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INHALATION THERAPY USING BACTERIOPHAGES IN THERAPY-RESISTANT INFECTIONS

Fortschritte der biologischen Aerosol-Forschung-Jahren 1957-1961, pp 403-409

Dr. J. Hoeflmayr

In view of the growing resistance against antibiotics, it is vitally important that we try to find ways to counteract this development. The seriousness of the situation may be illustrated by the fact that we have had a definite increase in septic deaths since 1956; by comparison, we have noted a strong drop in deaths due to infections (20) especially between the years 1950 and 1955. In this connection we find that we often have viruses here which in the past very rarely were involved as pathogenic germs; here we have, for instance, Pyocyaneus or the staphylococci which in part -- perhaps as a result of adaptation or selection -- have developed absolute resistance against antibiotics in the course of time (6, 11, 12, 17). If we want to explain this situation somewhat further, we might mention the concept of hospitalism here. Hospitalism -- which our medical ancestors called hospital necrosis, has in practice been hardly ever encountered since the introduction of antiseptic and aseptic procedures. At a time when it is fashionable to offer all items of daily use in sterile and hygienic plastic packages, we are bound to feel that we have somehow failed in our efforts because we must now once again come back to this problem. Wellknown authors (7, 10, 15) just recently wrote about this again and pointed out the dangers which have caused many of our clinicians to worry. No one could really deny that the almost reckless use of antibiotics is mainly responsible for this and very often more or less renders us helpless in certain cases of illness. Farsighted clinicians warned us as long as 10 years ago, when we were still students, that we should not hastily treat any little infection with penicillin.

It is correct that hospitalism still plays a very minor role among independent doctors, thank God. According to past experience however there is hardly any doubt that this danger will spread from our clinics to the individual doctors.

If we should discover any new possibilities for treating infections, then we should look at these possibilities only from the angle that such a therapy would have to preclude the formation of resistance as much as possible. Therapy with bacteriophages fills ~~the requirement~~. The fact that this therapy has so far met with skepticism is due to the results which, until a few years ago, did not come up to expectations (19). If we try to track down the reason for the failure of the earlier bacteriophage theraphy, we will find that this was mostly due to the biological properties of the phages. The bacteriophage is a virus which can multiply only on a living cell, that is to say, on a bacterial cell. The cell which is thus hit is destroyed and the lysis of the bacterium again produces about 50 bacteriophages (1). Once

~~we~~ look at ~~them~~ this way, they ~~will~~ appear to be the best means for fighting bacterial infection, especially if ~~we~~ consider the circumstance that here -- in contrast to the antibiotics -- ~~we need not expect any~~ resistance. ~~Now~~ It is important to know that the bacteriophage has high specificity. Therefore, therapy can be effective only if the administered phage encounters its homologous bacterium.

The disadvantage of our earlier phage preparations was to be found not only in the inadequate breeding methods but above all in the fact that only about 1-2 phage strains were available. If we consider the large number of pathogenic bacteria strains, which play a role even in a very simple infection or which at least at times might play a role, then we would have to set up two requirements. First of all, in order to have a wide range of effectiveness, such a therapeutic substance would have to contain a large number of various phage strains. Second, it is necessary that phages which would come into consideration for therapy should have sufficient virulence with regard to pathogenic viruses.

We used the preparation (Diriphagen ®: Dr. Heinz Haury Chemical Plant, Munich) because we believed that this preparation met the requirements we just set up. According to information received, this preparation contains 180-200 different phage strains and thus has a broad spectrum of effectiveness. In addition, it also contains so-called aimed antimicrobics which act against those bacteria that reveal primary phage resistance. We might note here that both the phage components and the added microbics in every ampoule are standardized and meet the requirements for biological standardization as regards phage effect (18). If we mention the two therapeutic components, that is the bacteriphages and aimed (directed) antimicrobics, we are really not fully describing the effects mechanism as such. We have a third factor here. What we are dealing with here is the stimulation of the inherent defenses of the body which are bound to be aroused and which are based on the following: In breeding phages and antimicrobics, the pathogenic microbes used for this purpose give rise to lysates. But these lysates are not eliminated; instead they are also fed into the body. They act like antigens and lead to the formation of antibodies which in turn are specifically directed against the bacteria to which lysates were added (5). This reaction requires a latency period of about 8-10 days. The value of this antibody formation is hard to estimate in the individual case. We can get some specific figures on this only if we determine the phagocytosis capability; but this must be done in the clinic. Any new therapy is very often impaired by the fact that we do not employ it until other, more familiar measures have failed. We must admit that we did not use Deriphagen until we had some patients in whom other preparations had not produced success. This is further by reports from other authors who

achieved surprisingly good results with this preparation (2, 3, 4, 19).

As a matter of principle, any medication is to be administered in the form of an inhaled substance only if this form of treatment had definite advantages over other forms of administration (16). The advantage of aerosol treatment with a phage preparation is certain because, as we said before, these viruses develop their bacteriolytic aspect only in case of direct contact with the bacteria germs. This contact possibility does exist in case of tracheal and pulmonary illnesses, unless special pathological-anatomic obstacles obstruct the breathing. The main indication for aerosols are the bronchitis cases and chronic ones are prevalent here (14). They also represent the largest group among our 29 sickness cases on which I would like to report briefly here. (At this point I would like to thank my colleague Dr. Theobald in Ansbach for letting me use his data.) The patients were selected solely on the basis of the fact that earlier treatment had been without success in their case. Most of the patients were referred to me from other sources. Doctors had tried just about everything with these patients, starting with expectorating and secretolytic therapy and all the way to antibiotic therapy.

I would like to mention that our patients were subjected to bacteriological examination. It turned out that only one case revealed a light sputum finding. The expectoration of the other controlled patients was abundant and ranged all the way to massive with cocci. In about two thirds of the cases we had streptococci and in one third of the cases we had predominantly staphylococci cultures. I might also mention that of course all patients were given x-rays before and after treatment.

Aerosol treatment was administered every day. The duration of the individual sessions usually lasted 10-15 minutes. The average number of inhalations administered amounted to 11, the smallest number was 3 (this involved a subchronical tracheobronchitis), and the largest number was 40.

Figure 1 shows the result of our treatment. The first column shows the total number of all patients treated; then we have the number of patients cured which abounted to 55.1%; then we come to those who showed substantial improvement and on the right we have those patients who did not improve as a result of therapy. It might be interesting to note that we essentially achieved the same results as Huber (9), despite the fact that we had less patients to work with; Huber had published his findings with tetracyclin aerosols in children earlier. I shall come back to this later.

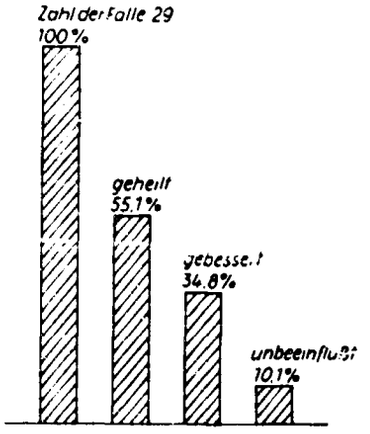

Figure 1. Clinical results with Diriphagen.
Key: (a) number of cases; (b) cured;
(c) improved; (d) no improvement.

Figure 2 shows the results of bacteriological examination. Here we note that the patients who were cured or who improved a great deal as well as the patients who just improved reveal exactly the opposite percentages with respect to the cases which we can consider as clinically cured or improved. In no case did we have expectoration which was completely free of viruses -- not even, as you can see, in the cases which turned out to have been clinically cured. And we do not get agreement even in the cases which did not show any improvement at all. It is interesting to note here that one woman patient with a hemorrhage bronchitis was listed in the column of patients who were not cured. But since the sputum culture was considerably reduced she had to be counted in the group of patients that had improved bacteriologically.

To what extent can we explain this discrepancy between the bacteriological and clinical reports? We know from treatment with penicillin inhalation that there are changes in the bacteriological sputum flora frequently though not always (14). Here we obviously have an elimination of the sensitive flora in favor of the more resistant germs. Now, whether this residual flora has a pathogenetic significance of its own, we could only tell from the further course of the illness. As far as our results are concerned, we would like to believe that, in the case of cured patients, we were dealing with viruses which do not have any pathogenic effect in vivo. The subsequent observation period of about 2 months seems to confirm this assumption. But only the bacteriologist can clear this up for us.

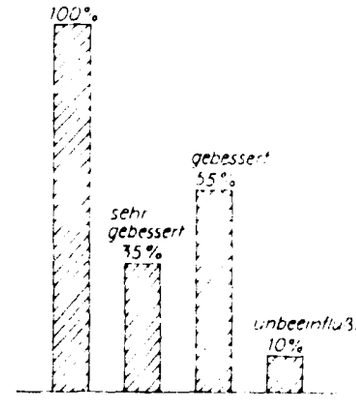

Figure 2. [illegible] results [illegible]
Key: (a) [illegible] (b) [illegible]
(c) [illegible] ent.

[illegible] proved [illegible] titute [illegible] result [illegible] of this [illegible] we do [illegible] that the [illegible] condition [illegible] bacteriol[illegible] [illegible] ; it was [illegible] getting [illegible] ent. [illegible] the cases th[illegible] [illegible] 10% which is quite reasonable when we consider the therapy resistance [illegible] the earlier treatment measures; here we are dealing with one case of asthmoid bronchitis, one case of bronchial bronchitis with bronchiectasis and one case of purulent bronchitis. We were not able to determine any regular, lawful relationship between the therapeutic tendency and the clinical picture. We were likewise unable to find any differences in regards the way the upper or lower respiratory tracts were affected. If we look at the patients (b) who were treated with tetracycline and if we make a comparison then we would, in addition to the numerical difference, [illegible] we realize that we actually treated only those cases which had resisted therapy earlier. Figure 2 shows the results of the two forms of treatment. Here we note the differences in the columns headed both "cured" and "improved." Therapy including tetracycline resulted in more cured cases but we achieved a higher percent[illegible] of improved cases. If we add up the two groups each time (see Figure [illegible]), we will find a difference which is just as insignificant as that in the column headed "unimproved." Bacteriological findings were not considered by Huber so that we cannot make any comparisons here.

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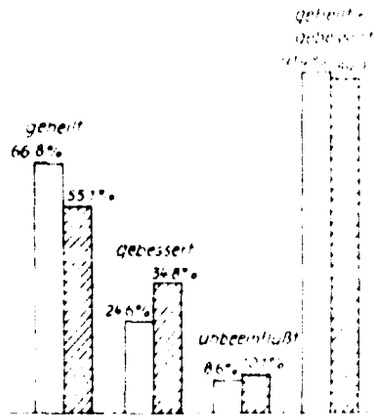

Figure 2. Comparison of results after tetracycline and Diriphagen treatment (tetracycline: white columns; Diriphagen: shaded columns).
Key: (a) cured; (b) improved; (c) no improvement; (d) cured and improved.

In the beginning, we aerosolized Diriphagen undiluted, following the first session, occasionally closer at subfebrile temperatures. We assume that we were dealing with a reaction to the decay products of the bacteria. This assumption is quite obvious after investigations on guinea pigs did not offer any indication for a sensitization through Diriphagen (3). Later on we used a dilution with physiological NaCl of up of 1:[illegible] and did not observe any more by-effects.

In conclusion I would like to say a word about the problem of the delimitation of the area of indications do not allow us to make any generally applicable conclusions. As regards our success in the treatment of the selected indication with Diriphagen, one might say that the preparation proved its worth. The value of antibiotics in acute and serious cases in which there is danger to life should not be talked down. In our opinion, bacteriophage therapy can give us a chance to meet the often raised and justified demand for a curtailment of the use of antibiotics in connection with certain indications. Here we would like to include the infectious bronchitis cases. We therefore think that it would be desirable for someone to check our results.

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