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

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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, 10). 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.

shake our belief in the separate identity of the two varieties.

In the first place, assuming these differences do exist (34), I agree with Cobbett (3) when he says that "von Behring's theory as to the causation of phthisis, so far as it relates to infection by cow's milk, cannot be accepted," on the ground that, with remarkably few exceptions, the bacillus isolated in phthisis belongs to the human variety. Calmette (10), at the International Tuberculosis Congress held last year in Rome, stated that, over the age of 16 years, 98.09 per cent. of all fatal cases of tuberculosis were due to the human tubercle bacillus (see also 35); since, over the age of 16 years, the vast majority of deaths from tuberculosis result from phthisis, it follows that the human variety accounts for practically all the cases of phthisis (36), and not the bovine variety, as von Behring's statement would imply.

In the second place, assuming the "seeds of phthisis were laid in infancy by the drinking of cow's milk," in the face of these statistics there would have to be postulated a mutation of bovine into human tubercle bacilli, and this, in our present state of knowledge, we cannot accept. Statistics culled from all sources agree in assigning to the bovine variety of the tubercle bacillus varying percentages of cases of tuberculosis under the age of 16. Calmette (10) gives 26.5 per cent. up to the age of 5 years, and from 5 to 16 years a percentage of 25. At the same time it cannot be questioned but that considerable divergences in percentages may be obtained (34). Presumably the source of infection is cow's milk, which, in its turn, is infected chiefly through tuberculosis of the udder, though the bacilli have been shown to be present in the milk of tuberculous cows in the absence of actual affection of the udder itself, either directly or indirectly, by reason of the contamination of the milk by the cow's tubercle-laden faeces (37). Incidentally, this country has a long way to go before it attains to the measure of freedom of its dairy cattle from tuberculosis such as obtains in Denmark. Chiefly through the instrumentality of Professor Bang of Copenhagen, legal statutes enact the separation of herds, by means of the tuberculin test, into two separate divisions, followed by the gradual elimination of reacting animals. The success following these measures has been remarkable, and affords an example of how the problem of infected milk is best attacked.

Surely if the intestinal mucosa is the chief portal of entry, and cow's milk the chief source of the tubercle bacillus, we would reasonably expect to find a very much higher percentage of cases due to bovine infection. As a matter of fact you will note that even under the age of 5 years (see also 36), nearly three-quarters of the cases of tuberculosis are traceable to infection from a human source.

We have travelled far since Koch (38) startled the scientific world by declaring that infection in the human was wholly, or practically so, due to the human variety of the tubercle bacillus, but I think some of us must retrace our steps from having advanced too far in the opposite direction.

The broad facts are these: that whereas bovine infection does occur in infancy and childhood to the extent of 25 per cent., the remaining 75 per cent. of the cases, and practically the whole of the cases after the age of 16 years, are due to the human bacillus.

Ritter and Vehling (39) have found that cases of tuberculosis, where the disease was recognized in childhood, or where, owing to infected relations, infection was more than probable, would appear to run a milder course, and be more amenable to sanatorium treatment, than cases where the disease was not recognized in childhood and where the relations were not infected (see also 40). In support of their contention that previous infection renders the disease less virulent they adduce evidence from Turkey to show that, in districts where the disease is almost unknown, tuberculosis, when it does occur, runs a very rapid course. While, as a corollary, they affirm that the ordinary healthy adult, in this and other countries similarly situated as regards the disease, possesses a more or less complete immunity (see also 41).

This opens up several important questions. It suggests that if immunity can be so produced (42) how much better it would be to produce it artificially, as proposed by Calmette (43), than to run the grave risks attending infection by the usual method. It suggests that persons infected with tubercle bacilli in early life are capable of dealing with fresh infections without difficulty. It suggests that bovine infection in childhood may possess an immunizing effect in later life, and that infection by tubercle bacilli in milk, provided they are not present in too great numbers, may have that desired effect. It suggests that where previous infection can be excluded, the disease runs a course very different from that run where previous infection cannot be excluded. It suggests that miliary tuberculosis, if not due to an overwhelming infection of tubercle bacilli, is due to infection on virgin soil, and that the more common cavernous tuberculosis is to be regarded as a phenomenon of a certain degree of immunity.

How are we, then, to account for the undoubted high percentage of infection—a percentage which I gave reasons for supposing to be very much higher than is generally conceded—in infants? In other words, what are the portals of entry of the human variety of the tubercle bacillus in infancy?

On the one hand, it cannot be denied that, where one or both parents are phthisical, or where the infant comes into direct contact with persons suffering from phthisis, the chances of infection, both by way of the respiratory system and the alimentary tract, are considerable, and no doubt infection does certainly occur in this manner (44). It is also reasonable to suppose that, where the infective material is abundant, where the dose, in other words, is high, the infant should develop tuberculosis of the miliary type, especially if the predisposing factors are in evidence, and the natural forces of defence weakened (45).

On the other hand, the possibility of the transmission of tubercle bacilli through the placenta must not be altogether disregarded, as would almost appear to be the case at the present time. With the exception of Baumgarten (46), who, it seems, has held the view of antenatal infection for some years, observers in general assign but very little importance to this portal of entry. Schmorl (47) goes even so far as to say that, unless the placenta is definitely diseased, infection by this channel is impossible. One of the strongest arguments used by those opposed to placental transmission is the extreme rarity of congenital tuberculosis (9, 48, 49). It is undoubtedly rare, and, when it does occur, exhibits generalized characters (49). But because congenital tuberculosis is rare, or rather because generalized tuberculosis occurring before or immediately after birth is rare, is, to my mind, no argument against the transmission, in very many instances, of the tubercle bacillus by way of the placental circulation.

In the first place, when we take into consideration the enormous proportion of our population who are definitely tuberculized, well over 90 per cent. (43), and whose systems are constantly being infected with the tubercle bacillus; when we realize that pregnancy, with its stress and debilitating effects, renders the organism less ready to cope with and destroy the infections as they occur (33), we will not be surprised if, in the circulating blood of the mother (50, 51, 13), there may exist tubercle bacilli in far greater numbers than are to be found under normal conditions.

In the second place, when we understand that it has been shown that the normal mucous membrane of the intestine may constitute a portal of entry of the tubercle bacillus and leave no sign by which one can recognize its penetration (see also 52), it is difficult for us to believe that the cells of the chorionic villi, though they be endowed with properties not yet thoroughly understood (53), can prevent the passage of such an extremely resistant body as the tubercle bacillus into the fetal circulation.

Lastly, when we surmise that the bacilli thus introduced into the fetus may, after all, be relatively few in number; that the lesions they produce may be prefollicular and eventually retrogressive; that, as we have before noted, von Pirquet's reaction may yet be absent, it will be very difficult for us to deny the possibility, or even the strong probability, that such manner of infection does occur, that antenatal infection constitutes a portal of entry of the tubercle bacillus.

To sum up, then: the portals of entry of the tubercle bacillus, especially in childhood, include the respiratory system, the alimentary tract, the mucous membrane of the naso-pharynx, the skin, and, lastly, the placenta.

The significance of these many portals is evidenced in the practical tuberculization of the community (48), and is of interest in the detection of the source of infection, both human and bovine.

The questions that yet remain to be solved concern the latency of the infection contracted in childhood. Where do the bacilli live? Do they live in the tuberculous glands and old lesions so frequently found *post mortem*? Do they there remain quiescent for indefinite periods, capable, when the time comes, of setting up disease, as exemplified in the recent attention drawn to pulmonary tuberculosis resulting from extension from tuberculous bronchial glands (54, 55)? If so, how are we to account for the negative results obtained by Cobbett (3) after inoculating animals with the tuberculous tissues? Do the bacilli live in the blood and tissues generally (50, 51, 13), having established a *modus vivendi*, wherein they are tolerated but not allowed to multiply to any extent? This may be so, and thus the vast majority of the people in this country are in reality tubercle carriers, awaiting some impairment of the powers of resistance—to quote von Behring—in order to become obvious sufferers from tuberculosis.

Much might be said regarding the view that the first infection in childhood, by conferring a partial immunity, determines that, in the largest proportion of cases in adult life when tuberculosis does supervene, the disease shall run its most chronic form with cavity formation in the lungs (55, 56), and not the acute miliary form.

From what has been already brought forward it will be seen that, although the problems that tuberculosis still offers for solution are of far-reaching consequence, still the recognition of the portals of entry and the source of the infection places us in a stronger position than formerly, and enables us to say, in the words of the resolution adopted at last year's International Congress, "Prophylaxis of tuberculosis must principally be directed towards the suppression of contamination from man to man, and principally in the family, and, whilst contamination of man by bovine infection is of less frequency, it is, nevertheless, necessary to maintain all measures against infection from this source."

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THE VARIETIES OF TUBERCULIN IN THE TREATMENT OF TUBERCULOSIS.

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IN the paper which I published in the BRITISH MEDICAL JOURNAL in 1903 I ventured to suggest that a considerable amount of tuberculosis in children was caused by the bovine tubercle bacillus. Since that time a great amount of scientific investigation has been carried out over the whole world, and especially by our own Royal Commission, with the result that we are now certain of the following conclusions:

1. That the great mass of tuberculosis occurring in the human subject in the form of pulmonary tuberculosis is caused by the human bacillus (*Typus humanus*), and is conveyed from person to person by infection.
2. That a considerable amount of so-called surgical tuberculosis in children and adults is caused by the bovine bacillus (*Typus bovinus*), received into the alimentary canal through milk and food.

Originally of a common species, the bacilli have, owing to long environment in different hosts, assumed marked characteristics, so that we are able, experimentally, to divide them into two types:

1. *Bacilli of the Typus humanus*, which cause:
   - (*a*) Pulmonary tuberculosis and pleurisy.
   - (*b*) Secondary tuberculous enteritis.
   - (*c*) Tuberculous laryngitis.
   - (*d*) Fistula in ano and possibly some other lesions.
2. *Bacilli of the Typus bovinus*, which cause:
   - (*a*) Primary abdominal tuberculosis.
   - (*b*) Tuberculous lymph glands.
   - (*c*) Bones and joints (probably).
   - (*d*) Genito-urinary tuberculosis.
   - (*e*) Acute miliary tuberculosis.
   - (*f*) Lupus. Meningitis.
   - (*g*) Pulmonary tuberculosis (a small percentage).

I have for the last ten years separated my wards in hospital into human and bovine wards, and after an observation of over 6,000 cases of tuberculosis, I am impressed with the fact that it is rare to see lesions of the human and bovine type associated in the same patient. In fact they seem to be antagonistic to each other, so that one rarely observes a patient suffering from pulmonary tuberculosis develop any other lesions beyond those mentioned in the human group. It is also rare for cases of gland or bone tuberculosis to develop true pulmonary tuberculosis except in the course of a general systemic infection.

It is necessary to mention this clinical fact to explain my reason for using tuberculins of the opposite strain in the treatment of the disease. There seems to be little doubt that a mild infection by bovine bacilli in the human body, such as neck glands, by way of the alimentary canal, will protect against an infection by human bacilli, and it is most probable that a large number of people are immunized against pulmonary tuberculosis in after-life by having been infected in early childhood by bovine bacilli through milk or food. In all the experimental work throughout the world it has been found to be a rare occurrence to find both types of bacilli in the same body.

Variations in Virulence.

Whether or not a patient is going to be destroyed by tuberculosis seems to me to depend on two important factors: (1) Virulence of infection; (2) individual resistance.

The variability in virulence of the tubercle bacillus is