Bronchial obstructive reactions and Haemophilus influenzae
Zwan, Jan Cornelis van der

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Summary and Desiderata

The original aim of this study was to determine if type III allergic reactions, resulting from bacterial infections of the lower respiratory tract, contribute to the clinical picture in Chronic Non Specific Lung Disease (= CNSLD) (Fletcher, 1*).

In chapter I and II attention was focused on Haemophilus influenzae, being the most frequent bacterium found in the sputum of patients with CNSLD. Specific precipitins against Haemophilus influenzae were a feature of patients with CNSLD (Burns, I). This prompted us to study the occurrence of these precipitins in patients and controls and to see if this could be correlated with clinical, laboratory and bacteriological data. It had been shown, that increased cigarette consumption, increasing age, decrease in FEV₁ and bronchiectasis in patients with mucopurulent chronic bronchitis were correlated with a prevalence of specific precipitins against Haemophilus influenzae (May, I; Blackburn, I; Gregg, I; Burns, I). This study confirms these findings but shows that it is the presence of Haemophilus influenzae in the sputum, which determines the presence of serum precipitins to Haemophilus influenzae in our patients (table 8, p. 23).

The following question was asked in chapter III: could the presence of Haemophilus influenzae in the bronchial tree together with precipitins against it in our patients with CNSLD (p. 50) result in a type III allergic reaction as is seen in patients where Aspergillus fumigatus is present in the lung (Adrichem, I; Stevens, I). Inhalations of suspension with killed Haemophilus influenzae in patients with specific precipitins resulted in an early and late bronchial obstruction, the latter accompanied by malaise, rise in temperature and leucocytosis with eosinopenia. The inhalations were performed after informed consent of both patients and controls. Pretreatment by disodium cromoglycate did not inhibit the early reaction, suggesting that a type

* The numbers refer to the chapter where the reference can be found.
I allergic reaction was not involved. The late reaction was not inhibited by steroids. Controls without CNSLD and without specific precipitins however, showed a late reaction as well after inhalation of the bacteria. To explain this the presence of endotoxin was presumed.

Endotoxin was demonstrated in *Haemophilus influenzae* by the Limulus lysate test (Royas-Corona, IV) and the lethal effect in mice after specific potentiation with Actinomycin-D (Pieroni, III).

It was therefore suggested that an endotoxic activity might play a role as well in the afore mentioned bronchial reaction or that toxic activity was superimposed on a type III allergic reaction.

To be able to demonstrate if either endotoxin or specific precipitinogen in *Haemophilus influenzae* was responsible for the bronchial obstruction after inhalation of the killed bacteria it was necessary to purify the endotoxin as well as the specific precipitinogen. This procedure is described in chapter IV.

Endotoxin was extracted by means of a chloroform-aether-phenol procedure described by Galanos (IV).

The toxic properties of *Haemophilus influenzae* endotoxin were comparable with that of *E.coli* as measured in the Limulus Lysate test.

The precipitinogens, in which the protein characteristics are critical, were freed from endotoxin by ultracentrifugation and chromatographic procedures after ultrasonic disruption of the bacteria.

Inhalations of *Haemophilus influenzae*, endotoxin and purified precipitinogens in patients with CNSLD and controls are described in chapter V. *Haemophilus influenzae* inhalations induced a biphasic bronchial obstruction as was shown in chapter III, for patients with a hyperreactive bronchial tree.

Controls and patients with a normal histamine threshold however, had neither an early nor a late reaction. The late reaction however, was present in the provocation tests described in chapter III. This might be explained by the fact that in the latter experiments *Haemophilus influenzae* were grown on agar, whereas in chapter V the microorganisms were grown in Levinthal’s broth. A striking difference in the concentration of proteolytic activity was demonstrated in organisms obtained by these two culture methods. This activity had been assessed because biphasic bronchial obstruction had been described following inhalation of bacterial proteolytic enzymes (Pepys, I; Dijkman, I) and a similar effect had been presumed in the biphasic bronchial obstruction induced by *Haemophilus influenzae*. It may be that the high content of proteolytic activity contributes to the reactions described in chapter III and to the clinical picture in bacterial infections of the lower respiratory tract, when sufficient proteolytic activity is present.
Endotoxin causes an early and late bronchial obstruction in patients with 
CNSLD and a lowered histamine threshold. The late reaction is attended 
with malaise, fever and leucocytosis. The early and late reactions are not 
blocked by pretreatment with disodium cromoglycate or an anticholinergic 
drug. Pretreatment effects of steroids in this situation need to be determined 
before it becomes likely that endotoxin does not act as a precipitinogen.

Bronchial provocation with purified precipitinogens causes only a late 
bronchial obstruction with associated malaise, fever and leucocytosis in 
patients with CNSLD, who had a lowered histamine threshold and with spe-
cific precipitins in their serum. This reaction is blocked by pretreatment 
with inhaled steroids, suggesting a type III allergic reaction.

In conclusion bronchial obstructive reactions occur after inhalation of 
*Haemophilus influenzae* in absence of proteolytic activity in patients with 
CNSLD and a lowered histamine threshold in whom specific precipitins are 
demonstrated. It may be presumed, that the direct bronchial reaction is 
caused by its content of endotoxin, whereas the late bronchial reaction is the 
result of a toxic action and a type III allergic reaction.

Further studies should be performed to elucidate the mechanisms menti-
oned above.

Immunofluorescence of lung tissue and skin reactions using the compounds 
described above should be carried out in similar groups of patients as studied 
above to confirm the hypothesis of the presence of a type III allergic reaction.

The role of the proteolytic activity of *Haemophilus influenzae* in bronchial 
obstructive reactions has to be evaluated by assessment of the proteolytic 
activity of *Haemophilus influenzae* grown in the bronchial tree, purification 
of this compound and by using it in bronchial provocation tests. The action of 
endotoxin in the bronchial tree should be studied, for instance to see if endo-
toxic tolerance develops to small doses of endotoxin repeatedly administered 
at 24 hours. This might indicate that tolerance exists in those patients who 
have continuous large amounts of *Haemophilus influenzae* in their bronchial 
tree but no fever.

The conclusions of this study require bronchial provocation tests to be 
carried out in a larger number of patients.

Bronchial provocation of a part of the bronchial tree with the bacterial 
compounds is necessary to assess if the bronchial reactions provoked by an-
tigens inhaled in the whole bronchial tree, represent the reactions occurring 
during a bronchial infection, which is usually a more localized proces.