exactly, and, in the light of modern experience, most of us will hesitate to draw the line sharply between tuberculous infection of a degree consistent with health and tuberculous infection just severe enough to constitute disease. But, of all the tuberculin tests, the subcutaneous method of Koch remains the most valuable in diagnosis. It depends upon general and focal reactions which are, in themselves, evidence of active disease, and, when elicited by tuberculin, may be accepted as diagnostic of clinically active tuberculosis. The only thing against it is its risk, and, in my opinion, there is no excuse for taking any avoidable risk in the attempt to establish a diagnosis.

I have indicated one kind of case in which Koch's original test may be applied with safety, and there are doubtless fairly numerous cases in which the subcutaneous test may be used without ill results by experienced physicians. Apart from these, it appears to me that the Mantoux test, applied with due skill and interpreted with discretion, is calculated to give valuable information, whether positive or negative, in the earlier years of life, and that, apart from the diagnosis of clinically active tuberculosis, this test is invaluable as a means for determining the distribution of infection in communities in which epidemiological investigations are contemplated. On the whole, for purposes of diagnosis in man, the tuberculin test, in all its varieties, is definitely inferior to the combined radiological, physical, and laboratory examinations which have come to be the routine methods.

THE POSITION TO-DAY OF TUBERCULIN IN TREATMENT*

BY

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The introduction of tuberculin was one of the great tragedies of medical research. Premature in its birth, damaged by the excessive zeal of its earliest exponents, or foster-parents—for Koch himself was cautious in his original claims—it has received the fate of the cripple, at times excessive care, at others neglect. Forty-two years have elapsed since its first introduction, and it remains a baffling and elusive enigma, in spite of an almost incredible amount of investigation, scientific and otherwise. To-day some authorities claim that it is not specific in its effects, and that it should be entirely discarded in treatment. On the other hand, there are enthusiasts who claim a specific and curative action for it and recommend its use widely, while there are others who have used it continuously for many years and are convinced that it has a definite though limited value. The time would therefore seem ripe for a critical and practical review of its effects in treatment. If this discussion could serve to clarify the position, especially to determine which of the three attitudes I have just mentioned is the correct one, then a notable success will have been achieved.

I should like to put forward the following points for discussion:

1. Is tuberculin useful in treatment?
2. If so, what are the indications and contraindications for its use?
3. What forms is it best to employ?
4. Dosage—spacing and limit of doses.
5. How should it be given?
6. How does it act?

* Read in the Section of Tuberculosis at the Centenary Meeting of the British Medical Association, London, 1932.

TUBERCULIN IN TREATMENT

It may be worth while to consider briefly certain opinions concerning tuberculin.

(a) It is generally accepted that it is completely innocuous to a healthy non-tuberculous person, even in large doses, while in those who have been infected it produces the well-known tuberculin reaction with its three effects—local, focal, and systemic—in greater or less degree, depending on the form employed and the method of administration. It has been supposed until recently that this reaction is specific, and that it is an allergic phenomenon. Both of these contentions have now been called in question, since other protein substances are said to produce a positive reaction in tuberculous patients, and the skin effects have been stated to be due to a general non-specific hypersensitiveness to toxic substances in this disease.

(b) It is significant that its routine use has been greatly restricted in many sanatoriums, and entirely discarded in others; it receives scant mention in most textbooks of medicine and in special manuals on diseases of the chest. Fishberg, in the latest edition of his well-known textbook, joins the ranks of those who advise against its use; he does so on the grounds that it is not certain that its action is specific, that it is difficult to estimate accurate dosage, especially of different preparations, and that it is altogether wanting in therapeutic effects when given in infinitesimally small doses, and may be decidedly harmful in large amounts.

(c) I have always been much impressed by the fact that, in the so-called surgical localizations of the disease—that is, in glands, bones, joints, and the ocular and genito-urinary systems—tuberculin has a considerable vogue, and that, in these conditions, it is the three well-known preparations of Koch which are chiefly employed, whereas in pulmonary tuberculosis the varieties and modifications of tuberculin which have been advocated are remarkably numerous, extending to more than a hundred. This has always suggested to me that there must be some fundamental difference between medical and surgical tuberculosis, and it is evident that the effects of tuberculin have been disappointing in the strictly medical cases, notably in pulmonary tuberculosis. The fact that so many attempts have been made to modify tuberculin for medical as opposed to surgical use in treatment suggests that it has been found wanting in some respects. On the other hand, I cannot but feel that if it were entirely useless it would have been discarded long ago, and would not be the subject of a serious discussion forty-two years after its introduction. My own experience would lead me to believe that tuberculin has definite therapeutic uses, and that these are considerable in the localized or surgical manifestations, and strictly limited in the pulmonary forms of the disease.

INDICATIONS AND CONTRAINDICATIONS FOR ITS USE

In cases of pulmonary tuberculosis I have only found tuberculin useful in those patients in whom the disease has progressed satisfactorily towards arrest, but who are left with a small amount of expectoration containing tubercle bacilli. A short course of tuberculin may serve to get rid of the bacilli, to dry up the sputum, or to do both. Such effects alone, if established, would justify its use, since the patients are often enabled to return to their families and to their work without fear and without risk. Many employers will not take back a patient of whom it cannot be certified that the sputum is tubercle-free. Tuberculin has been recommended in chronic cases slow to settle down, of the type described by Inman as "resting afebrile, ambulant febrile." I am less sure of its value in such cases, and I think its effects

require very careful watching; but it is worth considering. The patient should be kept in bed till it is clear that the tuberculin is not producing any severe reaction, and at the first indication that there is hypersensitiveness to it, administration should be stopped or the dose reduced. I am convinced that tuberculin is of great use in some surgical manifestations, notably in localized genito-urinary tuberculosis, particularly where such localizations coexist with chronic or latent pulmonary tuberculosis and where surgery is impracticable or inadvisable. In localized ocular tuberculosis it can be very helpful, if cautiously used, with the strictest control of dosage, in collaboration with an ophthalmic surgeon.

Tuberculin should not be given in those cases in which there is active, spreading, caseous disease, or recent active "spread"; it is likely to be harmful by inducing a definite focal reaction, which cannot be controlled, and may be the means of increasing the softening of the caseous areas, or of spreading the disease. It should certainly not be given if there is any degree of continuous, remittent, or intermittent fever. The patient is already receiving more of the toxic products of the bacillus than he can deal with, and any administration of tuberculin is likely to do harm. It is generally recognized that it can only be harmful in any form of miliary tuberculosis, whether this be generalized or local. It should not be given if there is definite albuminuria, except where this is due to renal or vesical tuberculosis, since prolonged administration of tuberculin has been known to be followed by nephritis.

BEST FORMS IN WHICH TO EMPLOY TUBERCULIN

The varieties of tuberculin may be classified as follows:

1. Filtrates of cultures concentrated, or otherwise modified, especially on glycerin broth media. Of these, Koch's original or old tuberculin is the type.
2. Extracts from the bacillary bodies—Koch's T.O. and T.R.
3. Emulsions of ground-up bacilli—Koch's new tuberculin or B.E. Various processes may be applied before emulsification, as, for example, in Dreyer's diaplyte vaccine, in which the bacilli are treated with formalin and afterwards with acetone, with a view to removing their acid-fast characters.
4. Vaccines made from living attenuated cultures, of which B.C.G. is the type.

It should be recognized that any of these varieties may be made from human, bovine, or other sources. In this connexion I may perhaps note a fact which is not generally known, that the Therapeutic Substances Act, 1925, which is concerned with the preparation of many agents employed in treatment, restricts the name "tuberculin" to the first of these groups, and advises the term "tubercle vaccine" for any substance obtained directly from the bacterial bodies.

My own experience is limited to the three preparations introduced by Koch—namely, old tuberculin, tuberculin T.R. and B.E. There seems to be agreement on the bacteriological side that the tuberculin reaction does not vary in character with the preparation, though it may differ in degree. Attempts to detoxicate tuberculin or modify its toxic effects seem to succeed only in diminishing or destroying its beneficial effects. Personally I prefer B.E. for most medical purposes; it seems to be easier to control and to cause less severe reactions. In surgical cases, particularly tuberculosis of the epididymis, bladder, and prostate, I, in co-operation with my surgical colleagues, have used T.R. I have generally used the tuberculins or tubercle vaccines prepared from human bacilli, but in some ocular cases I have thought that bovine tuberculin has been effective where the human preparation has failed. It is sometimes recommended to start with the bovine tuberculin and later to transfer to the human preparation.

DOSAGE—SPACING AND LIMIT OF DOSAGE

The question of dosage is a difficult one. Believing as I do that tuberculin can be powerfully toxic and harmful if injudiciously given, I always start with infinitesimal doses in pulmonary cases, and I never increase the dose till it is clear that the patient is immune to the one last given. I aim at avoiding any general reaction, and therefore advise that the temperature be taken regularly for at least the day of injection and one or two days after. I usually begin with 1/500,000 mg., and if there is no reaction from this I give, three or four days later, 1/400,000 mg., and then, at the same intervals, 1/300,000 mg., 1/200,000 mg., 1/100,000 mg., or smaller increases if the patient is sensitive. After this the doses can be more rapidly increased—that is, 1/75,000 mg., 1/60,000 mg., 1/45,000 mg., and so on, but I usually extend the interval to seven days by this time. Provided there is no serious reaction and that there is clinical evidence of improvement, I am prepared to go on slowly increasing the dose at weekly intervals or sometimes at ten-day periods till I reach a dose of 1/500 mg., but I rarely go beyond this. Occasionally, when doses of this amount or larger, are reached, severe local reactions may occur, with marked local infiltration in and under the skin and even caseation and softening. This need not necessarily interrupt the treatment, but suggests longer intervals or smaller doses. In surgical cases in which there is no pulmonary lesion it is not necessary to start with such small doses, and T.R. may be used commencing with 1/10,000 mg., and working up by weekly doses to 1/1,000 mg., at which level it may be maintained for long periods.

METHOD OF ADMINISTRATION

Tuberculin can be administered by the mouth, subcutaneously, intracutaneously, and percutaneously by injection. I have used almost exclusively the subcutaneous method, as the dosage would appear more easy to control. Each of these methods has, however, had its exponents, and can apparently give satisfactory results.

ACTION OF TUBERCULIN

In my judgement the weak point in tuberculin treatment is that it is impossible to foretell the degree of focal response to any dose, or to control its degree except by the most cautious graduation of dose, and unfortunately a severe reaction occasionally follows a very slight increase in the amount to which the patient has previously been immune.

It has been generally assumed that its action is specific and that it is beneficial chiefly by its focal effects, tending to hyperaemia and subsequent increase of reactionary changes, leading to fibrosis and arrest. It is clear, however, that a high degree of tuberculin tolerance can be achieved without any permanent benefit, and sometimes without any definite clinical amelioration.

I have been forced to the conclusion that tuberculin only helps in medical cases, when the conditions approximate to those in surgical conditions—that is, when the focus of disease is localized and non-toxic. In other words, when the lesion is relatively circumscribed and not pouring out toxic products into the circulation tuberculin can be helpful; on the other hand, when it is spreading and locally infective, tuberculin is dangerous. The exception is, I believe, when a chronic local lesion is just sufficiently active to produce slight rise of temperature, owing to the extra-ventilation of the lungs occurring from slightly increased exercise. The very cautious administration of tuberculin may turn the scale, but I think even here there is risk, unless the greatest care is taken.

It is clear that there is still scope for much research, and the recent work on the special effects of various chemically

separated fractions derived from tuberculin or tubercle vaccines affords some encouragement. It has been shown by Sapin, Doan, and Forkner that the lipid fractions of tuberculin lead, when injected, to proliferation of epithelioid cells, while Seibert has demonstrated that the protein fraction induces necrosis in a tuberculous animal and not in one free from that infection. Tuberculin and tubercle vaccines are powerful substances. It is certain that they can do harm. What I hope may emerge from our discussion is a clear conception of the conditions under which they can be helpful. I am still hopeful that a real specific treatment will eventually be discovered on bacteriological lines, and I think the biochemists, with the bacteriologists, may eventually provide the solution of this difficult but fascinating problem.

THE COMPARATIVE PHYSIOLOGY OF THE MENSTRUAL CYCLE *

BY

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Research on reproduction chiefly owes its remarkably successful growth in the past fifteen years to the excellence of an organized method that is built on a basis of interlocked histological and experimental observation. By this means the oestrous cycles of many mammals have been elucidated, and various reproductive hormones have been discovered and isolated. Unfortunately for physiological knowledge, it is a method that is not readily applicable to human beings, and the difficulty of obtaining well-documented normal histological material of the human uterus and ovaries, together with the impossibility of conducting experimental research into the human menstrual cycle, has prevented agreement about many essential points that must necessarily be settled before profitable comparison between human and other mammalian reproductive mechanisms can be instituted. Actually, such comparison was being attempted more than thirty years ago, when the question of the homology of the menstrual cycle could not have been of more than academic interest. Many still treat it as a purely academic problem; theirs, however, is an unsound attitude, a reaction to years of seemingly sterile discussion. Today, with preparations like oestrin and "anterior lobe hormones" that are ready to be applied in clinical medicine, the question of the homology of the menstrual cycle is of distinct practical importance. The human placenta and human urine are the common sources of the supplies of reproductive hormones used in laboratory practice. The biological properties of the substances extracted from them are determined by experiment on lower mammals. The attempt to apply these substances in morbid human conditions should, as far as possible, be rational and non-experimental. To attain this ideal, full consideration must be given to the similarities and dissimilarities between the menstrual cycle and the oestrous cycles of lower mammals.

SEXUAL-SKIN ACTIVITY IN PRIMATES

In approaching this question of homology, it must be remembered that not only man but all the Old World primates that have been studied have a menstrual cycle, and that considerable advances in our knowledge of the menstrual cycle have been made through the study of apes and monkeys. This fact raises the question whether or not the cycles of all primates can be regarded as being

the same in type. The common characteristic of all is bleeding from the uterus approximately every four weeks. Although the differences between the cycle of one primate and that of another do not affect this phenomenon, they are nevertheless conspicuous. Thus, in some Old World primates the skin of the external genitalia—and also of neighbouring parts of the body—is specialized, and forms a highly sensitive area which, at regular times in the cycle, swells or becomes highly coloured, or does both. Other Old World primates, including man, do not exhibit such changes, and their only external physical manifestation of the cycle is the menstrual bleeding. These questions have been discussed at length elsewhere,^{29, 30} and it was concluded that the general plan of the cycle is the same in all the primate species that manifest activity of a "sexual skin." Menstruation normally occurs at fairly regular intervals of about thirty days. Immediately after its onset the skin around the external genitalia becomes red in colour and swells, reaching a maximum before the middle of the cycle. Shortly after the mid-point the activity of the sexual skin, as a rule, suddenly decreases, and the skin resumes its quiescent appearance, which continues until the onset of the next bleeding, when it again becomes active.

The main variation in this kind of cycle is in the actual character of the external changes. They are very pronounced in animals like baboons and chimpanzees, the swelling of the sexual skin in the former being sometimes as large as about one-eighth of the normal volume of the trunk of the animal. In others—for instance, some macaques—the changes are very slight, and such catarrhines can hardly be differentiated from the group which includes man, where there are apparently no external changes. Another factor which varies is the time after the mid-point of the cycle taken by the skin to resume its quiescent appearance. Although the initial change seems to be abrupt in all primates, the further absorption may be slow, as, for example, in rhesus monkeys, or very rapid, as in some baboons. Instead of these differences confusing the issue, however, they significantly add to our understanding of the menstrual cycle as a characteristic of Old World primates.

Thus, since the time relations of sexual-skin activity and menstrual bleeding are approximately the same throughout Old World primates, it may be inferred that the physiological mechanism of the skin is the same in all. Actually it has been shown that it is the oestrous hormone, oestrin, which activates the sexual skin in such widely different genera as *Macaca* (macaques),¹ *Papio* (baboons),²³ and *Cercocebus* (mangabeys).²⁷ The physiological evidence thus indicates that sexual-skin activity is an oestrous phenomenon, in the sense that vaginal cornification is in the mouse. The facts of behaviour point to the same conclusion. Observations recorded elsewhere³⁰ show that those subhuman primates which experience pronounced external cyclical changes are more sexually active in captivity than those that do not. They also show that sexual activity in normal conditions varies directly with the degree of activity of the sexual skin. For example, female baboons are more receptive during the period of swelling than at other times.

Catarrhine primates could therefore be arranged in a series showing all degrees of externally visible oestrous changes. The period of functioning of the oestrous hormone, so far as can be judged, is much the same in all, irrespective of the actual character of the sexual-skin changes. In the absence of conflicting data, it thus seems legitimate to infer that in catarrhine primates which do not show external changes in a sexual skin, the period of homologous oestrous hormone activity is also the same. Accordingly, although knowledge of normal changes occasioned by the oestrous hormone during the human

* Read in opening a discussion in the Section of Comparative Medicine at the Centenary Meeting of the British Medical Association, London, 1932.