pelvic operations is by no means uncommon, but it is an extremely rare event for pulmonary embolism to happen in this form of thrombosis. The oedema of the leg associated with this common form of thrombosis is usually attributed to obstruction of the iliac and femoral veins by internal clot, but there is in addition infection of the lymphatics, and this causes a hard painful swelling of the thigh in consequence of interference with the lymphatic circulation. Surgeons know well that during operations in the armpit the axillary vein is occasionally cut. This accident is easily repaired by the application of a ligature to the vein above and below the opening. No oedema of the limb follows. When the axillary lymphatics are blocked by perilymphangitis due to an extension of mammary cancer, a solid oedema of the limb ensues. This is true of the lower limb. The femoral vein is sometimes wounded accidentally by the surgeon in the course of an operation, but it is safely controlled by an encircling ligature placed above and below the hole in the wall of the vein. No oedema follows, nor is the circulation in the limb impaired.

Reservoirs of Clot.

It often happens that a *post-mortem* examination is made on a patient who has died in consequence of a pulmonary embolism, and the source of the embolus cannot be found. In considering embolism of the pulmonary artery in relation to hysterectomy it is necessary to point out that the pelvis contains two potential reservoirs of blood clot—the iliac veins and the ovarian veins. Experience, however, teaches that the external iliac veins are the common source of the fatal clot.

An embolus large enough to fatally plug the pulmonary artery comes, as a rule, from large vessels like the iliac veins, the caval veins, or the right auricle. Virchow pointed out that it is not uncommon for an entire thrombus to slip out of a vein, and an elongated thrombus from a venule may appear to be too thin to obstruct a large vessel, but, when such an elongated thrombus reaches its destiny, it is doubled up by the blood stream and serves as an effective plug. An embolus too small to occlude the pulmonary artery may lodge on the ridge separating the right from the left branch, becoming what is called a riding thrombus; such a clot may act as an autochthonous thrombus, and induce the formation of additional clot such as will fill and fatally occlude the main trunk and both branches of the pulmonary artery, as well as many of its subdivisions in the lungs.

Pulmonary embolism may occur as a sequel to hysterectomy at any time from the hour of the operation onward to the thirtieth day. In the majority of instances it happens about the twelfth day, and many observers have noticed that the detachment and transit of the clot is usually preceded by movement, such as getting out of bed for the first time after the operation, even sitting up in bed, but more particularly in straining during defaecation; sometimes it is deferred until the patient is apparently well, and when about to leave the hospital she may fall dying across the bed, on the floor of the ward, or in the courtyard of the hospital. The periodical literature of surgery and gynaecology contains many instances of these dramatic forms of sudden death due to post-operative pulmonary embolism.

The Bacteriology of the Clot.

The bacteriology of the clot is an interesting matter in relation to thrombosis and embolism. In the opening remarks it was mentioned that the common organisms found in infected uteri are streptococcus, staphylococcus, gonococcus, and the colon bacillus. The common micro-organism found in thrombi and emboli is the streptococcus; it is sometimes mixed with the staphylococcus, the *Bacillus pyocyaneus*, or the colon bacillus, but never the gonococcus. This is a matter of great interest. Extensive pelvic operations are often performed for damage caused to the uterus and the Fallopian tubes by the gonococcus, sometimes in the acute, but more often in the chronic stage of the disease. I have never had a case of pulmonary embolism as a sequel of an operation on the uterus or tubes when the lesion was the consequence of a gonorrhoeal infection. This seems to show that the gonococcus causes great irritation of tissues, and produces masses of adhesions,

but does not coagulate blood. The facility with which the streptococcus causes blood to coagulate in the living vessels is well known, and the extreme frequency with which thrombosis and its sequel, embolism, occur in connexion with cancer of the uterus is explained by the partiality which streptococci manifest for exposed cancerous tissue.

M. B. Schmidt found that when cancer particles enter the blood streams by invading lymphatics and veins they excite thrombosis, and the thrombus contracts upon and may ultimately destroy them. This prophylactic power of the blood prevents colonization of the blood stream, but I hold the opinion strongly that the thrombosis around the cancer particles is incited by the micro-organisms or their toxins which these cancer fragments contain.

It is undeniable that death from pulmonary embolism is especially frequent after abdominal hysterectomy performed for cancer of the uterus; it is far more frequent than after the removal of the uterus for fibroids, and the evidence indicates that the greater frequency of this catastrophe in operations for cancer of the uterus depends on the greater luxuriance of the flora in cancerous tissue, and that the streptococcus, of all the forms of micro-organisms which abound in such uteri, holds the greatest "enmity with blood of man."

In order to improve the results of abdominal hysterectomy performed for fibroids, surgeons must be more careful and more moderate in the use of buried sutures when closing the abdominal incision.

The risks of operations for cancer of the neck of the uterus will be lessened when surgeons, with the aid of bacteriologists, devise means to rid cancerous tissues of noxious organisms before undertaking hysterectomy. The widespread tilling of the pelvic connective tissue inseparable from the operation ironically called radical abdominal hysterectomy favours the sowing, growth, and rapid multiplication of streptococci, with the result that in many instances Death becomes the reaper.

It must be obvious to all thoughtful men that the surgeon in the operating room, as well as in the clinical ward, must look to the bacteriological laboratory for guidance, in the same way that the navigating officer on the bridge directs the ship, under the tutelage of the astronomical observatory, across the trackless ocean.

REMARKS ON ATYPICAL EXOPHTHALMIC GOÏTRE.*

By H. L. McKISACK, M.D., M.R.C.P.LOND.,
PHYSICIAN TO THE ROYAL VICTORIA HOSPITAL, BELFAST.

THE recognition of a well-established case of Graves's disease is one of the easiest tasks of a medical practitioner. The classical signs, with which we are all familiar, leave no room for doubt as to its nature. The chief of these are: Rapidity of heart beat, protrusion of the eyeballs, enlargement of the thyroid gland, tremor, sweating, flushing, sleeplessness, and other evidences of nervous excitement.

Functions of the Thyroid Gland.

It has been established both by clinical and experimental evidence that the thyroid secretion is necessary for the proper development of the bony structures and their maintenance, and also for the due development of mental power, for the growth and maintenance of fatty tissue, skin, hair, and nails. The sexual functions are stimulated by thyroid secretion. In myxoedema, where the secretion is deficient, amenorrhoea is the rule, while excessive menstruation is usual in the contrary condition of exophthalmic goitre. In pregnancy also the symptoms of Graves's disease, if previously present, become accentuated. A notable result of excessive thyroid action is stimulation of the sympathetic system, and it is from this action that many of the classical symptoms arise, and in particular irritability of the vasomotor system. This was well exemplified in cases No. 7 and 15, where a patch of hyperaemia, lasting for a considerable time, resulted from the slightest stimulation of the skin. In a lesser degree it was noticed in

* Delivered at a meeting of the Ulster Branch of the British Medical Association.

several of the other cases. Another effect of excessive thyroid secretion is diarrhoea. The thyroid gland exerts an inhibiting influence on the pancreas; hence diabetes, the result of pancreatic inefficiency, is a not uncommon consequence of exophthalmic goitre. Thyroid secretion increases the activity of nitrogenous metabolism and opposes the accumulation of fat, with the result that emaciation is usual in well-marked exophthalmic goitre, and may also be seen in many of the imperfectly developed cases. The thyroid gland is unique in containing a noteworthy amount of iodine, and it is found that the administration of iodine or its salts increases the activity of the gland, and may in susceptible subjects even produce some of the symptoms of exophthalmic goitre.

Etiology and Symptoms of Exophthalmic Goitre.

It is the difficulty in accounting for the alteration in the quantity or quality of the thyroid secretion that gives rise to the differences of opinion as to the cause of exophthalmic goitre. The simplest way to increase the quantity of the internal secretion in the blood is to administer the extract of the gland by the mouth. By this means the symptoms of excessive thyroid action, or "hyperthyroidism," may readily be produced. Inflammatory or degenerative changes of the thyroid gland may cause it to enlarge, sometimes with excess of function, more frequently the reverse. Emotions, particularly fear, are credited with being a cause of exophthalmic goitre. In this connexion it is noteworthy that the symptoms closely resemble a state of terror. Here the excessive activity of the gland may be produced by direct stimulation. It has been shown by Crile that the more powerful emotions have a definite influence on the functions of the body, either by stimulation or by inhibition of various glands. Breuer suggests that the emotion of fear producing vasomotor changes causes the gland to empty itself quickly into the circulation with subsequent compensatory activity, and perhaps hypertrophy. In another group of cases the thyroid is unequal to the task of supplying the amount of internal secretion required by the organism, and in order to overcome this deficiency the gland becomes hypertrophied with, in many cases, hyperthyroidism. It is in this class of case that the administration of thyroid extract by the mouth has been advised, on the assumption that the assistance of the swallowed extract would do away with the necessity for compensatory hypertrophy of the gland. (See case No. 9.)

Cases of exophthalmic goitre in which the majority of the classical signs are absent are apt to be overlooked, and I have no doubt we miss many that should be identified. In hospital practice I have not succeeded in observing more than a few of this class of case, but that, perhaps, is to some extent explained by the fact that such imperfectly developed cases are not usually sufficiently ill to be admitted to the wards of a hospital; no doubt, also, many have escaped my attention. In private practice we are more likely to come across such cases, and my experience only extends to twenty-one instances, to which I wish briefly to direct your attention. I have, of course, excluded the more common fully developed cases of Graves's disease.

The cases are too few to permit any reliable generalizations to be founded on them; but it will be observed that in all the heart-rate was above normal, and in practically all the patient was aware of the rapid beating, either in the form of general throbbing of the arteries or as palpitation of the heart. This is the symptom which should always arouse suspicion, and when combined with tremor and with even a slight protrusion of the eyeballs it may be accepted as an evidence of hyperthyroidism. This last-named sign was, however, absent in 15 of my 21 cases. Careful examination will generally reveal an increase in the size of the thyroid—sometimes only to a very slight degree. In 3 cases it was normal, in 5 it was of moderate size, in 2 considerable enlargement existed, and in 11 there was slight enlargement. Tremor was absent in 9 of the cases. Twelve of the cases were between the ages of puberty and 30, and the remainder were between 30 and 60. All but three were females, and one of the three men, while incomplete in the development of signs when first seen, soon progressed rapidly in an unfavourable course, and became a typical case in a very short time. Two of

No.	Sex.	Age.	Residence and Medical Attendant.	When First Seen.	Pulse-rate.	Exophthalmos.	Tremor.	Thyroid Gland.
1	F.	39	Belfast	4/3/02	140	0	0	+a
2	F.	21	Co. Down	11/10/05	110	0	a	+a
3	F.	26	Co. Antrim (Dr. Reid)	11/5/06	120	0	0	+a
4	F.	34	Somerset	4/6/06	110	0	a	N.
5	F.	54	Co. Down (Dr. Knight)	26/8/07	120	0	b	+b
6	F.	60	Co. Armagh (Dr. Donnan)	10/12/07	120	0		+c
7	F.	22	Co. Cork	1/6/09	116	?	a	+a
8	F.	25	Belfast	3/6/09	110	0	0	N.
9	F.	13	Belfast	10/6/09	110	0	0	+a
10	F.	47	Co. Down (Dr. Knight)	8/9/09	125	a	a	+b
11	M.	36	Co. Down (Dr. Knight)	2/2/10	115-130	a	a	+a
12	M.	24	Belfast	25/5/10	Fast	0	a	+a
13	M.	23	Co. Down	3/10/10	116	a	0	N.
14	F.	28	Belfast (Dr. M. Henry)	28/1/11	130	?	a	?
15	F.	32	Co. Antrim	6/2/11	126	0	0	+b
16	F.	24	Co. Monaghan	8/2/11	98	a	a	+a
17	F.	45	Co. Down	29/3/11	120	0	0	+b
18	F.	25	Co. Antrim	7/11/11	72-100	0	0	+b
19	F.	24	Co. Sligo (Drs. Quin and Craig)	18/12/11	130	*b	a	+a
20	F.	18	Co. Antrim (Dr. MacWilliam)	17/5/12	98	0	0	+c
21	F.	34	Co. Tyrone (Dr. Condy)	28/8/12	120	?	a	+a?
22	F.	44	Co. Down	18/10/12	115	0	a	N.
23	F.	50	Co. Down	18/10/12	120	0	a	N.

NOTE.—N=Normal. 0=Nil. a=Very slight. b=Moderate. c=Considerable. +=Enlargement. ?=Doubtful. *=One eye.

the cases, as already mentioned, showed marked vasomotor excitability.

Case 9 was an example of hyperthyroidism in a developing female at the age of puberty. The thyroid gland was slightly enlarged, and headaches, palpitation, flushing, and nervousness were present. These symptoms and the enlargement of the thyroid had only very recently attracted attention, and it seemed probable that the gland had become hypertrophied at puberty in the endeavour to meet the new demands upon its secretion caused by sexual development. Small doses of thyroid extract were therefore administered by the mouth, so as to assist the gland in its work, with the result that the hypertrophy disappeared and the patient got quite well after one or two relapses.

One of the most erratic of the cases is No. 18, in which there is apparently an alternating condition of hypo- and hyperthyroidism. The prevailing symptoms are perhaps those of deficient rather than excessive thyroid secretion. She is inclined to grow stout, is somewhat phlegmatic in manner and character, sleeps well at night and is often drowsy during the day; her hair falls out freely on brushing it, and her thyroid gland is distinctly enlarged—indications of a mild degree of myxoedema. She first came for medical advice on account of a hard, harsh cough, caused probably by the mechanical irritation and pressure of the gland. Her pulse ordinarily is about 70. After a short course of small doses of thyroid extract, the contrary condition of hyperthyroidism appeared, and when the extract was stopped the tachycardia, palpitation, flushing, etc., continued for a considerable time. There still remains a mixture of symptoms indicating an inefficient thyroid, while her functions are very sensitive to the help obtained by the thyroid extract given by the mouth.

Case 19 was of interest owing to the fact that only one eye projected; the other symptoms of exophthalmic goitre were typical. The patient's sister, however, told me that six months previously both eyes were equally projecting in about the same degree as the one eye then was.

The last two cases are inserted in order to draw attention to a large group of cases, many of which are probably examples of hyperthyroidism. These are generally, and

no doubt correctly, described as functional disturbance due to the menopause. It must be remembered that many cases of true exophthalmic goitre begin about this time of life. We know also how intimate is the relation between the sexual functions and the thyroid gland. It therefore seems probable that the ordinary menopause symptoms, which so closely resemble those of hyperthyroidism, are largely the result of temporary hyperthyroidism.

Treatment.

As regards the treatment of these atypical cases, it differs in no material respect from that of the fully developed disease. I do not propose to occupy your time with this aspect of the subject, but I should like to ask the members to give a trial to the x-ray treatment. This procedure seems to offer a fair prospect of reducing the activity of the gland, without having to subject the patient to the risk of an operation for the purpose of removing a portion of the gland or ligaturing some of its vessels.

Finally, I would suggest that the name "exophthalmic goitre" be as far as possible discarded, and that the condition be spoken and thought of as "hyperthyroidism." This term would include all degrees of the abnormal condition, while the more usual description, "exophthalmic goitre," merely suggests two of the chief, but by no means the most constant, symptoms.

THE PORTALS OF ENTRY OF THE TUBERCLE BACILLUS, ESPECIALLY IN CHILDHOOD.*

BY

E. EMRYS-ROBERTS, M.D.,

PROFESSOR OF PATHOLOGY AND BACTERIOLOGY, UNIVERSITY COLLEGE OF SOUTH WALES AND MONMOUTHSHIRE, CARDIFF.

AN enormous amount of work has been undertaken during recent years with regard to the tubercle bacillus, but certain landmarks stand out prominently. These are, first, the differences which distinguish the human from the bovine variety of the tubercle bacillus, and, secondly, the extended use of von Pirquet's reaction.

There exist portals of entry of the tubercle bacillus that have long been recognized. For example, no one denies the transmission into the lungs of tubercle bacilli suspended in air in minute particles of moisture or in dust. Recent experimental evidence has amply demonstrated this very important avenue of infection, and has incidentally shown that the number of bacilli required, all things being equal, to set up pulmonary tuberculosis is relatively small as compared with the number necessary to induce tuberculosis elsewhere—as, for example, into the intestinal tract (1, 2).† No one questions transmission through the intestinal tract, especially in infancy, and here, again, experimental evidence shows that not only may the bacillus induce a lesion in the gut, but may enter the intestinal wall without producing a lesion at the seat of entry (3, 4, 5, 6). No one, again, questions transmission through the naso-pharynx; there is ample evidence, both clinical and experimental. Transmission can occur also through the skin, as was demonstrated in the case of a former colleague of mine, who contracted, presumably in the *post-mortem* room, a tuberculous lesion on his hand (see also 7). Experimentally, transmission through the unbroken skin has been demonstrated (8). Lastly, we reach the antenatal avenue of entry. Omitting for the present this last portal of entry, we may say, with Calmette (9), that "the more frequent channels of invasion are the mucous membranes of the natural cavities of the body, particularly the digestive and pulmonary epithelium, and to these may be added the naso-pharynx." Whether we can go further with him and say, "Of these the digestive path is the one most commonly chosen," is open to question.

Few observations have been so startling, or have had a more profound bearing on the problem of tuberculosis than the extended application of von Pirquet's reaction. Numerous statistics are now available, and Calmette (10), reviewing them, shows that, up to the age of 1 year,

9 per cent. of all children give positive results, up to the age of 2 years 22 per cent., from 2 to 5 years 53 per cent., and from 5 to 15 years 80 per cent. This reaction, which indicates tuberculous infection, has been controlled by statistics obtained from *post-mortem* records, and Binswanger (11) adduces a remarkable agreement between the two sets of figures (see also 12, 13). The reaction is carried out by the use of Koch's old tuberculin. The one forearm is scarified and a few drops of undiluted tuberculin introduced, as in vaccination, the other forearm being inoculated with normal saline in order to act as a control. The development in the course of some days of an inflammatory reaction is acknowledged to indicate the presence of tuberculous sensitiveness—that is, that the person so reacting has circulating in his blood serum certain specific antibodies to the tubercle bacillus—antibodies present owing to an infection, recent or remote, active or quiescent, by the tubercle bacillus. The reaction partakes of the character of anaphylaxis (14), inasmuch as the local inflammation is the result of poisonous products resulting from the disintegration of the introduced tuberculin, which has been acted upon by the two elements in the patient's serum, complement and antibody. There appears to be no specificity regarding the use of human and bovine tuberculin (15), and there does not appear to be any agreement between the intensity of the reaction and the extent of the tuberculous lesion (16, 17),† though the reaction tends to become feeble or absent in severe cases, probably due to the using up of antibodies and complement. It is not my purpose to discuss the subcutaneous (18) injection of tuberculin for diagnostic purposes, or to enter into the evidence so afforded of focal as well as local reaction (19), as full comparative statistics are not yet available.

Does this relative absence of von Pirquet's reaction, then, mean that infants possess a greater insusceptibility to tuberculosis, even when, as above, substantiated by *post-mortem* findings? Two points have to be taken into account in meeting this observation: First, that in children, and especially infants, antibodies are deficient (20), or, at any rate, their non-detection would seem to warrant such a statement; and, secondly, in the *post-mortem* room it is unquestionable that the disease may not be recognized macroscopically as the tubercle is often in the prefollicular stage (21, 22). I would ask especial attention to these explanations of the non-detection of tuberculous infection in infancy, as I shall refer to them later when dealing with the antenatal transmission of the infection.

The full significance of the extended application of von Pirquet's reaction has been held to justify von Behring's (23, 24) pronouncement in 1903:

The seeds of phthisis are laid in infancy through the intestinal mucosa, remaining latent until the powers of resistance happen to become impaired; the disease then becomes active. The tubercle bacilli are usually introduced in cow's milk and absorbed through the intestine.

No doubt von Behring has felt justified in his prophetic utterance by the statistics of von Pirquet (25), Hamburger (26), and a host of other observers (27, 28, 29), which would seem, at first sight, so eminently to substantiate his pronouncement.

But there exists a most important stumbling-block to the full acceptance of von Behring's theory, even though supported by the advocacy of Calmette and his school. It is the placing upon a scientific basis the grounds for distinguishing between two varieties of the tubercle bacillus, the human and the bovine (30, 31). Briefly, they consist, first, in the constant inoculation differences—that is, the rabbit succumbs to a progressive generalized tuberculosis in four to five weeks' time after inoculation with the bovine strain, but exhibits retrogressive lesions with the human strain; and, secondly, in the inconstant, but occasionally useful, cultural differences, as evinced by the comparatively easy and luxuriant growth of the human variety. The allusion in the report of the Royal Commission to peculiar quasi-intermediate forms occurring in lupus and in tuberculosis of the horse (see also 31), while they give us to pause in being too insistent on the distinctions which serve to separate the human from the bovine variety, cannot, I think, in the face of the very many unsuccessful experimental attempts to convert the one variety of bacillus into the other (32, 33, 8), completely

* A paper read before the Cardiff Medical Society.

† The figures in parentheses refer to the bibliography at end of paper.

‡ Morland (*Lancet*, 1912, ii, p. 688) suggests the contrary.