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FATAL CASES OF ALLERGIC CONSTITUTIONAL REACTIONS

With some Comments

By

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It cannot be denied that specific antiallergic treatment may give rise to undesirable side-effects, which may sometimes be extremely violent and even fatal in rare cases. Such unfortunate events sometimes caused specific desensitization to fall into discredit and to be considered by some authors as a dangerous form of treatment (8). However, in the course of time it was realized that a number of these tragic events were due to lack of knowledge, e.g. testing with too highly concentrated allergen extracts, or to the lack of adequate therapy of the side-effects. Gradually with experience in allergic diagnosis and therapy, the risk was reduced.

In the course of the past 3 or 4 years, however, 5 deaths have occurred in Scandinavia owing to specific antiallergic treatment, in all cases by experienced physicians with extensive knowledge of the clinical features of allergic diseases. When this can happen, there is every reason to attempt to find out the causes and—if possible—to take preventive measures.

CASE REPORTS

The five cases, four of which have been previously published, will be briefly reported here.

Case 1.—Previously published by O. Andrup (1).

A man, aged 37, who had had bronchial asthma from the age of 2 years. He said that he had been treated with an autogenous vaccine "several years ago". His past history suggested bacterial allergy. Cutaneous allergy could not be demonstrated. The Ecg. was normal.

He was treated with a bacterial vaccine 0.2 ml of a dilution 1:10 (= 100 million bacteria per ml). A week later the patient appeared with pronounced asthma; he was given 0.3 ml of a bacterial vaccine of the same dilution. 4 days later the patient was found dead in his room. He had not attended work for 2 days.

Autopsy showed no signs of violence. There was pronounced emphysema; in the myocardium an allergic reaction was revealed with increase of perivascular connective tissue, fibrinoid degeneration and cellular infiltrations resembling Aschoff's nodules.

The case was interpreted as a bacterial allergic response to the bacterial vaccine.

Case 2.—Previously published by E. W. Flensburg (5).

A 1-year-old child with bronchial asthma, treated with an autogenous vaccine. Following an injection of 13 million bacteria the patient developed coryza and cough. The same day the child was given another injection of 26 million bacteria; this caused a violent attack of asthma, which subsided gradually in the course of the next week. The third injection was given 14 days after the second. Though only a dose of 1.3 million bacteria was administered, the patient had a violent attack of asthma. A week later he received the fourth injection, a dose of only 1300 bacteria which nevertheless caused cough and wheezing. The fifth injection, 2600 bacteria, was given five days later and also gave rise to cough and wheezing. Four days later the sixth injection, also of 2600 bacteria, was given. 10 hours after this injection the patient developed a violent reaction, starting as asthma, but gradually passing on to a state of alternating motor unrest and shock-like exhaustion. The child slowly became worse and died 2 days after the sixth injection.

Autopsy showed bronchitis with scattered atelectatic and emphysematous areas in the lungs, but otherwise nothing abnormal.

Case 3.—Previously reported by O. Midttun (6).

A man, aged 37, who had had asthma since his boyhood. He gave a vigorous positive skin test to dust. While in hospital the patient was treated with rush-desensitization with an extract of house dust from his home. On the same day the patient tolerated injections of 0.10 and 0.20 ml of a concentration of 1:10. At 3 p.m. he was given an injection of 0.30 ml. About 1 minute after the injection he had a severe, constitutional allergic reaction. Adrenalin was administered both hypodermically and intracardially, but the patient died in 8 to 10 minutes with symptoms of asphyxiation.

Autopsy showed emphysema and enlargement of the right ventricle of the heart, but otherwise nothing abnormal, especially no emboli.

Case 4.—Previously published by Salén and Björnstjerna (7).

A boy, aged 13, with asthma and pronounced positive skin tests to horse scales and dog's hair, and also weak reactions to dust and raw milk. During a stay in hospital the patient was subjected to rush desensitization with extracts of horse scales and dog's hair from June 5th to the 20th. On June 20th the following doses were administered:—

At 8.30 a.m.	extract of horse scales 1:10	0.40 ml,
at 10.30 a.m.	„ „ dog's hair 1:100	0.70 ml,
at 1.00 p.m.	„ „ horse scales 1:10	0.60 ml.

The patient was observed half an hour after the last injection and stated that he was feeling well. At 3.15 p.m. he was seen playing with another patient. At 3.30 p.m. the patient came to his bed and lay down on all fours with violent coryza, dyspnoea and universal itching. During the next few minutes he became increasingly dyspnoeic; he was given 0.4 ml of a 1 per mille solution of adrenalin hypodermically and oxyphyllin intravenously, but nevertheless soon became unconscious and died within 15 minutes after the onset of the attack. Adrenalin was finally injected the heart, but without effect.

Autopsy showed acute dilatation of the lungs, bronchitis, inflammation of the bronchial walls with oedema and cellular infiltrates with numerous eosinophils. The mediastinum was normal.

Case 5.—Not previously published¹.

A man, aged 47, with bronchial asthma. He had a vigorous positive skin test to purified house dust, doubtful reactions to mould fungi and pollen, and negative reactions to dog's hair and feathers. In October, 1951, desensitization was instituted with extracts of purified house dust, and from February 1st, 1952, he received a maintenance dose of 1.0 ml of a 1:100 dilution once weekly. Except for slight local reactions the patient tolerated the first four maintenance injections without inconvenience. The fifth injection was given on February 20th, 1952. 8 or 9 minutes after the injections the patient felt sick, complaining especially of nausea. In the course of the next minute he became unconscious, pulseless, cyanotic, with involuntary evacuation of excreta. The patient had gone to the physician's lavatory, and had to be carried into the consulting room; he wore a woollen pull-over with very tight, long sleeves. It was difficult to deal with the unconscious patient and to have the tight sleeves tucked up over the

¹ My thanks are due to the University Institute of Forensic Medicine, Copenhagen, for permission to publish extracts of autopsy record E 8/52 of the institute, and to the patient's doctor for kindly informing me about the patient's history.

elbows. Compression was applied proximal to the site of injection, and adrenalin was administered both hypodermically and intravenously, but the patient died in a few minutes.

Legal autopsy, March 3rd, 1952, autopsy record E 8/52:—

Diagnosis: Anaphylactic shock?

Bronchial asthma.

Acute and chronic emphysema.

Bronchiectasis.

The lungs showed chronic emphysema and acute, bullous emphysema. All bronchi and bronchioles contained viscous mucus with moderate to considerable amounts of eosinophilic leukocytes. There was oedema of the alveoli, and this, too, contained copious amounts of eosinophilic leukocytes. The spleen was slightly enlarged, with proliferation of the reticulum and some eosinophilia. Otherwise the findings at autopsy were normal.

The ampule with house dust extract was sent for pharmacological examination and nothing abnormal was found.

COMMENTS

The five cases were pathogenetically identical. There can hardly be any doubt that the cause of death in all cases was allergic or anaphylactic. Aetiologically and clinically they can be divided into two groups: Cases 1 and 2 were caused by bacterial vaccines, and death did not occur until after a comparatively long latent period. Cases 3, 4 and 5 were caused by non-bacterial antigens, and death occurred from a few minutes to 2½ hours after the injection of antigen.

Case 1.—Details in this case are insufficient, and therefore a safe deduction can hardly be made. The probable conclusion that can be drawn is that another injection of bacterial vaccine should hardly be administered to a patient with bacterial allergy if the first injection has provoked an asthma attack (for details, see Case 2).

Case 2.—This patient's death was caused by a dose of vaccine which was only one ten-thousandth of a previous dose which had been tolerated. Flensburg considers that this suggests that the preceding injections may have caused further sensitization of the child. This is undoubtedly correct; but the proper explanation of the death must presumably be that a

bacterial-anaphylactic condition was produced in an organism with *bacterial allergy*, and that the patient died of anaphylactic shock. A sufficiently sharp distinction has hardly been made previously between the spontaneous occurrence of bacterial allergy and the "experimentally" (or therapeutically) produced anaphylactic reaction to bacteria.

Allergic conditions may occur with both proteins, carbohydrates, lipids and other substances as antigens; they occur spontaneously, and form antibodies which generally cannot be demonstrated *in vitro*. Anaphylactic conditions can only be produced by proteins; they do not occur spontaneously but only when, after a preceding sensitizing injection, the protein concerned is re-injected after a certain interval. The optimum of this is about 2 to 3 weeks, but may be either shorter or longer. In anaphylactic conditions, antibodies demonstrable *in vitro* generally are present.

In Case 2 a fortnight passed between the second and the third injection; this is sufficient to induce anaphylaxis in the patient. If the bacterial-allergic conditions are thought to be due to allergy to the carbohydrates of the bacteria, it is not improbable that bacterial vaccines in certain circumstances (too long intervals between the injections) may produce quite a different form of hypersensitiveness, a protein anaphylaxis. This is the probable explanation of the patient's death in Case 2 of an injection which was only ten-thousandth of a previous dose of antigen that had been tolerated. Therefore it may not be a case of increased sensitization to the original allergen but one of induced anaphylaxis to bacterial proteins.

The conclusion to be drawn from this is therefore that in treatment with bacterial vaccines the intervals between the injections should not exceed from 5 to 7 days, and might even be reduced to from 3 to 5 days. If an injection is followed by a sufficiently pronounced systemic reaction, i.e. asthma, Quincke's oedema, universal urticaria or collapse, the treatment with vaccine should be discontinued and not resumed for the first 3 to 6 months. Discontinuance for a period of from 3 to 6 months is recommended here because it is known that

anaphylactic sensitization in animal experiments is most pronounced between the 20th and the 60th day, and because it is known from experience that inoculation against common colds can be repeated without any risk at intervals of 6 months.

The last three cases were of different nature; these were forms of allergy of spontaneous occurrence to house dust from the patient's home, animal hair, and house dust respectively.

Case 3.—Midttun pointed out himself that the probable cause of death in this case was intravenous injection of antigen and, as the shock occurred within a minute after the injection, this view can presumably be accepted.

Case 4.—This patient was closely observed for 30 minutes after the last injection of antigen had been given. He had then been feeling well for $2\frac{1}{4}$ hours, after which he died in a state exactly corresponding to experimentally produced anaphylactic shock in guinea-pigs. It cannot be denied that an observation of this nature is rather discouraging and inexplicable, but several factors have undoubtedly been involved. First and foremost there may be a cumulative effect. Even though Salén & Björnstjerna do not attach great importance to this, it cannot be denied that the patient had received on the same day three injections of a very concentrated antigen, and according to Cohen & Rudolph (3) the pollen antigen is present in the blood as late as 48 hours after a pollen injection. It is therefore probable that the three injections of closely related antigens may have had a cumulative effect. The conclusion is that it is best to give desensitizing injections at intervals of a couple of days, and that rush desensitization, even when performed during the patient's stay in hospital, must be considered somewhat more risky than the ordinary form of ambulant treatment.

Furthermore, we have to consider Vaughan & Black's (9) experiences that physical exertion after an injection increases the tendency of the organism to shock, and that constitutional

reactions are especially frequent on hot days. Salén & Björn-stjerna's case occurred in summer (June 20th), and shortly before his death the patient had been seen playing with another patient. Rush desensitization should therefore only be performed while the patient is confined to bed; and in general (also in the case of ambulant treatment) the patients should be told to avoid physical exertion after desensitizing injections of antigen.

Case 5.—The death of this patient apparently occurred owing to a coincidence of unfortunate events. The patient received the fifth injection of a dose which had been tolerated four times previously. It cannot have been a case of intravenous injection, as the symptoms did not appear until 8 or 9 minutes after the injection. It was unfortunate that the patient owing to (involuntary?) evacuation of excreta had gone to the lavatory, where he was found unconscious, and that he wore a pull-over with tight sleeves. The physician in charge has stated that this interfered with the rapid compression of the arm into which the injection had been given and with exposure of the other arm with a view to intravenous injection of adrenalin. Owing to these circumstances, valuable time was lost, and death occurred.

The conclusion to be drawn from this case is that when signs of a systemic reaction begin, the patient should not be lost sight of, and not be allowed to go to the lavatory alone, even when he seems otherwise to feel well. Some patients will go to the lavatory owing to precipitancy of defaecation but, this may involve a risk under these conditions, and it must always be possible to give an injection of adrenalin under these circumstances.

CONCLUSIONS

- (1) In bacterial-allergic conditions treated with bacterial vaccines the intervals between the injections of vaccine should not exceed 5 days. If pronounced systemic reactions should occur in connection with an injection of a bac-

terial vaccine, it is advised to discontinue the treatment and wait from 3 to 6 months before it is resumed.

- (2) A distinction should be made between bacterial-allergic conditions of spontaneous occurrence and induced, bacterial-anaphylactic reactions.
- (3) Intravenous injection of antigen is a technical error. Desensitizing treatment should therefore not be left to a nurse or to the patient's husband or wife.
- (4) Owing to possible cumulative effect, rush desensitization is generally more risky than the usual desensitizing treatment with an injection every other day.
- (5) If rush desensitization is indicated, this should only be performed when the patient is in bed in a hospital.
- (6) With imminent allergic systemic reactions, the patient should not be lost sight of for one moment.

It has not been the writer's intention to discourage the use of specific desensitization; he is too convinced of its usefulness to do so. But it is intended to advise taking everything into account and to point out the elements of danger, stating also how these can be best avoided. Specific antiallergic treatment should not be left to persons other than doctors, who by means of rapid and proper treatment can ward off most of the risks. In a few cases, for instance in Case 5 reported here, even the most skilled may fail, but this should not cause us to consider specific desensitization as an especially dangerous form of treatment. Considering its usefulness and the resulting widespread use of the treatment, the risk is already now very slight. It will be described in a subsequent paper in what manner it may in all probability be further reduced.

Finally it may be mentioned that Waldbott (10, 11, 12) has advocated the view several times that there exists a connection between status thymico-lymphaticus and allergy, and that enlargement of the thymus can be demonstrated with a striking frequency in patients who have presented constitutional reactions. Similar observations have been made by others. In 1937 Dahl (4) reported from Norway the death

of shock of a patient with hay fever, treated with helisen; autopsy revealed status thymico-lymphaticus.

The autopsy records do not mention status thymico-lymphaticus in any of the cases reported in the present paper.

SUMMARY

Five cases of fatal allergic constitutional reactions occurring in Scandinavia in the course of the past 3 or 4 years are reported and commented on. It is concluded that specific desensitization should not be left to nurses or other non-medical persons. It is pointed out that bacterial vaccines for bacterial-allergic patients should not be administered with an interval between the injections longer than 5 days because of the risk of inducing a bacterial-anaphylactic condition.

In the case of rush desensitization the possibility of cumulative effects cannot be excluded.

With regard to prophylaxis and treatment of the allergic systemic reactions, reference may be made to the paper mentioned below (2).

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