

Original Articles.

THE DIAGNOSTIC AND THERAPEUTIC USE OF TUBERCULIN.*

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THE DIAGNOSTIC USE OF TUBERCULIN.

THE use of tuberculin for diagnosis in tuberculosis, though suggested by Koch in one of his first papers, was for some time completely overshadowed by the great possibilities that Koch claimed for its therapeutic use. Following the period of "tuberculin delirium," tuberculin was seldom used and was long regarded as highly dangerous. Had it not been for Trudeau, Osler, and a few others who boldly put into practice their belief in its diagnostic value, tuberculin would have been laid aside in this country as fully as it was in England. The paramount necessity of making an early diagnosis in pulmonary tuberculosis has emphasized the value of every test which offers us the slightest help. In Germany, the sanatoriums have been filled with patients in whom the diagnosis of tuberculosis depended in many instances upon the results of the tuberculin test. However, some suspicion and fear about this test has lurked in the minds of many men, but these, almost without exception, are those who have made but little or no use of it. As I have said, this is true of many physicians in England, and particularly true of the medical profession in France. All these men, however, were forced to recognize its great value in tuberculosis in cattle, and many are coming slowly around to the position that the subcutaneous use of tuberculin for diagnostic purposes is attended with far less serious consequences than the failure to make an early diagnosis. When late in 1906 von Pirquet began to write about the cutaneous test, and particularly when Wolff-Eisner in May and Calmette in June of last year advocated the instillation into the eye, of weak dilutions of tuberculin, the opponents of the subcutaneous method, realizing the great value of tuberculin as a diagnostic means, were ready to test fully these methods.

THE CUTANEOUS METHOD.

The cutaneous method consists in putting a drop of diluted old tuberculin, preferably 25%, upon the skin, and then with a lancet, quill or von Pirquet's "scratcher" (Schaber), a slight abrasion of the skin under the drop of tuberculin is made. Only the most superficial layers of the epithelium need be removed as it is only necessary to open the superficial lymph channels, and it is unnecessary and even undesirable to draw blood. The technic to be employed is practically the same as that used in vaccination against smallpox, and the dangers of secondary infection are exceedingly slight. At a distance of about one inch a control abrasion should be made under a drop of 50% glycerin and .1% phenol in physiological saline solution. Care should be exercised not to carry tuberculin on the instrument to the

control, and where large numbers of patients are vaccinated a platinum-iridium instrument that can be heated has been advised. Both places at first become slightly red and then normal in color. The reaction, Wolff-Eisner thinks, should be separated into three great classes: first, what he terms the normal reaction of the tuberculous individual; second, the late reaction, each of which may be marked, strong or unusually strong; and third, the quick, but very weak and fleeting reaction, often overlooked [first, favorable (more so if stronger), third unfavorable, second fully inactive]. The early reaction begins in about three hours with slight redness which in twenty-four hours reaches its height and in forty-eight hours has markedly retrograded. In a comparatively few hours a slight elevation or papule appears which is more apparent to the touch than to the sight. In some instances it takes the form of a wheal which later changes into a papule. In rarer instances a bleb, small vesicles or a form of herpes may occur.

In the late reaction the intensity increases each day to the fourth or, indeed, it may only begin on the third or fourth day, and may persist for three or four weeks. The papule is firmly indurated and may suggest the post-mortem tubercle.

A slight staining of the skin remains afterwards in each case and the subjective symptoms are usually very slight. The patient may feel that something is wrong with his arm and it may itch. Lymphangitis may occur and the glands in the axilla may become slightly tender when the vaccination is made on the arm.

THE CONJUNCTIVAL METHOD.

The ophthalmic, or (as Wolff-Eisner thinks that we should call it, and he has considerable right upon his side) the conjunctival test, is even more simple in its technic than the cutaneous test. It consists in putting a drop of a 1% solution of old tuberculin, prepared freshly every eight days, into the eye. The patient should hold the head well back and the lid should be held down for one-half minute after the tuberculin has been dropped on the lower lid. It is better if possible to warm the tuberculin but this is not necessary. The patient should be warned not to wink and not to close his eye until absolutely necessary. He should not rub it. In children the occurrence of lachrymation may wash out a large amount of the tuberculin. Calmette has used a 1% solution of purified tuberculin. This solution is too strong and has caused some unpleasant consequences. If the precipitated tuberculin be used it is much wiser to use at first a 1:250 solution in one eye and if this cause no reaction then to employ a 1:100 solution in the opposite eye. The dose should not be repeated in the same eye. In six to twenty-four hours the conjunctiva becomes slightly reddened. Many observers have noticed that this begins first and often occurs more intensely about the caruncle, but Wolff-Eisner has not observed this, though he thinks, however, that theoretically it should take place. The reaction may vary considerably in degree. Reddening of

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the palpebral and slight reddening of the ocular conjunctiva is the most usual occurrence, but the reddening may be more intense with a mucofibrinous exudate. In a few instances all these symptoms are more pronounced and even a slight ecchymosis may occur. A strong reaction is accompanied with itching, a feeling as if a foreign body were in the eye and at times with some photophobia, but usually these symptoms are very slight and may be readily controlled by the use of a boric acid solution containing a little camphor water, or a drop or two of a 3% solution of cocaine, either alone or with a drop of a solution of adrenalin, 1:1,000. After the conjunctival test a few general reactions have been observed. The redness of the conjunctiva usually disappears in twenty-four to forty-eight hours, but may persist for several weeks, and recur when tuberculin is administered subcutaneously.

THE SUBCUTANEOUS METHOD.

The introduction of the conjunctival and cutaneous tests will force us to change our nomenclature in regard to the tuberculin test. We shall now have to speak of the tuberculin test as conjunctival, cutaneous, subcutaneous and possibly dermic. The latter method has been the form that has been most extensively used. Koch's original tuberculin should always be employed for the subcutaneous test as it is the form of tuberculin about which we know most. It should be recalled, however, that even this form cannot be accurately standardized. The dose required to produce a reaction in a healthy individual is very difficult to ascertain, but Koch has stated that 10 mgm. never produces a typical reaction in a normal person. The interesting work of Schreiber, who in forty newborn infants failed to get a reaction to 50 mgm. of tuberculin, suggests that even to the subcutaneous test an individual who has never been injected with tubercle bacilli would not react or else that the mechanism of the infant in regard to tuberculin is differently constituted from that in the adult.

The method that has given me the greatest satisfaction is first to give an injection of physiological saline solution and then, if the patient fails to react, to give $\frac{1}{2}$, 1 and 5 mgm. in three and four day intervals. Since I have been using this method I have found that all patients have reacted to 5 mgm. or less. A repetition of a small dose several times, as suggested by Loewenstein, does not produce a reaction in all tuberculous patients, and considerably prolongs the ordeal. The tuberculin is usually given at night, and in the majority of instances the reaction occurs eight to twenty hours later. In a few it may occur as early as four or five hours, and it cannot be denied that slight reactions which occur as early as this may fail to cause the patient a restless night, and consequently be overlooked, but I cannot believe that this occurs frequently. A reaction may take place, especially during tuberculin treatment, as late as the second or third day, and for this reason it is unwise to inject the tuber-

culin oftener than every three days. A typical reaction consists of pain, tenderness, redness and swelling at the site of injection, headache, malaise, an increased tendency to cough, possibly more or less expectoration than usual, some oppression in the chest or pleurisy, and, at times, some gastrointestinal symptoms, such as nausea and vomiting. Some elevation of temperature is rarely absent, though I do not believe that it is absolutely necessary to have a rise of temperature if the other symptoms are characteristic. In some instances rise of temperature occurs alone and should reach $1\frac{1}{2}^{\circ}$ to 2° at least to be characteristic. The absence of any change in the physical signs in the lungs is no proof that a reaction has not occurred, but the occurrence of such a change points conclusively to a pulmonary infection. If an indefinite reaction occur it is wise to repeat the last dose which may be given sooner than I have mentioned. When the larger doses of tuberculin are given the reaction must be absolutely typical. Early non-acute cases of tuberculosis always react to the smaller doses. The day after the injection of tuberculin it is the practice of many physicians to keep the patient in bed, but theoretically, the patient should be under the same conditions before and during the test. Consequently, for some months I have not confined the patients to whom I have given tuberculin to bed but have cautioned them about over-exercise and allowed them to be up and about. The danger of over-exercise is the production of a severe reaction.

CONTRA-INDICATIONS.

Cutaneous test.—There are, as far as I know, no contra-indications to the use of the cutaneous test.

Conjunctival test.—According to many authorities, this test should be used only when there is no history of any inflammatory disease of either eye. Conjunctivitis, however, Wolff-Eisner believes, is only of importance in that it masks the reaction, but many authors do not agree with him. Iritis and tuberculous changes of the inner eye are absolute contra-indications. Wolff-Eisner believes that if used, it should be given in a dilution of 1:100,000. Great caution should be exercised in the use of this test in children with scrofula, for phlyctenular conjunctivitis and keratitis have occurred. The test is not devoid of all danger as a case which has recently been reported in the BOSTON MEDICAL AND SURGICAL JOURNAL by Mackay shows. In this case a 1% solution of precipitated tuberculin was used, and ten weeks after the test and following severe conjunctivitis, there was still "a little redness of the conjunctiva with slight photophobia resulting in some narrowing of the palpebral fissure."

Subcutaneous test.—The subcutaneous method should not be used when a patient's oral temperature reaches 100° at any time during the day. When the physical signs are extensive or when great dyspnea, recent hemoptysis, within a month, general glandular involvement, meningitis, heart disease, nephritis or epilepsy are

present it should not be used, though exceptions under certain conditions may be made when the nephritis is slight or if a very small dose be used in general glandular involvement. It is wiser to avoid the use of tuberculin for two or three weeks after a febrile attack of unknown cause, and in some hysterical patients an injectio vacua will produce a rise of temperature.

Comparative value.—The comparative value of the three tests is difficult to determine at present. Some observers have obtained a reaction to the cutaneous test in three fourths of all individuals, though Wolff-Eisner has been unable to obtain it in more than one half, and criticizes the results of others. It has been definitely shown by von Pirquet and others from autopsy records that the percentage of reactions to the cutaneous test follows very closely the incidence of tuberculosis in children. Rarely present at first, it increases up to nearly 70% between the tenth and the fourteenth years, and inasmuch as the Hamburg autopsy records show latent and active tuberculosis to be present in about 72% of patients at this age, it is seen that the cutaneous test reveals very accurately the presence of both active and latent tuberculosis. Inasmuch as we know that a large percentage of all mankind have or have had at some time a tuberculous infection, and furthermore inasmuch as it is of little or no clinical significance to know that an inactive encapsulated tuberculous lesion that has been latent for years is present in the body, it appears that the cutaneous test alone is of little practical value.

The conjunctival test occurs in but one sixth of all individuals tested, and according to Wolff-Eisner reveals only active or "half-active" lesions. The autopsy statistics uphold this statement. Why the conjunctiva should react differently from the skin can be explained by the difference in the length of time the tuberculin is in contact with the part, for it is readily and rather quickly carried off through the tear duct.

The value of the subcutaneous method is more difficult to determine. Undoubted proof exists that none of these methods produce reaction in all cases of tuberculosis, and a number of observers have suggested prognostic data which are based upon this failure to react. As has been stated previously, early cases of tuberculosis react to smaller doses of tuberculin, and it is an interesting fact that the opponents of the subcutaneous method have been able to produce so few authenticated instances where post-mortem examination revealed no tuberculosis after a positive tuberculin reaction. The observations of Warthin, who has proved that only by microscopical examination can tuberculosis be excluded, have made it difficult to prove that reaction to tuberculin ever occurs in any patient who has not had a tuberculous infection. Without doubt the subcutaneous method, when a dose of 8 to 10 mgm. is given, causes a number of patients who have more or less inactive tuberculosis to react. The results of Franz with apparently healthy army recruits has undoubtedly shown that a large number of latent

lesions do react to tuberculin. You will recall that three fifths of the individuals that he tested reacted. This figure closely coincides with the number of reactions following the cutaneous test. It is interesting, on the other hand, to compare the results obtained by Raviart who obtained a reaction to the conjunctival test in 43% of 623 patients in the hospital for the insane with the results obtained by Madison at Danvers, who noted a reaction to the subcutaneous tuberculin test in 40% of 400 consecutive insane patients. Madison's patients were all women and he used up to 10 mgm. of tuberculin.

From what has been said it appears to me that in many instances the properly applied conjunctival test will reveal a lesion of tuberculosis as accurately as the subcutaneous method, but that we have no reason to suppose that the subcutaneous method betrays a latent inactive encapsulated lesion of no clinical significance any more frequently than the conjunctival test. I have mentioned a number of circumstances, for example, conjunctivitis, iritis, and tuberculous lesions of the eye, in which the conjunctival test is contra-indicated. In all such patients we shall still have to depend upon the subcutaneous method. I have used it in a large number of cases for eight years, and I have yet to see, as a consequence, anything more than a slight temporary untoward result.

After the consideration of these three methods it seems to me that where time is not a very important factor the best course for us to pursue when we wish to apply the tuberculin test to a patient presenting suspicious symptoms or physical signs of tuberculosis, is first to use the cutaneous test, and if he fail to react to this we can with some degree of certainty attribute his symptoms to some other disease. If he react we can then use either the conjunctival, when no contra-indications exist, or the subcutaneous method, in which I must confess, I have still greater confidence. Another plan, suggested by Wolff-Eisner, is to use first the conjunctival test and then if no reaction occur, due either to faulty technic or to the absence of an active lesion, to apply the cutaneous test, which acts as a control. If this fail, the patient, he thinks, may be said to be free from tuberculosis, but if it be positive, a second conjunctival test in the opposite eye should be used. A third method of procedure which I believe should be used only when time is pressing, is to apply both conjunctival and cutaneous tests simultaneously. I feel that the conjunctival test, like the subcutaneous test, should be used only when all other means of diagnosis have been exhausted and that, as far as danger is concerned, I should be willing to submit as readily to the one as to the other, preferring, as I have stated above, the subcutaneous test. I must confess that I still hesitate to say that a patient does not react to the tuberculin test until the subcutaneous test has been found negative.

There are many points that I have not touched upon to-night that I hope will come out in the discussion.

THE THERAPEUTIC USE OF TUBERCULIN.¹

Since Koch first announced his discovery of tuberculin in 1890 a few men have continuously employed the various forms of tuberculin in the treatment of pulmonary tuberculosis. To the moderate but strongly grounded faith in tuberculin that Dr. Trudeau has manifested for many years, in spite of the fact that some of his co-workers frequently urged him to discontinue its use, we owe to-day the widespread use of tuberculin as a therapeutic agent in America.

THE VARIETIES OF TUBERCULIN.

When it is realized that nearly sixty forms of tuberculin have been prepared some idea of the amount of work that has been done along this line of treatment in tuberculosis can be obtained. The vast majority, however, of these forms have been very little used clinically. The old tuberculin, originally proposed by Koch in 1890, is still used extensively to-day, and while all these varieties have been suggested many still report better results with this original tuberculin, which is really a heated glycerin-bouillon extract of the tubercle bacillus. A second tuberculin proposed by Koch, Tuberculin R., is the form of tuberculin that Wright and his followers have been using in England, controlling the doses by a study of the opsonic index. Koch stated that it contained 10 mgm. of solid substance in each cubic centimeter, but in reality, as Ruppell has recently pointed out, it contains but 2 mgm. The 10 mgm. was the amount of the solid substance that was used in its preparation, for if one evaporates the finished product it is found that each cubic centimeter contains but 2 mgm. The mistake that Wright has recently made in basing his dosage on the fact that it contains 10 mgm. of solid substance instead of 2 mgm. is the mistake that has been frequently and widely made through the inexact description of its preparation. The Bacillen Emulsion, a third variety of tuberculin, advocated by Koch, consists of a .5% emulsion of living, virulent, pulverized tubercle bacilli, in a 50% solution of glycerin in water. More recently a filtrate through porcelain of bouillon upon which tubercle bacilli have grown has been warmly advocated by Denys. Spengler has stated that this was the original tuberculin that Koch used and later discarded when he made old tuberculin. Spengler himself has concentrated this broth filtrate, heating it only to a low temperature, and advocates this variety of tuberculin very strongly. Denys thinks that this form of tuberculin is 10 to 100 times stronger (more toxic) than old tuberculin, but Baldwin has shown that old tuberculin is far more toxic for guinea pigs. The split products which Vaughan has obtained from the tubercle bacillus are certainly very interesting. He thinks that the non-toxic part may produce within the organism an increased bacteriolysis of the tubercle bacillus. He has not yet, however, definitely proved, as far as I know, that this non-

toxic product is specific. The criticism that the various emulsions first contained living tubercle bacilli was undoubtedly justified, for Trudeau and Baldwin found living bacilli in Tuberculin R., and Thellung and von Meissen in Bacillen Emulsion. The various preparations of von Behring have never been fully described and have not met with extensive use.

Great difficulty has been experienced in standardization of tuberculin, and even to-day there is no accurate method of standardization. Its toxin varies in strength even when prepared from the same tubercle bacillus, grown on the same media under exactly the same conditions, and consequently when changing from one brew to another the dose should be reduced. The chemistry cannot of course be gone into, but it may be stated that nearly all of the tuberculins contain a greater or less quantity of the specific nucleic acid.

METHODS OF ADMINISTRATION.

Tuberculin has been administered in every way in which it is conceivable to get it into the body. The method first suggested by Koch was by subcutaneous injection. More recently when he wished to obtain a high agglutinating power in the serum he gave bacillary emulsion intravenously. Few others have employed this method.

Tuberculin has been given by mouth in the form of keratin coated pills after neutralization of the juices of the stomach with the bicarbonate of soda. Others have taken no cognizance of the peptic digestion in this form of administration. The work of Calmette and some of his assistants has shown that partial immunity in calves may be obtained by the use of tuberculous milk, and Ravenel and others have shown that tubercle bacilli in emulsions of fats are rapidly absorbed in the dog. The results, however, of oral administration are very unsatisfactory and the dosage is inexact. The same objections may be advanced against administration by inhalation. Spengler advocates the use of a percutaneous method in cases where hypersusceptibility is present, but this method is hardly necessary, for tuberculin can be given in such dilutions as to avoid all reaction. The rectal and intra-pulmonary injections of tuberculin cannot be recommended.

Subcutaneous injection still stands to-day, as at first, the most exact and most efficient method of administration of tuberculin. While a few advocate the injection of tuberculin in the neighborhood or into tuberculous foci no proof has been adduced to show that such a procedure is of any advantage and, in fact, there are some theoretical objections to it.

Nearly every form of tuberculin must be diluted to enable one to measure the small doses that must be used at first. The best diluent is .25% carbolic acid in physiological salt solution. This may be used for emulsions, though Koch recommended that only salt solution be used for this form of tuberculin. The high dilutions should not be kept over two weeks and are best preserved on ice in a dark place. I will not go into the

¹ Dr. Brown has contributed a chapter on this subject to a work on Tuberculosis, edited by Dr. Arnold C. Klebs, and to be published by D. Appleton & Co.

details of dilutions but would like to add that the absolute dose any patient is getting of tuberculin is far less important than the relative dose. For this reason a syringe may be used for making the dilutions providing that the same instrument be always employed. In passing, I might speak of the syringe which has been made for me by a Boston firm and is divided into hundredths of a cubic centimeter. The needle is the finest that can be procured, and as a practical point, I would suggest to you that after using it you rinse it out with alcohol, lay it aside and use it for no other purpose. The syringe should be boiled before using. [I will pass around a schema which is used at the Adirondack Cottage Sanitarium in the preparation of the dilutions of tuberculin.] Rubbing the skin vigorously with a piece of cotton or a clean towel with 95% alcohol is all that is necessary. The tuberculin should be given well under, not in the skin nor in the fascia. It is best given 4 to 8 cm. from the spine in the lower interscapular region or below the angle of the scapula. The sites of former injections should be avoided. When the physician administering tuberculin is or has been tuberculous, he should avoid freeing his syringe of bubbles of air by squirting some of the tuberculin into the air, and he should also wash his hands carefully after administering tuberculin, otherwise he may react.

DOSAGE AND INTERVAL.

The most important point in the successful treatment of tuberculosis by tuberculin lies in the selection of the proper dose and interval. The unfortunate accidents, indeed, I might say fatalities, which occurred at first were due to too frequent and vastly too large doses. During the period of tuberculin delirium a patient often received 1 mgm. and on the following day, in spite of the fact that he had a severe general and local reaction, in spite of the fact that his temperature reached 104°, he was frequently given another dose. This method was continued in a number of cases until the patient died. As I said a little while ago, the absolute dose of tuberculin is far less important than the relative dose. The most important point in regard to the beginning dose is that it shall be of such a size that it will produce no symptoms whatsoever in the patient. If there is any doubt about this it should be repeated several times. Patients vary greatly in susceptibility to tuberculin, a variation which Sahli states lies between 1 and 10,000. Tuberculin is usually given twice a week, but I am firmly convinced that this depends in a number of cases more upon the convenience of the physician who administers it than upon any other reason. I do not believe that it should be given more frequently than twice a week and that is the interval that I have usually employed, but whether as good or even better results would not be obtained with longer intervals is impossible to say. Both the beginning dose and the interval have been directly affected by the idea that many physicians have that a certain dose must be reached. How this came about is difficult to understand. It is well recognized

that individuality of idiosyncrasy plays an important part in the dosage of all drugs. I have told you how the individual varies in regard to his susceptibility to tuberculin, and I am firmly convinced that we should not allow a question of the final dose to exert any influence upon either the interval or the beginning dose. When it is realized that a delayed reaction may not take place until sixty hours after the administration of tuberculin it is clearly seen why tuberculin should not be administered at intervals of less than three days. The increase of the dose has really divided the tuberculin camp into two sections; one headed by Wright insists that the increase of the dose, except to a certain very small quantity, is not necessary. In other words, it strives to produce an immunity which is indicated not by the patient's resistance to tuberculin but by the power of his leucocytes to phagocyte tubercle bacilli. The other camp strives to produce immunity to tuberculin claiming that if a patient can be immunized to tuberculin his cells will be able to resist, to engulf and finally to overcome the tubercle bacillus more readily. There are some very interesting facts to be presented on both sides. I cannot go into them to-night, but I shall simply say that in the guinea pig phagocytosis of the tubercle bacillus occurs very readily and that in this animal this phenomenon may explain why the guinea pig is so susceptible to tuberculosis, for when a cell has once engulfed a tubercle bacillus it may wander to some distant part of the body and dying there set free the tubercle bacillus which has been but little affected by its sojourn in the cell. On the other hand it is also of interest to note that guinea pigs are very insusceptible to tuberculin and that the tuberculin immunity which can be produced in them is not an indication that they will resist tubercle bacilli. However all this may be, the majority of observers have given tuberculin in increasing doses.

Few attempts had been made to determine the exact effect of any single dose of tuberculin until Wright announced his opsonic index method, but the inherent difficulties connected with this method detract greatly from its practical value. In giving tuberculin we must therefore decide upon what method we are going to pursue in regard to the increase of the dose. In some forms of tuberculin the symptoms seem to be a sufficient guide. Pardoe has obtained far better results in the treatment of tuberculosis of the genito-urinary organs by the use of Tuberculin R. than he has by any other line of treatment. He gives tuberculin in increasing doses until the patient shows some signs of over-stimulation; for example, increased frequency of micturition. The dose is then reduced, and this reduced dose is given for a long time without any attempt to increase it. In other words, he has found from the symptoms the limit of tolerance of the patient to tuberculin and then keeps well within this mark. Wright, himself, determines the opsonic index in practice very much less frequently than many of us have been led to suppose. As long as a patient continues to do well on a certain dose which increased

his tuberculo-opsonic index he gives this dose. When, however, there is some reason to suppose that the patient is not getting as much benefit, and does not feel the good effects of the tuberculin, then he believes it is time to take again the opsonic index. Hastings, of New York, has found that it is necessary in these cases to take the index every other day for four or five times, in order to determine the exact effect of a single dose of tuberculin. The index must go up and remain up for several days, or else the dose is not properly graduated for the needs of the patient. This method seems to give the best results in the treatment of surgical tuberculosis. There is possibly, however, another explanation of this which I shall mention later.

The older method of giving tuberculin is to increase the dose, avoiding all symptoms until the patient becomes immunized to tuberculin. The opsonic index is disregarded in this method and Kinghorn and Twichell have found in pulmonary tuberculosis that whether the inoculation was made during the negative or positive phase, the index was as likely to go up as down. They used chiefly the old tuberculin. Auto-inoculation may account in part for this, and it is of interest to note that the Wright school has never been enthusiastic about the results obtained in pulmonary tuberculosis by method.

By this clinical method, which is well borne by patients with pulmonary tuberculosis, every attempt is made to avoid hypersusceptibility. By this I mean a tendency on the part of the patient to react much more readily to tuberculin. In other words, when slight symptoms have been ignored and the dose increased, the patient has a more or less marked reaction, consisting of pain, redness and swelling at the site of the injection, headache, malaise, often some symptoms connected with a gastro-intestinal tract, such as nausea and vomiting, at times increased cough and expectoration, oppression in the chest or pleurisy, together with some elevation of temperature. The succeeding dose is reduced, but the patient reacts again. He may also react to several doses, each reduced in turn, and the only course left open for us is for a time to discontinue the use of tuberculin. Every effort must be made so to increase the doses of tuberculin as to avoid this hypersusceptibility. As I stated before, the successful treatment with tuberculin is like the successful treatment of the disease. Both require great care in regard to small details. There should be perfect understanding between the patient and the physician who gives him tuberculin and he should be told that the only way to a successful issue is to report any deviation of symptoms from the usual course. [I will pass around a couple of little booklets which I have found of great value in enabling patients to convey to me their exact condition after a dose of tuberculin.]

The time of the injection is chiefly important in regard to the observation of symptoms arising after the inoculation. I am led to believe that the convenience of the person who administers

tuberculin has had more to do with the selection of the time when it should be given than other factors. At the Adirondack Cottage Sanitarium it has always been given at night, and I believe this a much better time inasmuch as the reaction following tuberculin rarely occurs earlier than ten hours after the injection. Another important point is the fact that the maximum temperature during the day has been attained by that time. The morning remission, Sahli thinks, may obscure the reaction but, studied in connection with the symptoms, this does not seem at all probable to me. For these reasons I am inclined to believe that the best time to give tuberculin is during the late afternoon or evening.

The recent tests based upon the susceptibility of the skin and conjunctiva to tuberculin have suggested that we should pay more attention to the local or skin reaction at the site of injection. The susceptibility of the skin to tuberculin varies greatly with different patients. Some fail to show a single reaction throughout the entire course; others react in this way to every dose of tuberculin. In many instances not only the site of the last injection but the site of one or more previous injections may also be reddened, elevated and painful to touch or pressure. Recently I have been endeavoring to convince myself of the connection between the skin and the general reactions. I have not yet arrived at any very definite conclusions, but so far I can state that a slight skin reaction may be disregarded and the dose increased. In a number of instances the dose may be slowly increased where the skin reaction is marked without much danger of producing a general reaction, but I do not advise such a course. Another point of interest is the fact that this reaction is more likely to occur when tuberculin is given subcutaneously in the limbs than on the trunk. Many patients suffer considerable discomfort when tuberculin is given in the lower arm but have little or no discomfort when it is given in the upper arm or in the back. I am at present in a number of cases trying to give tuberculin in the forearm to see whether or not the guide which this site gives us is of advantage in deciding the increase of the dose.

The "organ" or focal reaction has been looked upon as of considerable importance, both in diagnosis and in treatment. However that may be, a large number of patients who react to tuberculin and later develop physical signs in the lungs and possibly tubercle bacilli in the sputum show during the reaction no increase or indeed no physical signs when none have been present previously. Consequently, in regard to the lungs, I feel that this "organ reaction" is of little use, though some (von Ruck and others) believe that it is of considerable importance in determining the dosage.

The symptoms produced by tuberculin may be discussed under two heads, first, the localizing symptoms, and, second, the general symptoms. The former are not nearly as likely to occur as the latter unless pronounced reactions are produced, and consequently are of less importance. Increased cough and expectoration

always demand careful consideration, and it is wise often to omit several doses of tuberculin until these symptoms return to their usual level or at any rate cease to increase. Oppression in the chest is not frequently noticed. Pleurisy is at times present after reaction but other times is so constantly present as to be of little value as a guide. In some forms of genito-urinary tuberculosis these localizing symptoms have proved of the utmost importance as I have already mentioned in regard to Pardoe's excellent results. The occurrence of hemoptysis is very infrequent and, in fact, some claim that tuberculin not only prevents hemoptysis but can be safely administered while the patient is spitting blood. Personally I have always omitted the administration of tuberculin until the patient had ceased to spit blood for a week at least.

The general symptoms when the clinical method is used are the most valuable criterion that we have in regard to the increase of the dose of tuberculin. It is in regard to these that the mistakes are most usually made and for this reason many patients are given too large a dose of tuberculin. Any deviation from normal or the occurrence of the slightest and most trivial symptom that was not present before should be carefully considered. Due weight of course must be given to the occurrence of symptoms in neurotic patients. Pronounced symptoms should rarely occur if the dose has been carefully selected. Slight headache, malaise, a feeling of chilliness, are all very suggestive and even without the occurrence of the slightest rise of temperature require a repetition of the same dose. Pain in the limbs or joints, faintness, giddiness, sleepiness, fatigue, restlessness, nervousness, stimulation, rarely occur alone, but like indigestion, nausea, and vomiting are often present at the same time. Insomnia may mean a rise of temperature occurring during the night, and the patient should be advised to take his temperature during the night when suffering from insomnia. Other symptoms than these are infrequent, and when the dose is carefully selected these symptoms also rarely occur.

In some instances it is very difficult to decide whether or not symptoms are to be attributed to tuberculin, but in any case of doubt it is wise to do so and to grade the doses accordingly.

Rise of temperature, long looked upon as the most important guide in relation to the dose of tuberculin, I have left until last for, while it is present in many instances in a large number of patients, many of these symptoms may occur without any perceptible disturbance of the temperature curve. There is one interesting point in this connection, namely, that the broth filtrate, Denys's tuberculin, seems more likely to produce symptoms without elevation of temperature, while the Bacillen Emulsion very often produces a sudden sharp rise of temperature with pronounced symptoms without any previous warning. This is rarely true of Denys's tuberculin. In regard to rise of temperature the same rule applies here as applies to the other symptoms, — the slightest

deviation from the usual course must be noted and carefully considered. A rise of a few tenths of a degree, especially when accompanied by any other symptoms, means a repetition or a reduction of the last dose. When the temperature reaches 100° the last dose should always be reduced, and if this rise be accompanied by symptoms at all pronounced the reduction should be marked, that is, to $\frac{1}{4}$ to $\frac{1}{2}$ of the last dose. If the temperature goes higher than this, for example, to 101°, it is wise to omit several doses and then to begin with this greatly reduced dose. Tuberculin should never be given after a rise of temperature, until the temperature has become normal or has returned to its former level for a period of two or three days, and if the rise has been marked the former level should be maintained for a longer period before tuberculin is again given. If these rules are neglected it is very easy to produce so marked a degree of hypersensibility in the patient that tuberculin in almost any dose will not be tolerated.

The pulse range following tuberculin has been thought by some to be of considerable value in graduating the dosage, but this symptom is so easily affected by variations in the environment of the patient that it is difficult to interpret it properly and, indeed, unless taken by a nurse to whom the patient is accustomed, may be misleading. There is no doubt that tuberculin does somewhat increase the pulse rate. The weight is of more value in the selection of patients than it is in determining the dosage. If, however, the patient steadily and continuously loses weight it is often wise to interrupt the treatment until the nutrition becomes better.

Due consideration must be given to the occurrence of slight complications, for example, a coryza, a slight indigestion, or any complication arising during the course of treatment, for the reason that it may reduce the patient's tolerance and render him more susceptible to tuberculin. I have seen several cases where the patients acquired, for a time, at least, considerable intolerance through failure to observe these precautions.

From all this it may be seen that whenever any of these symptoms or signs, however slight, arise one of several courses is open: first, to repeat the dose, and this repetition may have to be made a number of times; second, to lengthen the interval; third, to reduce the dose; and, fourth, to omit the dose. The individuality of the patient and his susceptibility to tuberculin must be clearly borne in mind throughout the whole course. It is wise in every instance, when in doubt, to err on the side of too little rather than too much tuberculin.

From what has been said it is readily seen that it is difficult to bring every patient to the same final dose of tuberculin. The optimum dose, a point emphasized by Sahli, varies in my opinion for every patient and it is very unwise if, after large doses are reached, signs of intolerance to these doses manifest themselves, to attempt to push on to reach some fixed point simply for the reason that that is the dose that we want to

attain. Harm in my opinion may result from such a course, and I am more and more convinced that as much benefit can be derived from small doses of tuberculin as from larger doses. It has been pointed out that it might be a good plan when the patient begins to show lessened susceptibility to tuberculin, to interrupt the treatment for a little while and then to return after susceptibility reappears to smaller doses. (Petruschky.) The usual final dose of many tuberculins, O. T., B. F., Beraneck's, etc., is 1 ccm., but I do not believe that we should attempt to reach this dose in many patients. As I said before, immunity to tuberculin does not mean immunity to tuberculosis. It seems to me that the wiser course to pursue, even though we attempt to produce tuberculin immunity, is to carry the patient up to that dose which only begins to produce symptoms of reaction. The dose should then be considerably reduced and slowly increased again. Very often the previous limit can be surpassed, but even if this is not possible no attempt should be made to carry the patient on in spite of the occurrence of reaction. The hypersusceptibility noted by Loewenstein and many others following a repeated small dose of tuberculin was first pointed out by Koch, who believed that it was very characteristic of tuberculin. Whether or not this hypersusceptibility produced by repetition of the same dose may not be called into play when small therapeutic doses are repeated is still an open question. I feel, however, that this must occur for otherwise I do not see how we can explain some of the reactions that I have obtained with very small doses.

Tuberculosis is a chronic disease, and usually when a patient applies for tuberculin treatment the disease has already existed for months if not years. The treatment of tuberculosis by any successful method depends largely upon the length of time it is followed and, as I have noted before, the observation of minute but essential details. It is therefore useless to expect much from a short course of tuberculin. In fact it is wiser not to give any patient tuberculin until it has been fully explained to him, and until he agrees to continue the treatment for at least five or six months. In many instances tuberculin should be administered over much longer periods, a year or indeed fifteen months, and then after a period of intermission a second course should be begun.

In regard to any schemata for dosage, I would say that tuberculin cannot be given by rule of thumb, and he who has not the most profound respect for it will sooner or later come to grief. The usual method of giving tuberculin in the proportion of .1, .2, .3, .4, .5, .6, .7, .8 and .9 of the solution employed means a variation in the increase from 100% down to 11%. I first varied this by using the following scale: 1, 1.5, 2, 2.5, 3, 4, 5, 6, and 8; and then giving .1 of the next solution which is always 10 times the strength of the preceding. In this the increase varies frequently from 50% to 20%. Fewer reactions it seemed to me occurred with this rate of increase. More recently, however, Weber's law of sense percep-

tion has been taken note of, and a logarithmic scale was computed for us by the late Mr. E. G. Pope. I will pass around several copies of this scale and in it you will notice that in going from .1 to 1 ccm., or as I have noted it in the table, from 1 to 10, the increase, which is always in exactly the same proportion for each column, varies, of course, with the number of doses in each column, that is, from two to twelve doses. I have usually employed the column headed "6" where the rate of increase has been throughout about 50%. I may say that the rates of increase vary from about 300% in the column headed "2" to about 20% in the column headed "12."

Selection of patients. — The theory of the action of tuberculin plays an important part in the selection of patients for treatment. As far as we know to-day, tuberculin requires that certain properties of the cells must still be present. An antitoxin could not be found by Trudeau, Baldwin, and a number of capable observers, though more recently some men who have followed new lines of research have announced the discovery of an antitoxin in the cells. If tuberculin requires an active response on the part of the organism to produce any beneficial effect it is readily seen that it is useless to give tuberculin to patients who are so far advanced in the disease that the cells have lost all powers of resistance and fail to respond to any stimulation. Consequently, it is useless to give tuberculin to patients with acute types of the disease or to patients who fail to react to the toxins which we know must be present within their systems. The most probable theory for the explanation of the action of tuberculin is that it is an enzymogen which sets free in the body certain disintegration or digestion products of the tubercle bacillus which are stored in greater part in the cells near the seat of disease. This endotoxin produces the reaction which follows when a sufficient quantity of tuberculin has been given to a patient who is susceptible to its influence. More recently Wolff-Eisner has combated this view and believes that tuberculin owes its efficiency to the fact that it contains "splitter" products of the tubercle bacillus. You will remember that these fragments of the tubercle bacillus have been found by Spengler in sputum which apparently contained no definite tubercle bacilli. A tuberculous infection, at any time, Wolff-Eisner thinks, creates within the body certain bacteriolytic properties which may persist for years. When tuberculin is introduced into the organism in any way these bacteriolytins attack the minute bits of bacilli and set free the endogenous toxin which in turn produces both the local and the general reaction.

It has long been known that typhoid fever seems to exert some retarding influence upon the tuberculous process; at least we may say that it does not fan into activity a smouldering process. More recently it has been shown that the cutaneous and conjunctival tuberculin reactions are very likely to occur in patients recovering from typhoid fever. It is well known that a large amount of bacteriolytins must be present during

the convalescence from this disease, and it has been suggested that these bacteriolysins may in part attack the tubercle bacilli or may attack, if Wolff-Eisner be correct, the minute fragments of the tubercle bacilli which are contained in the tuberculin. From this it is seen that an overdose of tuberculin would set free more endotoxin than is required to stimulate the organism to the production of antibodies of any sort. It is also readily seen that where reaction to tuberculin is absent in far advanced cases it may be due either to failure on the part of the cell to react to tuberculin or to lack of bacteriolytic substances.

Tuberculin, Sahli believes, acts like digitalis in cardiac disease, and is not only a specific, but a functional therapeutic means which acts only in a definite way on the toxin susceptibility of the organism. It neutralizes, as it were, this susceptibility and so enables the natural healing powers of the body, which for a time have been unable to exert themselves on account of the toxin, to come into play.

However all this may be, it is certain that tuberculin should be administered therapeutically only to those patients whose general condition is good. Patients with elevated temperatures should rarely be given tuberculin unless the temperature seldom goes above 99.5° to 100° and is normal or subnormal in the morning. If the minimum rarely falls below 100° little can be hoped from tuberculin. A tendency to hemoptysis, slight dyspnea, a persistently rapid pulse, dry pleurisy existing for some time, are no contra-indications to the use of tuberculin but demand care in its administration. Slight complications need have little weight in the selection of patients, but all acute complications are contra-indications. Nephritis unless tuberculous is a contra-indication for most persons, but some patients with a few casts and slight albuminuria seem to do well under the treatment. Marked nervousness is, in my opinion, no contra-indication as tuberculin affords a mental leverage of great force to many nervous patients who can attribute to tuberculin instead of to the disease many symptoms or slight exacerbations which otherwise would cause great mental disturbance. Syphilis and valvular disease of the heart if always well compensated are not to be looked upon as contra-indications. Pregnancy is also no contra-indication. When signs of extensive softening and ulceration have occurred, it is wise to administer tuberculin in very small doses with very small increases, or to avoid its use altogether.

The duration of the disease has little bearing upon the selection of patients except that it is an indication for the use of tuberculin when patients have tried for some time other forms of treatment without benefit.

Selection of tuberculin.—The selection of tuberculin is a difficult subject. Many observers still believe that the old tuberculin gives as good results as any of the later modifications. It is, however, in its preparation subjected to considerable heat, and recent work with various toxins has led us to believe that heat above 60°

C. may in part, at least, destroy their efficiency. For this reason many have come to believe that the unheated products of the tubercle bacillus are to be preferred to those subjected to heat. Among the unheated products may be mentioned T. R., B. E., and Denys's tuberculin. The first two are really emulsions of the tubercle bacillus, the latter, as you know, the sterile filtered broth upon which the tubercle bacillus has grown and which probably owes whatever value it possesses to the fact that during the growth of the tubercle bacillus some have died and disintegrated in the medium. At present there is no proof forthcoming to show that the tubercle bacillus secretes any product during its growth. However this may be, excellent results have been obtained with the broth filtrate, or B. F. as it is known, and it is far easier to use because it is much less toxic. It is possible that it may contain some products that we have been unable to determine, and it appears to me, theoretically at least, that the best tuberculin for use would be an emulsion of tubercle bacilli in the broth filtrate. Our results at the Adirondack Cottage Sanitarium during the past year with B. F. have not been entirely satisfactory, and at present we are giving a number of patients this mixture. The mixture consists of equal parts of the ordinary .5% emulsion, known as B. E., and B. F. There are many interesting points in connection with the selection of tuberculin which I cannot go into, such as the fact which many observers have overlooked that the tubercle bacillus is already in the organism which we are striving to benefit. It is also known that man possesses comparatively good resistance against the tubercle bacillus, slight against the tubercle toxin. For this reason it might seem sufficient to immunize him against the toxin to render him capable of overcoming the tubercle bacillus. Whether the endotoxin of the tubercle bacillus is ever set free by any chemical processes, whether the old tuberculin represents the true endotoxin, are points that are still open for discussion, and the use of such a tuberculin as I have suggested seems to me to overcome both these difficulties.

Treatment during the administration of tuberculin.—Until recently, it was thought unwise to give tuberculin to any patient who was not constantly under a doctor's immediate supervision, in other words, who was not in a sanatorium or hospital. Recent practical results, however, have shown that this is not necessary, and furthermore, they have shown that ambulant patients and patients at work may be given tuberculin in carefully graded doses, so that not only no harm may accrue, but that the patient may derive great benefit. This means that the former rule that the patient should remain in bed or at rest in a reclining position the day of and the day following injection does not need to be enforced. I do feel, however, that where possible, patients should take less exercise the day after the injection of tuberculin. Rise of temperature to 100° for more than two hours necessitates, in my opinion, rest in bed during that day and the greater part of the next, or until the temperature becomes and

stays normal, though practically when accompanied by very slight symptoms the temperature is almost invariably normal the second day even if the patient does not remain in bed.

Many medicinal substances have been administered in conjunction with tuberculin, but seem of little value. Various toxins or secondary organisms have been suggested for use in connection with tuberculin but have yet to be thoroughly tested.

The effects of repeated doses of tuberculin upon the animal economy have not been thoroughly worked out. The weight seems to be little affected. Changes in the blood have been noted by a number of observers, but the results are still conflicting. I have mentioned the change in the phagocytizing power of the polymorphonuclear leucocytes.

The untoward results are very interesting, particularly in regard to the mobilization of the tubercle bacillus. Baldwin was unable to find any evidence that tuberculin, even in large doses, produces this effect. The work of Liebmman, who found many tubercle bacilli in the blood following tuberculin injections, has never been verified and I think can be discredited on account of faulty technic. The sputum and the urine are affected somewhat, but usually only following reactions. An antipyretic effect is unquestionably present in many patients.

The results obtained from tuberculin are exceedingly difficult to determine. It must not be forgotten that tuberculin is a powerful toxin, that if administered carelessly it may produce great and irreparable harm. The vast majority of men who have used tuberculin seem to be convinced that it has some beneficial effect. I myself am firmly convinced of this while I have some difficulty in proving from the results that I have obtained that a markedly beneficial effect is present. In fact, I think the present status of tuberculin may be expressed in a few words: Tuberculin when properly given does no harm, may produce no apparent immediate results, but may markedly benefit an individual patient who can follow at the same time the hygienic-dietetic treatment while in a health resort or at home and at rest. It may even prove of benefit to those who must continue at work. Small doses and careful increases are most important, and by following these very closely some patients, even in advanced stages, reap great benefit. The immediate and ultimate results of treatment are often improved, fewer relapses occur, and more patients lose the tubercle bacilli in their sputum.

RESEARCH WORK IN NUTRITION IN THE TROPICS.—Dr. Hans Aron, of Berlin, Germany, has been appointed professor of physiology in the Philippine Medical School, Manila. Dr. Aron will devote special attention to the question of tropical foods, and the Philippine administration has placed \$2,000 at his disposal for the purchase of laboratory apparatus.—*New York Medical Journal*.

PERMANENT STENOSIS OF THE DUCTUS COMMUNIS FROM INFLAMMATORY INFILTRATION OR CICATRICAL CONTRACTION OF A DUODENAL ULCER.

IMPLANTATION OF THE DUCT AT ANOTHER POINT IN THE DUODENUM. GASTRO-ENTEROSTOMY.

RECOVERY.

BY HORACE PACKARD, M.D., BOSTON,
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This case is deemed worthy of record because of the complexity of symptoms presented, the remarkably complicated pathological conditions exposed on exploratory incision and the equally remarkable recuperative power exhibited by the patient in the convalescence.

In February, 1907, I was summoned in consultation by Dr. O. R. Chadwell over a case of very profound icterus. The patient was a man of medium height, spare in his build, sedentary in his habits, engaged in intellectual pursuits and with very pronounced ideas on food and nutrition—a vegetarian. His frugality had been carried to such an extent that he, at times for considerable periods, partook of nothing in the way of nutriment but nuts and raisins. His first attack of jaundice occurred about three years prior to my relation with his case. Under treatment this had cleared up and in the intervening time up to the present illness he had pursued his usual routine of life.

One month ago he had again become jaundiced coincident with an attack of grippe; the stools became clayey and the urine very dark. He had pain in the epigastrium and right hypochondrium, chills and one attack of nausea. No subscapular pain. The stools later had become very black and were still so.

Physical examination disclosed general icterus of the highest degree of intensity; emaciation; heart and lungs normal; abdomen flat and of normal percussion note, except in the right hypochondrium where an elongated oval smooth tumor could be easily detected on palpation, extending from the region of the eighth costal cartilage to below the level of the umbilicus. The tumor was evidently the gall bladder, enormously distended, such as is not infrequently met as a result of plugging of the cystic duct by a gallstone. So profound icterus, however, could hardly be explained by such a physical condition, therefore it was assumed that there must be some pathological condition in the common duct which had brought about complete obstruction to the overflow of bile. The most plausible theory was plugging by a biliary calculus. At the same time there was the disquieting fact of intensely black stools which could be accounted for in no other way than by the escape of blood into the intestinal tract. Accepting this theory the question then arose, What causes such escape of blood, and has the well-known hemophilic tendency of the icteric state anything to do with it? There had been no symptoms indicative of ulcer of the stomach. There was no history of black stools prior to the attacks of jaundice, and as far as I could learn, no