How far we may safely go, how nearly we may venture to approach totality of extirpation of an acromegalic adenoma, time and experience only will tell.

We know from clinical experience, just as we have learned from the canine experiments of Camus and Roussy, of Bailey and Bremer, and from the experiences of Smith with the rat, that serious consequences ensue upon damage to the hypothalamic centre. It is a region to be shunned lest diabetes insipidus, excessive adiposity, and even a fatal cachexia supervene. It is for this reason that operations for the congenital suprasellar cysts I have spoken of are particularly difficult and hazardous. On the other hand, transphenoidal operations from below are even more blind, and there is the added risk of a cerebro-spinal rhinorrhoea and infection. Sometimes one, sometimes the other route is preferable. I am not here to plead for either, for this is a side issue on which surgeons, given time, will come to an agreement.

We have seen that there are an enormous number of secondary factors to be considered, which lie quite apart from the mere tumour and its pressure effects. That the hypophysis is primarily concerned with growth the brilliant studies of Evans and Smith that I have quoted leave unquestioned. No less definitely do these experiments show that it is an activator of the reproductive organs. Nature has provided that neither the pathological giant nor dwarf should reproduce his kind. These states, which necessarily originate in pre-adolescence, are represented by corresponding ones which set in later in life when normal skeletal growth has been attained. In these circumstances, too, for different causes apparently in the counterposed states of hypophyseal overaction and underaction, the functions essential to reproduction are interfered with. But this is only the beginning of a long sequence of alterations in other glands, affecting the thyroid and pancreatic islets in ways we partly understand, the parathyroids, adrenal cortex, and the rest in ways we do not.

Lastly, and not the least important, are the final stages in the two conditions of glandular insufficiency and overactivity: on the one hand the tissues atrophy with resultant senility and cachexia; on the other hand, splanchnomegaly and tissue hypertrophies are produced which, as in the case of the heart, lead to equally dire consequences. The surgeon who would operate on acromegaly must avoid the Scylla of the former in dodging the Charybdis of the latter. Not until some practical form of substitution therapy is at his call will he properly run the risk of overdoing his extirpation, for a daily homoplastic transplant so strikingly effective in the hypopituitary rat is out of his reach.

I have attempted in this address to bring some order out of the therapeutic chaos which envelops the subject of the pituitary disorders. Whether I have succeeded does not particularly matter. Order will some day come, and the best that can be done in the circumstances is to give hints in that direction. Hints, after all, may serve a useful purpose. Did not Lettsom so entitle as "Hints, Designed to Promote Beneficence, Temperance and Medical Science," a three-volume series of his suggestive articles? I was encouraged in the preparation of this address by one of his paragraphs, written on June 23rd, 1773, proposing the establishment of this Medical Society.

Many useful facts [he says] are lost from the want of a proper opportunity of conveying them to the world; and though, when considered separately, they might not be of sufficient importance to claim the attention of the publick; yet when a number of them may be collected together, they may become highly deserving of notice. To such facts, when properly authenticated, the Society will always be particularly attentive.

And so, in respect to the memory of that industrious, successful, and many-sided man, your founder, if I shall have given for your guidance the latitude and longitude of this "Little Vandyke" of Medicine, the pituitary body, somewhat more precisely, I shall be well content.

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THE RATIONAL BASIS FOR TUBERCULIN THERAPY.

BY

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Now that we begin to understand the part played by the allergic inflammatory reaction in the healing of tubercle, tuberculin, which possesses the power of stimulating this reaction, should come again to the fore as an important therapeutic measure.

It is now nearly forty years since Koch¹ announced to the world that he had discovered a "lymph" which possessed curative powers in tuberculosis. After the furore which followed the announcement had passed it was generally believed that the lymph had failed, but certain observers saw hope, for results were not uniformly bad. Healing did occur in certain instances. Members of the small group which was favourably impressed continued their studies and observations. Koch, while disappointed, did not despair. He knew that in the difference in reaction of animals toward first infection and reinfection lay the basis for a specific therapy for tuberculosis; and its attainment was of such great moment to a world which was yielding up one-seventh or more of its population to this disease that he persisted in his search in spite of all opposition.

Tuberculosis Healed by Allergic Inflammatory Reaction.

It is well to recall the observation which caused Koch to believe in the possibility of a specific cure for tuberculosis. It follows his description of the difference in reaction of animals to first and successive inoculations of bacilli, either dead or living, as follows:²

"After I had observed this particular fact I investigated it under every conceivable condition, and finally proved that dead cultures of tubercle bacilli rubbed up and mixed with water could be injected under the skin of healthy guinea-pigs in large doses without any effect beyond a local necrosis. (Those injections which were free from living bacilli were the simplest and surest means of producing necrosis.) Tuberculous guinea-pigs, on the other hand, were killed by the injection of relatively small quantities of such killed cultures, in from six to forty-eight hours, according to the size of the injection. A dose insufficient to kill the animal might produce an extensive necrosis of the skin at the point of inoculation. If the emulsion was diluted so that it was only slightly opaque then the animal remained alive, and if the injections were repeated with intervals of one or two days a marked improvement in the condition took place; the ulcer at the site of inoculation became smaller and finally healed, a thing which never occurred without such treatment. The swollen lymph glands became smaller; the state of nutrition improved; and if the disease process was not too far advanced and the animal was not losing strength too rapidly, a state of quiescence ensued. In these observations there is found a basis for a cure for tuberculosis."

The important part of this observation is that if the dose was sufficiently small, and if repeated at two- or three-day intervals, the animal not only remained alive but showed improvement. The ulcer at the site of inoculation healed—"a thing which never occurred without such treatment."

The fact that tuberculosis heals itself by inflammation occurring as a result of allergic reaction called out by bacilli escaping from foci already existing within the host or from infections coming from without is now universally recognized.³ In natural infection immunity is built up by repeated reinoculations of bacilli, the source usually being the original focus or some successive focus produced from it. Immunity is built up in experimental animals by repeated inoculations with small numbers of bacilli, always short of the number necessary to cause uncontrollable infections. Each infection that is overcome leaves the host with an increased resistance to future infections. Stimulation of unhealed foci previously existing is a part of the reaction following reinfection. It also follows the injection of bacillary protein. Uhthoff⁴ reported ten cases of ocular tuberculosis treated by old tuberculin, when large doses were being used. He started with 0.5 or 1 mg. He produced violent focal and general reactions, and even noted a spread of the disease in three instances, but all

ended in healing. Königshofer and Maschke also reported a case of corneal tuberculosis which healed after one violent focal reaction. The same tendency to heal following reactions is seen in foci existing in parts of the same lung distant from the site of a reinfection or in the opposite lung, or in the larynx, glands, testicle, or other organ. While these reactions give the picture of acute inflammation, they are a part of the allergic response. Focal reactions caused by reinfection and the injection of tuberculin seem to be identical.

Caseation and Fibrosis: Acuteness and Chronicity.

Two distinct processes go on side by side in tubercle: caseation in the centre, and fibrosis at the periphery. These occur in both primary and secondary tubercle. When fibrosis predominates healing results. Even caseous tubercle often heals by an encapsulating fibrosis encroaching upon the tubercle and penetrating toward the centre of the caseous mass. The allergic reaction, according to its severity, varies between two distinct effects—proliferative and destructive. In most distinguishable reactions evidence of both is present. Slight reactions show a predominance of the proliferative or productive effects, and severe ones of destructive effects. The acuteness or chronicity of the tuberculous process depends on the relative predominance of these phenomena, as has been so well described by Aschoff.⁵

"The manner and course of the process varies between two extremes of reaction with numerous transition forms. On the one hand, one has to deal with marked chronic cases with a definite tendency to healing in the individual foci. . . . Here the productive character of the reaction characterized by the occurrence of granulation tissue with its histocytic elements (the so-called epithelioid cells), the giant cells, lymphocytes, and plasma-cells, predominates. This avascular tissue caseates slowly. It either becomes surrounded by a hyaline ring, or else goes over to a specific hyaline scar, without caseation. Such a productive reaction is to a certain extent characteristic of a special state of tissue immunity, and is a token of increased resistance. On the other hand, there are cases which run a more acute or subacute course following reinfection. Here, within the respiratory passages, the characteristic exudative reaction is mostly in evidence. This consists of large exudative cells (alveolar epithelium, wandering histocytes) and a marked amount of fibrin containing varying numbers of leucocytes, which has a tendency to rapid caseation and softening. Encapsulation and healing meet with difficulties. The exudative reaction is a sign of lowered resistance, a rapidly progressive destruction."

The important fact is that chronic tuberculosis, which is accompanied by marked immunity of the host, is characterized by repeated slight reactions due to repeated new infections of small numbers of bacilli, in which production of new tissue predominates; and furthermore, that these same phenomena characterize slight tuberculin reactions. They are usually so slight that they are not even accompanied by elevation of temperature. Acute active tuberculosis, on the other hand, which is characteristic of relatively low immunity, is produced by repeated inoculations of large numbers of bacilli and is characterized by a markedly exudative process with caseation and necrosis. This same type of severe reaction is found when tuberculin is administered in very large doses. In other words, small doses of bacilli or tuberculin in the tuberculous animal or man stimulate fibrosis and favour chronicity, while large doses of bacilli or large doses of tuberculin, particularly if often repeated, favour caseation, necrosis, and acuteness.

Tuberculin possesses Immunizing Properties similar to Bacilli.

Tuberculin, when introduced into the tissues, has at least some of the properties of living and dead bacilli. Both living and dead bacilli will cause histologic tubercle, which is a non-specific tissue response; both will create an immunity response in the host; and both will call forth an allergic reaction favourable to healing in an individual, animal or man, who is already infected. Certain experiments seem to indicate that tuberculin possesses all of these properties, though the first two in very slight degree. It has recently been shown that tuberculin will produce histologic tubercle,⁶ although previously this had always been denied. Certain preparations containing the bacillary wax might easily do so. Immunity has also been reported as having been produced by tuberculo-protein in non-tuberculous animals, although it is of slight degree and

evanescent. But tuberculo-protein will call forth the specific allergic reaction in tuberculous individuals, increase the existing immunity, and promote healing in a manner similar to living or dead bacilli. Herein lies its claim as a therapeutic measure.

We cannot separate tubercle from the allergic reaction, because this immunity response begins as soon as infection is well established. Skin sensitiveness, which is an indication of the presence of allergy, begins to show shortly after inoculation, and is well established in from three to five weeks, according to the severity of the infection, being shorter in severe and longer in mild infections. While it is possible for the body to wall off and encapsulate particles of inanimate substances and hold them imprisoned indefinitely, it is questionable whether it could encapsulate and retain permanently viable tubercle bacilli without the aid of the specific cellular response. Allergy is established only in response to tubercle bacilli and their products. We accept it as a measure of the patient's resistance, and note that it is increased by repeated infections provided they are of such size that the host can manage to bring them to a state of quiescence. Reports from the Saranac Laboratory are in harmony with others on this point, as follows⁷:

"A long series of unpublished experiments from the Saranac Laboratory and the experience of many other observers indicate that reinfected animals live at least twice as long as those receiving only one inoculation."

If the host is able to overcome a very severe reinfection, his allergy or immunity is correspondingly greatly increased. Aschoff⁸ says:

"The more markedly chronic phthisis of an organ develops in connexion with the generalization period, and the longer it exists, granting the presence of a sufficient amount of resistance in the individual, the more thorough will be the immunization and the more difficult it will be for the exogenous infection to engraft itself upon the lungs, or, if it occurs, the less rapid will be its progress. Should the individual skip the generalization stage, or the metastatic spread come to a rapid termination, then the immunization process will be broken off prematurely. The reinfection will take hold more readily and will lead more quickly to a progressive chronic phthisis."

It is estimated by Aschoff that about 40 per cent. of primary infections heal completely and protect the individual from further infection. The remaining 60 per cent. have reinfections. Aschoff is so convinced of the necessity of establishing immunity through infection in order to protect the child and then to heal it through allergic reaction that he suggests⁹:

"Absolute prophylaxis against infantile infection will be desirable, then, only when we shall be able to replace the naturally induced immunity by an artificial one, or else completely get rid of the most serious infection of later life. It would be well worth while in our battle against phthisis if we could at least induce a limited artificial infection on top of the primary infection, and thus dam back the metastasizing process."

While such a suggestion does not seem practicable just now, yet it may not be so far off. The immunization of infants by living non-virulent bacilli, as carried out by Calmette, brings the probability of such a course nearer.

The time to cure tuberculosis is when the lesion is small. The 60 per cent. of tuberculous individuals who show reinfection because their primary focus fails to heal deserve careful attention in the programme for the prevention and cure of tuberculous disease. Every such case must be looked upon as a potentially active clinical tuberculosis. What prevents such an outcome in any of this group is that reinfection in certain instances builds up a protective mechanism to such a degree that exogenous infection is barred. The allergic property of the cells encapsulating existing foci is stimulated, sealing up the patient's own bacilli and preventing them from becoming a further menace. Small doses of bacilli repeated at not too short intervals will do this; but, so far, we can only depend on the accident of natural reinfection, which too often proves unreliable by producing a spreading disease which does not stop until beyond bounds.

Tuberculin has the property of utilizing the allergic reaction in healing. It will stimulate the defensive inflammatory response and aid in walling off infection. It is in these early cases of failure to heal that tuberculin is especially valuable. I have treated many of the children of parents who have been under my care during the past

twenty-five years. I have found that tuberculin has been able to produce just the effect that Aschoff speaks of as being so desirable. Children up to the age of 10 or 12 years respond readily to tuberculin, and even those who show evidence of more than average infection respond more readily when it is added to other measures for relief.

Needless to say, the ideal cases of tuberculosis for tuberculin treatment are the same as for any other form of treatment—those with limited areas of involvement in which fibrosis predominates. The exudative type is not so favourable for treatment, but need not be excluded. In many a patient suffering from the exudative type of tuberculosis its character can be changed, so that fibrosis becomes the dominant characteristic; and just as small reinoculations produce this effect in the natural course of the disease, so can small doses of tuberculin aid in establishing the same result if injected at not too short intervals.

It has long been recognized, even by those who are not particularly inclined to use tuberculin, that patients in whom the healing process has come to a standstill are often helped by tuberculin. Many curable cases of tuberculosis can secure sufficient stimulation of their immunizing forces to produce healing without any artificial or therapeutic aid. The reactions produced by their own reinfections are sufficient. But Nature sometimes fails, and it is often highly desirable that the allergic reaction should be still further invoked in order to bring about focal response. Stimulation of the allergic reaction can only result regularly from reinoculations of bacilli, or from the administration of dead bacilli or bacillary protein. Therefore in all instances when further allergic reactions are desirable to complete encapsulation of foci, tuberculin may be used advantageously. Those who follow out a satisfactory treatment including tuberculin secure a larger percentage of favourable results with fewer relapses than those who omit tuberculin from their treatment. This fact should be inferred because of the specific power which resides in tuberculin when properly administered to stimulate fibrosis.

In its property of fortifying an already established immunity and utilizing the allergic response in the formation of fibrosis lies the main claim for the therapeutic value of tuberculin. This, however, is not its only property. When employed improperly it has the property of favouring caseation and necrosis in a tissue which is already prone to take on these changes. This is what many clinicians fear, but such fear is displaced by experience. It is now plain that reinfections caused by small numbers of tubercle bacilli, which occur at not too frequent intervals, increase immunity and favour healing by producing an encapsulating fibrosis; and that reinfections caused by large numbers of tubercle bacilli, particularly if repeated at too frequent intervals, depress immunity and favour the spread of the disease by producing necrosis and softening of caseous foci. This is identical with the effects of small and large doses of tuberculin. Small doses of tuberculin may produce no reaction at all in the tuberculous focus; larger ones may cause only a slight hyperaemia about the periphery of the tubercle with the exudation of a few cells and the formation of fibrous tissue. Still larger ones produce more pronounced effects; and very large ones cause marked exudation with softening of the caseating foci.

There is nothing in this to frighten a trained physician. It simply emphasizes the necessity of learning how to use tuberculin so as to obtain the healing effects and avoid the destructive action.¹⁰ I can speak from an experience extending over thirty years, including the treatment of several thousand patients, and wish to emphasize the fact that it is possible to obtain the fibrosis-producing effects and avoid those which cause necrosis. Rarely do we get a temperature reaction of more than 100° during the entire treatment of a patient extending over a period of months; yet we secure the beneficial focal effects necessary to promote healing.

The danger from reactions is very much exaggerated in the minds of many. Only such reactions as greatly depress the patient's immunity are harmful. The patient's reinfections frequently give temperatures up to 100° or 101°, lasting four or five days, with no ill effect following;

and, as Aschoff says, the larger reinfections, if they are overcome by the patient, leave him with his immunity very much increased. Our attitude toward tuberculin reaction should be governed by what we know of the reactions caused by natural reinfection. Since the patient can build up a high state of immunity by repeated reinfections, so small as not to disturb the temperature curve, or cause other constitutional effects, and can also by such slight reactions build up a fibrous wall sufficiently strong to encapsulate his bacilli, we should emulate this natural method in our administration of tuberculin. This does not mean that we should have fear of an occasional focal reaction accompanied by temperature elevation. On the contrary, healing is often hastened by such an allergic response. We should, however, always endeavour to avoid severe repeated reactions.

Rise of temperature and constitutional symptoms are not necessary to focal reaction. Sometimes general response may be suspected by feelings of increased nervousness following the injection; but this must be definite, for patients are prone to blame the injections for every uncomfortable feeling that comes to them. Increased cough and expectoration is usually present short of temperature elevation, and by this the clinician may know that he is securing desired focal effects. Focal reactions are desirable, but severe focal reactions are unnecessary and usually to be avoided.

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CARBOLIC SATURATION IN THE TREATMENT OF CERTAIN TYPES OF STREPTOCOCCAL BLOOD INFECTION.*

BY

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THE object of this communication is to draw attention to the clinical possibility of introducing carbolic acid into the body in such large amounts that the growth of streptococci in the circulating fluids is thereby arrested, and the patient cured. In my hands this method has proved efficacious in streptococcal infections after scarlet fever, and those accompanying rheumatic fever, as well as other types of infection, and my experience leads me to hope that on a more extended trial it will be found that by its use the treatment of endocarditis, which is liable to accompany rheumatic fever, may be brought completely under control and robbed of all its power of mischief.

The treatment was first brought to my knowledge by the late Dr. William Carter of Liverpool about 1895, and consists in the administration of sodium sulphocarbolate in sufficiently large doses to give rise to the first symptoms of carbolic poisoning—namely, enfeeblement of muscular tone, general malaise, or a marked lowering of the temperature. The dose necessary to produce this degree of carbolic saturation is 20 to 25 grains every two hours, in the case of an adult, or an adolescent of 16 or more, and in the case of a child of 8 to 10 years a dose of 8 to 10 grains every two hours.

As this method of treatment, if it is to be both efficacious and safe, must be carried out with certain precautions, I give the following notes in the hope that it may be given

* Communication to the Association of Physicians meeting held at Newcastle-on-Tyne, May, 1926.