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Author: Grasset, E.

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Tubercle Endotoxoid in the Treatment of Tuberculosis.

E. GRASSET, M.D. (Geneva).
South African Institute for Medical Research.

Tubercle Endotoxoid contains in an atoxic form, the water-soluble proteinic and lipid antigenic fractions extracted from selected strains of Tubercle Bacillus by a freezing process.

In its original toxic form, this antigen, when injected intradermally in high dilutions (1 c.c. of 1:10,000,000 solution), into sensitised animals and tuberculous persons, produces local and systemic reactions of a toxic and allergic nature.

After detoxication with formalin for a period of six weeks at incubator temperature (in the presence of a hydrolyzed peptic medium which enhances detoxication), the resulting product is well tolerated, and can be injected into the same tuberculous persons, in doses up to 1 and 2 c.c. without producing any toxic symptoms or sensitising phenomena.

Our first clinical applications of Tubercle Endotoxoid, in the treatment of Tuberculosis, were started in 1935 on 50 tuberculous Natives at the W.N.I.A. Hospital, under the supervision of Dr. A. Girdwood.

Clinical diagnosis was confirmed in every case by radiographs and repeated finding of tuberculous bacilli in the sputum. All the patients showed acute pulmonary lesions, either unilateral or bilateral. Some were complicated with pleurisy or acute tuberculous peritonitis.

This first series showed the innocuity of the method, and the beneficial influence on the evolution of tuberculous infection.

The influence of the treatment was demonstrated in a large proportion of these patients by a gradual fall in temperature, improvement in general condition, and increase in weight. After four months of treatment (maximum time limit, after which patients are considered fit to travel and have the right to be repatriated), 34 per cent of the patients had sputum free of tuberculous bacilli.

Following these first clinical investigations, Tubercle Endotoxoid was used in several series of treatment, including both Europeans and Natives, in eight official hospitals and anti-tuberculous institutions in South Africa. A detailed account of the results of treatment with Tubercle Endotoxoid in 242 patients during the period 1935-38 has been published in "Tubercle" (Grassett 1939) (1).

Since this time several hundreds of tuberculous cases, comprising a variety of forms and organic conditions, such as pulmonary, peritoneal, intestinal, urinogenital, bone, skin, glandular, and ocular have been submitted to endotoxoid treatment under the supervision of tuberculous specialists in 24 civilian and military hospitals, chiefly in Africa.

From the scientific point of view, clinical studies in Native patients are the most interesting. The acute, uncomplicated form of tuberculosis, the rapid evolution of the tuberculous affection among a large proportion of this "primitive stock," constitutes the most appropriate clinical material for studying the human response to a specific anti-tuberculous treatment. These investigations have been followed as much as possible from the clinical, radiological, bacteriological, and pathological view points.

**Dosage.**

Tubercle Endotoxoid is administered in bi-weekly subcutaneous injections, starting the first week with two injections of 0.05 cc. each, and the second week with two injections of 0.1 cc. each. The dose then increases by 0.1 cc. each week up to a maximum of 1.5 to 2 cc. This final dose should then be repeated twice a week for several months, and at least once a week where there are material difficulties, such as the problem of outpatients.

In the majority of cases, a very mild reaction, or none at all, follows the administration of Tubercle Endotoxoid.

In particularly allergic cases, a somewhat more marked local reaction may be observed, especially at the beginning of treatment. This may be accompanied by a slight rise in temperature up to 1 deg. during the day following injection. These reactions, of a benign allergic nature, usually disappear during the course of treatment, apparently by a process of desensitisation.

**Clinical and Radiological Changes Following Tubercle Endotoxoid Treatment.**

Regarding the clinical changes which are observed in patients treated with Tubercle Endotoxoid, the therapeutic action of this product manifests itself both at the site of the lesions and on the general condition. Clinically, as might be expected, no early dramatic change is noticeable.

In Native patients, the most frequent early change observed in many cases after only a few weeks of treatment, is stabilisation in weight, which after a continual drop remains stationary and soon begins to increase. Night sweats, often very profuse, are among the first symptoms to wane, and disappear within a few months.

In febrile patients, a gradual fall in temperature is observed which usually coincides with the regression of the acute toxæmic symptoms, with reduction in the pulse, and respiration rates. More important changes occur during the second and following months, these being reflected not only in the general condition, but in the functions of the affected organs.

Coughing attacks are generally minimised, accompanied by a reduction in the volume of spu- tum, followed by disappearance of the tubercle bacillus in more than 50–60 per cent. of Native cases, after a period of several months to over a year of treatment, according to the severity of the lesions when treatment was instituted.

**Radiological examinations** show in some cases appreciable changes after only two to three months' treatment.

In Natives with early pulmonary lesions, i.e., localised or diffuse moderate infiltration, a gradual
clearing of the lesions is observed, often with slight fibrotic reaction.

Subsequent X-rays, after six to twelve months, show only limited sclerotic reaction, or only increased pulmonary markings.

When the treatment is instituted at more advanced stages, as in patients with extensive infiltration, or nodular lesions, the first change observed is a sharper outline of the lesions, as compared with the previous diffuse motting, evidence of the clearing of the inflammatory process in the more recently infiltrated areas. Radiographs taken during the subsequent months show a gradual transformation of the rapidly spreading acute type of the infection into the chronic fibro-caseous, or fibrotic type of the adult European, a transformation, which under natural conditions is very rarely observed among Natives, more especially in so short a time.

This combined clearing fibrotic process is intensified during the following months of treatment, and results in a gradual reorganisation and final healing of the lesions. This restoration of the process is also observed in more advanced cases, where rapid casation, followed by a break-down of the lesions, results in early cavitation.

Cavities, which before treatment presented ill-defined and rugged outlines, show after a few months treatment, a more regular shape, with well-circled walls.

The gradual reduction in size of the cavities is followed in many cases of small and moderate-sized cavities, by their complete occlusion with fibrotic scars.

The whole occlusion and healing process is observed in certain patients in four to six months.

Where large and multiple cavities are observed a partial occlusion of the cavities is nevertheless often seen, with fibrotic reaction of the neighbouring tissue and drying up of the cavities.

This type of advanced lesion is not infrequently found as a unilateral condition in Natives (usually confluent tuberculous bronchopneumonia) or coinciding with early discreet infiltration in the other lung. Under the usual hospital treatment, such cases present a curative cure after dissemination of the infiltration to the other lung.

Tubercle Endotoxoid, administered in the absence of other treatment to a good number of these cases—advanced unilateral—has proved in many of them capable of favourably influencing the evolution of these severe forms. A transformation of the acute caseous and ulcerative lesions into a chronic form is observed, resulting in a massive fibro-caseous block with pachypleural reaction. When the infection has already spread to the opposite lung, we have often observed an actual clearing, or fibrotic healing of this early infiltration, whilst in other cases a considerable delay in the spread of existing infection.

Artificial pneumothorax in the absence of Tubercle Endotoxoid, applied to such severe unilateral Native cases as we have seen, has usually proved unable to prevent the further extension of infection to the other lung. Similar observations have been made and reported by several American authors regarding collapse therapy in American Negroes. Cutler, Rodgers, and Cippes (2) insist on the necessity of early collapse in Negro patients, delayed treatment having proved disastrous. Brock (3) also emphasises the limitation of artificial pneumothorax in Negroes to early cases. Fisher (4), although a believer in artificial pneumothorax, selects his Native pneumothorax cases with great care, avoiding acute, rapidly spreading cases, and choosing only those cases with a certain degree of chronicity.

In collaboration with our colleagues in several hospitals, Dr. Meyer of Rietfontein Hospital, Dr. Guiness and Dr. Salinger of Victoria Hospital, Lovedale, we have tried combined collapse therapy and Tubercle Endotoxoid on Native patients with pulmonary lesions at various stages of the infection. In rapidly spreading unilateral cases with cavitation, artificial pneumothorax was instituted only after several months of endotoxoid treatment. In the cases where collapse was then still possible—for in many cases extensive fibrotic adhesions following endotoxoid treatment, render these attempts impracticable—collapse therapy then appeared to be well tolerated and proved beneficial as a result of the increased specific resistance and anatomical transformation in the type of lesions resulting from endotoxoid treatment.

The same curative, healing process is found to extend to tuberculous lymph glands, associated with pulmonary lesions or preceding them. At X-ray examination they appear, chiefly in children, as big masses, bulging on the sides of the mediastinum. In contrast to this casation, usually observed in control Native cases, in endotoxoid treated cases these enlarged glands gradually become smaller, as evidenced by successive radiographs. They undergo a fibrotic hard transformation.

These changes are especially well evidenced in the case of Native tuberculous children showing besides tracheo-bronchial glands, other groups of lymph glands affected, and easily accessible to clinical examination, such as cervical and submaxillary glands. These enlarged tender glands after a few months endotoxoid treatment become much smaller, harder, and painless to palpation, whilst discharging sinuses become dry and are replaced by fibrotic scars. These healing changes are usually accompanied by a gradual improvement in the general condition of children, and a considerable increase in weight.

The healing characters of the organic changes observed in endotoxoid treated patients are of a lasting nature. In many cases subsequent X-rays, taken after discharge of patients, show further progress, either increased fibrosis, calcification in advanced lesions, or resorption of the moderate fibrotic reaction, in originally less severe cases.

One of the main practical difficulties encountered in the treatment of Natives is in persuading them to remain in hospital long enough to consolidate the acquired improvement. To remedy this state of affairs we have organised, in the case of urban Natives, an outpatient system by which adults, many of them working again, or children, may continue their course of bi-weekly, or weekly injections in the respective hospital wards in which they were treated. Further opportunities have thus been taken to make periodical X-ray, weight, and sputum examinations.
In several cases early signs of reactivity of lesions following too early a return to work, often combined with malnutrition or intercurrent disease, can be controlled in time, and at a new series of endotoxoid injections started.

From clinical data from a series of Natives treated with Tubercle Endotoxoid in several Rand Native hospitals, also the Victoria Hospital, Lovedale, over 70 per cent. of the pulmonary patients treated with endotoxoid derived benefit from the treatment and showed signs of fibrotic healing, or of sclerotic reaction at the end of the treatment, coinciding with 50 to 60 per cent. conversion from positive tuberculosis sputum to negative sputum.

The fact that such fibrotic changes can take place as a general healing process in tuberculous Natives is per se particularly interesting, and constitutes a new feature in the pathogeny of the tuberculosis infection in this "primitive stock," as such a process is only exceptionally observed among African Natives with acute forms of the infection, or remains limited to such an extent as to seldom influence the rapidly fatal course of the disease.

Following endotoxoid therapy, unexpected delays in the rapid spread of the infection, followed by definite regression, and partial healing of the lesions, have been observed in a number of advanced Native cases with bilateral extensive infiltration and caseation, or with the miliary type of tuberculosis.

Reference to some of these cases, details of which are to be found in a recent paper, dealing specially with Tubercle Endotoxoid treatment in Natives (American Review of Tuberculosis, Grasset, 1944), shows the radiological and anatomo-pathological changes observed in such cases. Microscopic sections from post mortem material from such cases, which are part of our investigations being carried out with Professor Strachan, and D. B. G. Hooykaas, Pathological Department of the Witwatersrand University Medical School, confirm the marked fibrotic changes observed in the lungs of such treated cases. Particularly interesting productive fibrotic changes have been observed in several cases of miliary pulmonary tuberculosis, who died after a delayed period up to 14 months after the beginning of Tubercle Endotoxoid treatment.

In contrast with the soft exudative caseous type of infection usually found in the lungs and spleen of untreated Native children, the lungs of endotoxoid treated Native children show milky tubercle nodules which have undergone fibrotic transformation in various degrees, i.e., from transitional nodules with infiltration of the tubercle follicles by fibroblasts from the periphery, to typical follicles which have undergone complete fibroreorganisation by fibroblasts. In the latter no more vestiges of the biological structure of the follicles nor of the giant cells can be traced.

Tubercle Endotoxoid Treatment in Extra-Pulmonary Forms of Tuberculosis.

A similar therapeutic action and healing process is observed in other tuberculous conditions in patients submitted to endotoxoid treatment such as laryngeal, peritoneal, uro-genital, bone, skin, and eye tuberculosis.

Bone Tuberculosis.—During the last six years we have treated a series of Natives in the Johannesburg hospital, both adults and children, suffering from hip, spine, and other bone and joint tuberculous infections. They were usually admitted at an advanced stage with extensive osteomyelitis, bone destruction, cold abscesses, and discharging sinuses.

In four Native children with progressive tuberculosis of the hip and trochanter, regression of the involvement and calcification was observed radiologically within a year of endotoxoid treatment, resulting in ankylosis of the hip, healing of sinuses and a return to a good general condition.

Such restorative processes are but exceptionally observed in tuberculous Natives not treated with endotoxoid, more especially in Native children undergoing conservative or surgical forms of treatment.

Similar beneficial results have been obtained in various tuberculous skin conditions, either lupus vulgaris or tuberculous ulcerations.

Eye Tuberculosis.—To conclude this short review we will mention the very satisfactory results obtained under the influence of Tubercle Endotoxoid in the treatment of various tuberculous eye infections, or ocular manifestations of tuberculosis. Such conditions are rather frequently seen among Natives, and lead in many cases to panophthalmitis and blindness.

Conditions treated included tuberculous iritis, keratitis, solerokeratitis, and also cases of haemorrhagic syndrome of the back of the eye, commonly known as Eale-Coats-Landau disease.

As observed in many cases treated in collaboration with ophthalmic surgeons of the Johannesburg hospital, a progressive improvement follows endotoxoid treatment in a great number of cases. Similar therapeutic results have been observed lately in a large series of Native cases treated at the W.N.L.A. hospital by Dr. Boschoff. The improvement can be observed in some cases as soon as three or four weeks after the first injection, and manifests itself by a regression of the inflammatory process, a gradual clearing of the plastic membranes and nodules, appeasement of the oculor symptoms, and gradual recovery of sight.

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