showing mucosal ulceration.

THE WEDNESDAY LABORATORY MEETINGS

THE fortnightly meetings held in the Institute of Pathology during the past twenty years have been attended not only by members of the honorary staffs of all the hospitals, by pathologists, bacteriologists, and resident medical officers, but by many visitors from Great Britain and overseas. With Sir Thomas Houston, the doyen of Ulster laboratory workers, as "compere," and Professor J. H. Biggart as "producer," these meetings provide a rich and varied programme.

The case-histories are presented, some succinctly and some with a wealth of detail which can become an *embarras de richesse,* by members of staff or their deputies. Most of these stories are of diagnostic effort followed by therapeutic defeat, except when a surgeon can present a trophy safely won. Then the fierce light of the magic lantern throws truth upon the screen and there is epexegesis by the pathologist concerned. The discussion that follows, if often spirited, is always friendly, and Professor Biggart sums up with a judicial air and an inexhaustible bibliography which nobody ever seems to be able to contradict.

The thousands of lantern slides illustrative of pathological phenomena reflect credit not only on the pathologists themselves, but on the skill of the technical staff, of whom Mr. R. M. Stephen with forty-four years of service, and Mr. Mehaffey, our indefatigable photographer, are worthy of special mention.

In order that those interested can refer to cases already reported, a list will be published in this Journal at the end of each session. Appended is the list since October, 1946.

CLINICAL PATHOLOGICAL MEETINGS

During the past winter these meetings have been held fortnightly and the following is a list of the cases discussed :—

9th October, 1946 :

Lymphosarcoma of Stomach (A.5160).—Dr. Marshall.

Amœbic Dysentery (A.5089).—Dr. Marshall.

Calculus Pyelonephritis (A.5210).—Mr. McMechan.

23rd October, 1946 :

Neuroblastoma (A.5261).—Dr. Allen.

Lipoid Pneumonia (A.5228).—Dr. M. Frazer.

Libman Sach's Disease (A.5211).—Dr. Allen.

Inversion of Uterus (487/46).—Professor Macafee.

Giant Cell Tumour of Knee (480/46).—Mr. R. J. Withers.

6th November, 1946 :

Multiple Stenosis of Small Intestine (M.1795).—Mr. Loughridge.

Pathological Fracture in Osteomylitis.—Professor Crymble.

Polyarteritis Nodosa (A.5214).—Dr. Campbell.

Tuberculous Dactylitis (1152/46).—Professor Thomson.

20th November, 1946 :

Carotid Body Tumour (1307/46).—Mr. Bingham.

Purpura (A.5288).—Dr. McElderry.

Testicular Tumour (A.5240).—Dr. Blair.

Carcinoma of Thyroid (A.5135).—Mr. McFadden.

22nd January, 1947 :

Mitral Stenosis (A.5425).—Dr. Campbell.

Eclampsia (A.5322).—Jubilee Hospital.

Fibrocystic Disease of Pancreas (A.5290).—Dr. Parkes.

Reticulum Cell Sarcoma (A.5327).—Dr. Pantridge.

Squamous Carcinoma of Kidney (1146/46).—Dr. Barber.

Brain Abscess.—Mr. K. Hunter.

5th February, 1947 :

Parotid Tumour.—Mr. Loughridge.

Erythroblastosis Foetalis (A.5446).—Dr. F. McKeown.

Bronchiectasis (A.5368).—Dr. Allen.

Tuberculous Meningitis (A.5341).—Dr. G. Adams.

Elephantiasis of Leg.—Mr. Fraser.

19th February, 1947 :

Elliptosis.—Dr. C. Murdock.

Addison's Disease.—Dr. Pyper and Dr. R. A. Neely.

Tuberculous Pericarditis (A.5474).—Dr. Allen and Dr. J. M. Beare.

Meningitis Following Fracture of Skull.—Dr. F. Kane and Dr. M. G. Nelson.

Tumour of Tibia (42/47).—Professor Biggart.

5th March, 1947 :

Myeloid Leukæmia (A.5548).—Dr. Crozier.

Complications of Fractured Pelvis.—Professor Crymble.

Multiple Tumours of the Bone Marrow (A.5519).—Dr. Milliken.

Bronchiectasis (A.5511).—Dr. Neely.

Foreign Body in Lung (A.5075).—Professor Biggart.

Parathyroid Adenoma (C.8968).—Dr. Magill.

Renal Tuberculosis (A.5473).—Professor Biggart.

16th April, 1947 :

Intestinal Ulceration (A.5567).—Dr. Beare.

Chromophobe Adenoma (A.5579).—Dr. McKeown.

Head Injury (A.5616).—Mr. Calvert.

Renal Tuberculosis.—Mr. Woodside.

Diabetes Insipidus (A.5617).—Mr. Calvert (Dr. Blair).

30th April, 1947 :

Lymphangioma of Mediastinum (327/47).—Mr. Purce.

Syphilitic Aneurysms (A.5528).—Dr. Crozier.

Amloidosis Complicating Bronchiectasis (A.5489, A.5644).—Dr. McGeown.

Rheumatic Carditis with Extensive Coronary Involvement (A.5650). Dr. McSorley.

Subdural Hæmatoma (A.5393).—Dr. Allison.

14th May, 1947 :

Enterococcal Phage.—Sir T. Houston.

Cystic Disease of Testes (A.5427).—Mr. Loughridge.

Jejunal Ulceration (A.5691).—Dr. McKeown.

Hyperelastosis of Endocardium (A.5696).—Dr. Kirk.

Meningeal Spread of Glioma (A.5670).—Mr. Calvert.

REVIEW

THE PRACTICE OF MENTAL NURSING. By May Houliston, R.G.N., R.M.N., R.F.N. Foreword by P. K. M'Cowan, J.P., M.D., F.R.C.P., D.P.M. 1947. E. & S. Livingstone Ltd. Pp. 158. 7s. 6d.

THIS book is written by the senior sister-tutor, Crichton Royal Mental Hospital, Dumfries, as a result of her valuable experience in starting the first preliminary training school in a mental hospital. It is intended to give the junior student nurse a simple introduction to the study of psychology and psychiatry, and to the work to be carried out later in the wards. It is written in a pleasant style, and includes sections on occupational and recreational therapy, and psychotherapy, and a description of the duties of the psychiatric social worker in the mental hospital. This should provide interesting and profitable reading for all nurses. D. M. G.

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REVIEWS

RHEUMATISM

It is natural that a disease of the social and economic importance of rheumatism should occupy a considerable place in medical literature. Nevertheless, until the last few years, little of importance has been added to our knowledge of this crippling group of diseases. Significant advances in treatment, a closer study of the composition of synovial fluid and of the factors which influence the permeability of synovial membranes, offer at last a measure of hope to many sufferers. It is therefore with particular pleasure we welcome Dr. Ernest Fletcher's new book—"Medical Disorders of the Locomotor System."

It is to be hoped that the rather cumbersome title will not deter the general physician and the general practitioner from reading this admirable book. Except for interesting chapters on sciatica and brachial neuralgia it is not concerned with neurology, and the cerebro-spinal system is left severely alone. It is one of the most readable works in medical literature and is indeed a credit to British medicine.

The author wisely decided not to tie himself to any rigid classification and takes as a general definition of rheumatic disorders: "painful locomotor disorders of unknown ætiology." The clinical examination of the rheumatic patient is given in great detail and is illustrated with many photographs.

The section on rheumatoid arthritis is of outstanding importance and never has there been such a complete study of the treatment of this disease. Dr. Fletcher is perfectly frank in stating that his experience of a particular method is limited or that he has not succeeded in alleviating symptoms by another. Treatment by injections into joints is described in detail, including the recent work by Waugh on Lactic Acid injections.

Contributions on special subjects are by well-known authorities. For example, there is an excellent chapter on Fibrositis by W. S. C. Copeman, and Medical Diseases of Bone are in the capable hands of Donald Hunter.

The illustrations, paper, and binding show little signs of the age of austerity in which we live and we welcome a work of great medical value. T. A. K.

MEDICAL DISORDERS OF THE LOCOMOTOR SYSTEM, INCLUDING THE RHEUMATIC DISEASES. By Ernest Fletcher, M.A., M.D.(Cantab.), M.R.C.P. Edinburgh: E. & S. Livingstone Ltd. 45s.

ON THE CONTRIBUTION OF CLINICAL STUDY TO THE PHYSIOLOGY OF THE CEREBRAL MOTOR CORTEX: The Victor Horsley Memorial Lecture, 1946. By F. M. R. Walshe, O.B.E., M.D., D.Sc., F.R.C.P., F.R.S. Edinburgh: E. & S. Livingstone Ltd. Pp. 29. 1s. 6d.

In this memorial lecture Dr. Walshe pays eloquent tribute to his old friend and teacher, whose "name and fame are part of the imperishable tradition of medicine." He reviews in that clear and challenging manner which is all his own, the evidence which has accumulated to discard the

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Treatment is up to date, the method of administration and the collection of specimens is given in adequate detail.

It is good value at the price, five shillings. H. E. H.

ADVICE TO THE EXPECTANT MOTHER ON THE CARE OF HER HEALTH AND THAT OF HER CHILD. By Professor F. J. Browne, M.D., D.Sc., F.R.C.S. Edin., F.R.C.O.G. Eighth edition. Edinburgh: E. & S. Livingstone Ltd. Pp. 48. 9d.

This little brochure requires no commendation in this Journal, for several reasons: the author is almost as well-known in the Belfast Medical School as he is in University College, and has recently accepted the Honorary Fellowship of our Society; and his "Advice," now in its eighth edition, has become almost a "classic." He has had the collaboration of Mrs. Helen Heardman, who advocates the education of the patient to relax in the manner taught by Dr. Grantly Dick Read. The professor's sense of humour shows itself in his prescription of the works of Sir Walter Scott as a cure for insomnia.

TEXTBOOK OF MEDICINE. By various authors; edited by Sir John Conybeare, K.B.E., M.C., D.M.Oxon., F.R.C.P. Eighth edition. Pp. 1,170; illustrated Edinburgh: E. & S. Livingstone Ltd., 1946. 30s.

This well-known textbook of medicine needs no introduction to readers of the Ulster Medical Journal. Its popularity both with students and practitioners is amply proved by a comparatively short space of time which elapses before a new edition is required. This is the fourth since the outbreak of war. Sir John Conybeare and his sixteen distinguished collaborators can be congratulated on their success in bringing this eighth edition up to date in many particulars. The section on chemo-therapeutic substances in general and penicillin therapy in particular, has been expanded There is a new appendix on the various problems of aviation medicine. The tables of 'physiological normals' on the inside of the front cover are compact and useful for quick reference. One might quibble at the sparsity of information on several controversial and important subjects, but in general the textbook fulfils its function admirably. One wishes that fuller information had been given on such subjects as the absolute values and indices in hæmatology, oligæmic shock, and

punctate or "cortical mosaic" theory of the localization of movements by the unit representation of individual muscles, and stresses the importance, alike to physiologists and clinicians, of a wider appreciation of the importance of the hypothesis of multiple and overlapping representations of movements rather than muscles. In this admirable essay the author shows himself to share with Hughlings Jackson, whom he so greatly reveres, "a vehement and passionate interest in the relation of general principles to irreducible and stubborn facts."

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