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Bacterial Allergy to Secondary Organisms in Pulmonary Tuberculosis.

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Although it has long been known that secondary organisms occur almost constantly in the lung sputum of cases of pulmonary tuberculosis, particularly in the advanced cases with cavity formation, the possible clinical significance of the presence of such organisms has received little attention; and the consensus of clinical opinion has been that they are of little or no importance.

As far as the author is aware, no attempt has previously been made to determine such significance from the standpoint of acquired allergy. Experience over a period of 2 years has shown: (1) Pulmonary tuberculosis patients are often allergic (skin sensitive) to such secondary organisms. (2) Such allergy is sometimes accompanied by cough and expectoration not referable to the tuberculous condition. (3) Desensitization of such patients is often followed by improvement in cough and expectoration with coincident improvement in sedimentation rate, blood count and clinical condition. (4) A group of organisms often implicated in this connection is the Neisseria gram negative cocci, previously overlooked or ignored in this connection.

Organisms of the Neisseria group in the order of frequency as isolated in our studies are: *Neisseria perflava*—a large majority; *Neisseria sicca; Neisseria flava; Neisseria catarrhalis* (one instance, patient was not sensitive); *Neisseria subflava* (this has not yet been isolated in any of our cases). Two cases have been found with a double infection with the perflava and the flava. In each instance the case was sensitive to both types.

Another gram negative coccus has been isolated which ferments only dextrose, but by other cultural reactions does not belong in this group. Three cases with this organism have been found. This apparently undescribed organism will be reported elsewhere.

The determination of allergic patients naturally falls into: (1)

*This investigation was initiated at the White Haven Sanatorium, White Haven, Pa., continued at the Trudeau Research Laboratories, Trudeau, New York, and at the National Variety Artists Lodge, Saranac Lake, N. Y.

Isolation of the secondary bacteria. (2) Preparation of a proper antigen. (3) Determination of the sensitiveness of the patient.

Isolation of secondary bacteria: A small portion of the mucopurulent lung sputum is washed through many changes of sterile salt solution, to remove contaminating mouth bacteria, and is then stroked over 2 consecutive plates of dextrose serum agar. A drop of sterile blood is often mixed with the sputum at the time of stroking. Dextrose is added about 0.01%, as it increases growth and facilitates the recognition of the gram negative cocci. At the end of 24 and 48 hours, the plates are examined, suspicious colonies fished to plain hormone agar slants, or if too crowded to fish pure, are fished and replated. The gram negative cocci are recognized by the glistening opalescent appearance of the colonies which may have a lemon yellow color. The usual flora is rather restricted. Nonhemolytic streptococci are almost always present. *Staphylococcus albus* and the *Micrococcus tetragenus* are common. In a majority of the cases studied, gram negative cocci have been present. We have never found a case sensitive to the *M. tetragenus* and seldom to the *Staphylococcus* or *Streptococcus,* although the latter is worth a trial in the failure of other organisms.

Preparation of the antigen: An emulsion of approximately one to two thousand million organisms per cc. is prepared in physiological salt solution. Some of these strains do not make good emulsions but break up perfectly after heating. The emulsions are transferred to 5 cc. ampul vials, the rubber stopper is tied in and the vial dropped in boiling water for 35 minutes. The use of such boiled antigen may seem theoretically inadvisable, but experience has shown that such boiled emulsions retain an antigenic factor which causes skin reactions in the sensitive patient and are therapeutically useful. This will be reported later.

Determination of sensitiveness: The patient is injected intradermally with 0.05 cc. of the heated antigen and observed during a course of 15 minutes and again at the end of 24 hours. Two reactions are possible, an immediate reaction in the first 15 minutes, characterized by a wheal surrounded by an area of erythema, a reaction similar to that elicited by horse serum or egg white in the sensitive patient. This reaction fades in the course of a few hours and may or may not be followed by a secondary reaction, resembling a tuberculin reaction, with a swollen red area from 2 to 5 cm. in diameter. At times, one reaction occurs without the other, but either seems to be an indication of general sensitiveness.

Assuming that the mucous membranes of the bronchial system are sensitive, it seems logical to assume that the presence of such organisms or their products in the lung sputum acts as an irritative factor, causing increased cough and excessive expectoration and that a proper desensitization would in a degree relieve such symptoms. This hypothesis has been borne out by clinical experience.

Desensitization: Owing to the clinical condition of most of the patients treated, it is important to avoid general reactions, and small doses frequently repeated are employed. The first subcutaneous dose is the same as the skin test dose, 0.05 cc. Injections are made every second day, if no reaction persists, raising the dose gradually to a maximum of 0.5 cc. to 0.75 cc. The interval is then increased to 4 days and the dosage held at this point. Treatment to continue 6 weeks to 2 months. If the treatment is to prove beneficial, improvement is usually apparent within 2 weeks. Disappointments are naturally encountered, but a sufficient number of patients are definitely benefited under such treatment to justify the labor and care involved.

Four such cases of many are cited in detail:

Case E. C. Chronic case with a progressive lesion and cavity, Gaffky IV. Very bad cough. Surgical interference contemplated. Sputum examination. *Streptococcus non hemolyticus* isolated. Vaccine prepared. Skin test. Moderate rather doubtful reaction. Vaccination over period 2 weeks. Patient worse. Vaccination stopped. Second sputum examination. *Neisseria perflava* isolated. Vaccine prepared. Skin test—immediate and marked reaction. Vaccination, followed by immediate and progressive improvement. Continued for 2 months. Cough and expectoration markedly diminished. Gaffky count decreased. Blood picture improved and a marked improvement in clinical condition. Skin reaction markedly diminished.

Case E. J. Very chronic case, cavities in both lungs, very ill. No improvement on 6 months' bed rest. Very annoying and racking cough. Sputum examination. *Neisseria sicca* isolated. Vaccine prepared. Skin test—marked reaction. Vaccination over a 3 months' period. Cough markedly diminished. Blood picture very much improved. Sedimentation rate steadily decreased. General condition improved. Skin reaction negative at this time.

Case G. D. Relapse in chronic tuberculosis. Both lungs affected. Cavitation on one side. Terrific racking cough causing vomiting. Sputum examination. *Neisseria perflava* isolated. Skin reaction to

N. perflava marked, both immediate and delayed. Vaccination over 3 months' period. After first week, cough progressively improved. Sputum raised with ease, amount lessened. This was followed by progressive improvement in clinical condition, in blood count and blood sedimentation. Gaffky count became negative. X-ray plates showed clearing. Second skin test at end of 4 months shows marked diminution of immediate reaction and disappearance of secondary reaction.

TABLE I.

No.	Case	Diagnosis All Pulmonary Cases	Organisms isolated and employed for vaccination	Results
1.	E.C.	Chronic tuberculosis cavitation	*N. perflava*	Markedly improved
2.	E.J.	Very chronic tuberculosis, cavitation both lungs	*N. sicca*	" "
3	G.D.	Relapse in chronic tuberculosis. Very severe cough	*N. perflava*	Immediate and progressive improvement
4.	M.S.	Relapse in chronic tuberculosis. Severe cough. Tenacious sputum	*N. sicca*	Immediate and progressive improvement
5.	F.D.	Chronic tuberculosis cavitation. Spread	*N. flava*	Marked improvement
6.	K.V.	Chronic tuberculosis	*N. perflava*	Improvement
7.	N.Q.	" "	" "	Slight but distinct improvement
8.	M.J.	" "	Unknown gram. Negative coccus	Improvement
9.	T.G.	" " Chronic myocarditis	*N. perflava*	"
10.	L.G.	Chronic tuberculosis	" "	Marked progressive improvement
11.	K.P.	Chronic tuberculosis. Violent cough, persistent blood streaking	Pneumococcus IV *N. perflava*	Marked improvement in cough. Bleeding stopped
12.	P.H.	Asthmatic symptoms following arrested tuberculosis	" "	Improvement
13.	P.M.	Asthma of long standing. Tuberculosis arrested	" "	"
14.	L.H.	Excessive expectoration. Asthmatic symptoms. Arrested tuberculosis	Unknown gram Negative coccus	No improvement
15.	L.G.	Thoracoplasty case. Persistent cough and expectoration	Unknown gram Negative coccus	" "
16.	D.A.	Purulent bronchitis	*Streptococcus non-hemolyticus*	Immediate improvement
17.	T.C.	Chronic bronchitis complicating a chronic sinus infection	*Streptococcus non-hemolyticus* *N. perflava*	Marked improvement

Case M. S. Relapse in chronic tuberculosis. Terrific cough due to extremely tenacious quality of sputum. *Neisseria sicca* isolated from sputum. Marked skin reaction. Immediate improvement in cough on vaccination due to change in character of sputum. Became more watery and less tenacious. Vaccination over 3 months. Progressive improvement and return to work. Skin test at end of this period. Reaction very slight.

In Table I are given briefly the findings and results in 17 cases, of which 11 were acutely ill of pulmonary tuberculosis at the time of treatment.

It may be argued that improvement in the cases cited is due not to desensitization but to an immunizing process, *i. e.,* the production of antibodies.

Against this view are the noted facts that the skin reaction diminishes in intensity, that the local reaction about the point of injection noted with the first few doses, quickly disappears, that if the interval between doses is too prolonged (from 5 to 7 days) the cough is apt to return, to be relieved promptly on the subsequent injection, and that overdosage in the first stages of the treatment may be followed by an exacerbation of symptoms, all point to the validity of the sensitization hypothesis and that a desensitization is the determining factor in the control of symptoms. Furthermore, animal experiments with the boiled antigens have shown that this antigen does not stimulate the production of antibodies except in a minor degree. This hypothesis of sensitization is no different from that assumed in cases of asthma, suffering from bacterial allergy.

The possibility of a non-specific effect must also be considered. In the first case cited, "E. C.", the patient was first vaccinated with a streptococcus, to which she was only mildly sensitive and with no benefit. A subsequent vaccination with an organism to which she was markedly sensitive was followed by immediate improvement. Several similar instances have occurred indicating a considerable degree at least of specificity.

Conclusions. Sufficient experience has been gained to demonstrate that: (1) Tuberculous patients are frequently allergic to secondary organisms present in the lung sputum. (2) Such organisms are often of the Neisseria group. (3) Desensitization of the allergic patient may be followed by marked improvement of the symptoms, cough and expectoration. This method in certain cases is a valuable adjuvant treatment in cases of pulmonary tuberculosis.