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THE RISK OF SHOCK IN PERCUTANEOUS ADMINISTRATION OF ALLERGENS

*Report of a Case of Sudden Death in Connection with
Specific Desensitization*

By

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In evaluating the indications for investigatory methods in clinical use, a number of different considerations must invariably be taken into account. If any particular method be associated with risks for the patient, then their magnitude must be considered, the evaluation moreover being based on the measure of necessity of the examination. In the case of *indicatio vitalis* even examinations fraught with major hazards might well be justified or essential. Generally speaking, it must be considered incorrect to resort to such examinations without well-founded indications. Special cases and doubtful clinical situations occur, as is known, not infrequently. Here the decision will usually be dependent on the more subjective attitude of the responsible physician.

It seems essential that the evaluation be based on specialized knowledge in the relevant field—knowledge sufficient to preclude, as far as possible, technical errors or errors of judgement. Considering the development in virtually all branches of medicine of recent years, the *conditio sine qua non* in many cases will be the assignment of certain fields to specially trained physicians who at the same time possess satis-

factory training in the basic field from which the speciality stems.

The risks should be evaluated, moreover, both with respect to the degree and to the frequency of the hazardous factor.

The foregoing applies—*mutatis mutandis*—in equal measure to the establishment of indications for a number of more or less hazardous methods of treatment. Sudden deaths have occurred following intravenous administration or arsphenamine or, for example, theophyllamine, without having affected in the slightest our faith in, or use of, those therapeutic agents. Only a few years after E. Behring's diphtheria antitoxin came into more general use as from 1894, a number of sudden deaths from shock were reported in connection with the use of it.

We are here approaching the "*bêtes noires*" of allergy, namely anaphylactic or allergic shock following percutaneous administration of allergens for diagnostic or therapeutic purposes. The clinical trend in allergy has entailed the use of innumerable potential allergens in routine testing on an ever increasing scale. In cases where it has been possible in this way to establish an etiologic diagnosis, and where other circumstances have warranted specific hyposensitization and subsequent perennial treatment, the causal allergen has been used therapeutically. It is a question here of substances of antigenic character, mostly perhaps exogenous proteins, though not infrequently substances of non-protein nature, haptens, etc.

Anaphylactic or allergic shock may be produced, as is known, both in the diagnostic and in the therapeutic use of these allergens, even though "shock fragments" (itching, urticaria, asthma, rhinitis, angioneurotic edema, etc.) are much commoner. Several cases of sudden death from shock are known. We are not concerned here with shock produced by the use of sera, etc., but with that associated with conventional percutaneous administration of allergens for diagnostic or therapeutic purposes.

The questions on which we shall seek to throw light are as follows: Is the diagnostic and therapeutic use of allergens of such clinical importance as to be fully justified, notwithstanding the risks associated therewith? What is the magnitude and incidence of such risks? Their cause and the conditions under which they develop. The possibility of effectual preventive measures. Measures that should be taken in shock or danger of such.

The answer to the first question will depend upon a host of different circumstances which in this context can only be touched upon. In some allergy cases the history alone serves to show which allergen or allergens are of causal significance. An appropriate allergic questionnaire implemented by interrogation of the patient is of considerable value here. If the probable causal factors which thus emerge can be eliminated and the patient thereafter becomes symptom free, then testing will be unnecessary. But if elimination cannot be effectively carried through (as in occupational allergy, pollen and dust allergy, etc.), specific desensitization will be necessary in certain cases. If the determination of the degree of sensitivity on which the dosage must be based is carried out *lege artis*, i.e. with a minute initial dose and gradually increasing doses at requisite intervals, then the occurrence of allergic shock symptoms in connection with the titration should seldom if ever be feared.

Unfortunately, however, the conditions are seldom so favorable as outlined above; despite questionnaires, careful interrogation of the patient, etc., in most cases it is still uncertain which causal factor or factors play a role. In such cases a detailed antigen analysis will be necessary, and even the experienced investigator will often be astonished by the results. Cases clearly exemplifying this have previously been reported (1, 2).

The major value in principle of allergic skin testing is probably best illustrated by the fact that this method constitutes the basis of, and has made possible, our modern conception of allergy. The same importance should be attached

to our ability to establish a causal, etiologic diagnosis in many allergy cases as in the infectious diseases. The only question is: In what percentage of allergy cases can such a diagnosis be established?—on which point considerable diversity of opinion exists. We have earlier (1, 2) sought to estimate this percentage in a large series, having arrived at figures between 50 and 65 per cent. Rimington *et al.* (6) claim to have demonstrated dust allergy in no less than about 70 per cent of a major series of asthma cases. E. Bruun *et al.* (5) found positive skin tests in about 85 % of all asthmatics. The appreciably lower percentages reported by other investigators (P. Vallery-Radot, Rost and others) are apparently due to several reasons: dust allergy has not received sufficient attention at the skin tests; intracutaneous tests have not been carried out; the reliability of the extracts employed seems open to question; and, last but not least, the entire category of complicating infections, non-exogenous, intrinsic asthma, etc., has been regarded—without any objective grounds—as nonallergic. In a survey published in 1950, one of the present writers (7) treated the subject “Allergy and Infection”. According to the view expressed in that paper, there are good reasons for assuming that most cases of “intrinsic” allergy are of bacteriotoxic nature. Numerous means whereby this question might be explored still remain to be utilized.

On studying the relevant literature and examining the grounds on which a few authors have sought to vindicate their negative attitude to the diagnostic use of percutaneous allergen administration, one encounters the oddest combinations of insufficient orientation and difficulty in evaluating situations correctly. The book on allergy recently published by Rost (9) (1950) contains examples of quite bizarre reasoning.

The percutaneous allergen diagnostic method has, moreover, opened up the possibility of *causal therapy*. As regards the latter's value the situation can best be surveyed with regard to pollen allergy, in which specific desensitization has been carried out on a gigantic scale. Large series have been reported and good results obtained in between 55 and 85 per

cent of the cases (1, 2). It may be added that no comprehensive investigations, with special reference to the occurrence of polyvalent allergy and complicating infections, were carried out in most of the cases which failed to yield good results. It is highly probable that the unsatisfactory results in the minority of cases were due to the presence of other causative factors rather than an insufficient effect of the specific desensitization itself.

Specific rushhyposensitization has been utilized by us (Sallén) in the most divergent forms of exogenous "atopic" allergy. It has earlier (1943) (2) been shown, moreover, that the results emerge well from a comparison with those obtained in pollen allergy.

That the effect of specific desensitization is but transient and must therefore be maintained by means of perennial treatment, with one or two allergen injections per month, is well known. The question whether this trying after-treatment can be avoided in many cases, *and replaced by natural exposure* (regular, with short intervals), *has likewise been illustrated earlier* (1, 2).

We now proceed to our second question: The severity and incidence of shock reactions. Let us have the nomenclature question clear from the outset; for it seems evident that obscurity here has led to widely varying statements in the literature, so that they are virtually impossible to evaluate. This aspect of the matter has been exhaustively studied and illustrated a.o. by Vaughan and Black (8), according to whom a rigorous distinction should be made between what we have termed above as "shock fragments" and true shock. For the former, Vaughan and Black suggest the designation "systemic reactions", corresponding to what we (3) in an earlier paper (1948) called "clinical reactions" (1, 2). True shock they term "constitutional reactions". Between these two forms of reactions they feel justified in making a sharp distinction, writing as follows: "We feel that allergic shock is a much more explosive affair, developing with extreme rapidity, once it has started; and due in all probability to a quite generalized tissue

edema, including interstitial edema of the lungs, and to almost universal increase in capillary permeability". They point out how, in the absence of "restraining forces, the entire plasma volume could pass from the capillaries into the body tissues within ten seconds" (Vaughan & Black (8)). Whether this sharp distinction of Vaughan and Black between the two forms of reactions is theoretically justified may perhaps be open to question. Unquestionably there occur "clinical reactions", e.g. in the form of status asthmaticus, itching, urticaria, laryngeal edema, etc., with such a sudden onset and rapid development, as well as an effect on the general condition, that a state of full shock might possibly ensue unless prompt effective measures were taken. From the practical standpoint at all events, Vaughan and Black's distinction seems appropriate and should be accepted. It may be added that in genuine shock the onset is usually rapid, in most cases within 10 to 30 minutes after the injection, coming like a bolt from the blue without any premonitory symptoms in the form of "clinical reactions" (5). The latter may supervene, however, during shock and, above all, after it has subsided.

There appears to be considerably unanimity of opinion that *clinical* (*systemic*) reactions occur relatively frequently in connection with percutaneous administration of allergens; that their appearance is not necessarily due to defective technique or measures; and that they scarcely ever have a lethal outcome, provided rational counter measures are taken immediately. These considerations will be discussed later on.

The incidence of clinical or systemic reactions in connection with skin tests apparently varies to a considerable degree according to the nature and composition of the series, standardization of extracts, etc. A scrutiny of one thousand personal cases (Salén), mainly of asthma, shows that such reactions were observed in eleven (1.1 per cent). In all of these the skin tests had been carried out intracutaneously in one stage with extracts of the standard series (30 to 40 extracts). With regard to the incidence in connection with specific desensitization we could refer to an earlier review (1), in which no fewer

than 44.2 per cent of the patients who underwent desensitization at some time or other presented clinical reactions (urticaria, angioneurotic edema, etc.). In each case it was a question of rush desensitization. All of these clinical reactions were of a relatively mild nature and, with adequate treatment, rapidly subsided. By resorting thereafter to adrenaline and/or antihistaminics the specific desensitization of these cases could usually be carried through without any major difficulties. We have earlier (1, 3) shown that exceptions to this rule do occur, and we shall return to this matter later on.

In this connection it may be mentioned that Vaughan and others strongly caution against the use of rush desensitization, adducing in particular certain investigations conducted by Cohen *et al.*, according to which administered allergens are retained in the organism up to 48 hours, for which reason they consider that, to preclude a *cumulative* effect, allergen injections should not be given oftener than every third day. Our wide experience of rush desensitization argues strongly against this view, and recently published investigations should have conclusively disproved the theory of Cohen *et al.*

With regard to the occurrence of serious, life-endangering or fatal shock reactions in clinical allergy, a distinction might appropriately be made between those arising "spontaneously", i.e. under natural conditions of exposure, and those arising in connection with percutaneous administration of allergens¹. The former group chiefly includes those associated with oral administration of the causal allergen. Vaughan and Black, on studying the relevant literature, were able to trace about ten cases with conditions of shock produced by oral administration of nutritive allergenes (milk, egg, etc.), though none with a lethal outcome. In hypersensitivity to a certain drug or drugs, oral administration has resulted in full shock in ten to twenty cases, five to ten of them being fatal. In the majority it was probably a question of hypersensitivity to aspirin preparations. To the "spontaneous" shock cases should

¹ Shock associated with serum therapy is not taken into account here.

also be assigned those developing after insect bites. Vaughan and Black mentioned about ten such cases, including three fatal ones, following bee or wasp stings. Something over thirty sudden deaths from shock following bee or wasp stings have been reported in Sweden since 1918, the majority at least probably having been anaphylactic reactions¹. Spontaneous shock reactions due to inhaled allergens appear to be—in contrast to milder clinical reactions—exceedingly rare.

The occurrence of shock following percutaneous administration of allergens was recently (May, 1950) treated in a paper by Coleman Harris, Normal Shure and B. Hills. They pointed out that lethal shock had very rarely occurred in connection with allergen tests. The few cases which they collected from the literature are as follows:

1. Cooke (1922): Three-year-old asthmatic boy, died following intracutaneous testing with glue extract.
2. Lamson (1924): Five-month-old infant with eczema, died after intracutaneous testing with milk, egg, oats and rice.
3. *Reported* by Baagøe (1928).
4. Lamson (1929): Adult male, died five minutes after testing with buckwheat and ovomucoid.
5. Freedman (1935): Six-year-old boy, died after intracutaneous testing with horse serum.
6. Ferguson (1940): Six-year-old boy, died after intracutaneous testing with tetanus antitoxin.
7. Vauce and Strassmore (1942): Four-year-old girl, died after intracutaneous testing with silkworm, lambswool and kapok.
8. Hunt (1943): Death following intracutaneous tests with guinea-pig hemoglobin.
9. Wiseman and McCarthy-Brough (1945): 78-year-old woman, died after 17 intradermal injections of allergens.
10. Swineford (1946): Death following 64 intracutaneous injections of allergens.
11. Blanton and Stutphin (1949): 57-year-old woman, died after 56 intracutaneous injections of allergens.
12. Benson (1939): Two-year-old boy, died following injection of cottonseed allergen in an incorrect dose due to a mistake.

¹ These data are derived in part from the archives of a Stockholm daily newspaper. Probably the actual number of cases is considerably greater.

13. McGrash (1948): Six-year-old boy, died following technically incorrect testing with cottonseed.
14. Lastly, the authors' personal case: 25-year-old woman who died following tests with cottonseed.

In all probability the number of deaths from shock following percutaneous administration of allergens is considerably higher than the fourteen mentioned above. This is indicated for instance by an enquête conducted by Vaughan and Pipes to a large number of physicians. Van der Veer, Cooke and Spain, in a survey published in 1927, found 96 constitutional reactions among 14,280 therapeutic injections of pollen; Waldbott and Ascher (1936), 141 among 51,036 injections; Furstenberg and Gay, 75 among 29,547 injections¹.

Shock reactions may be caused by: incorrectly standardized extracts; wrong dosage; wrong dosages on changing from one extract to another; wholly or partially intravenous injection due to carelessness; insufficient attention to initial symptoms and preventive treatment necessitated thereby; insufficiently long observation of patient following the injection; mode of injection; the varying tendency of different individuals to shock reaction, etc., etc. However, a study of the literature with regard to these problems gives a singularly meager basis for evaluating them. Vaughan and Pipes, in a survey of 1935, found that the shock had occurred following subcutaneous (therapeutic) injections in 15 cases, following intracutaneous injections in six, and following scratch tests in two cases. But since no data were given on the total number of injections of each respective type, it is scarcely possible to draw any conclusions, either with regard to the quantitative relation or with regard to the causal significance of the mode of application.—Another report by Furstenberg and Gay is, in our opinion, of considerable interest, showing as it does the significance of *individual* disposition to shock: of 21 patients with shock reactions no fewer than 14 had them more than once; six had them no less than four times, and three as many as five times.

¹ Cited by Vaughan and Black.

On attempting to analyse the cause of shock in 75 cases, the same authors were unable to find even a probable cause in about 41 cases; in most of the other 34 the supposed causal factor was doubtful or merely probable.

Our own experience covers between twenty and thirty thousand allergy cases, in which standard tests with something like thirty to forty extracts were carried out in one stage intracutaneously; of this total approximately 20 per cent, or roughly six thousand cases, underwent specific desensitization, and at least one half of them subsequently received perennial treatment, i.e. one to two injections per month, usually for several years. No death occurred, with the exception of the one reported in the following. As regards the occurrence of true, non-fatal shock reactions we might refer to the following examples; together with a fatal case.

1. Polyvalent allergy case with excessive hypersensitivity to Brazil nuts. Full shock only a few minutes after intracutaneous injection of 0.10 ml Brazil nut (1:100) extract. Recovery time about one week. This case has earlier been described in detail (1). Titer: 1:10,000,000.

2. Case of pronounced hypersensitivity to unroasted coffee (titer: 1:20,000,000). Full shock a few minutes after intracutaneous injection of 0.05 ml raw coffee extract. Recovery time about one week.

3. Patient markedly hypersensitive to lycopodium powder. Specific desensitization was carried out and the patient submitted to perennial treatment with one injection every three to four weeks. On receiving her 11th injection a shock reaction appeared after a few minutes with total unconsciousness for about half an hour. She had had highly febrile influenza in the interval. The recovery time was two to three days.

4. Grass pollen allergy. Following desensitization the patient was placed on perennial treatment, which continued for two and a quarter years without producing any distress. After receiving her usual monthly dose she now remained in the waiting room under observation for about 30 minutes. No symptoms being observed. About ten minutes later severe shock set in, though without unconsciousness, as in the three preceding cases. The patient recovered in a few hours following treatment with adrenaline and theophyllamine.

5. About 1935 a twelve-year-old boy had been submitted to antigen analysis. He had polyvalent asthma, dust allergen probably being predominant. There was a very slight reaction to horse extract. About ten years later he worked as a medical student in a bacteriologic laboratory. He had noticed in recent years that asthma symptoms developed on exposure to horse. Since the

TABLE 1
Skin Titration.

Date	Extract	1:100	1:1,000	1:10,000	1:100,000	1:1 million
17/5	Horse 2611 ...			++	+	—
	Dog 2535		+++	±	—	—
8/6	Cow 1760	++	+	—	—	—
	Autodust 2760	++	+	±	—	—
	Cat 2350	—	—	—		

laboratory in question had just prepared a horse extract, he thought it would be interesting to carry out cutaneous tests with it. Shortly afterwards he was found dead.

Spoujitch and Danilovitch (1950) reviewed a large number (2, 776) of allergy cases in which over 25,000 allergen tests, mainly intracutaneous, had been carried out. They reported having found in this series two shock reactions but no deaths.

In the summer of 1950 we experienced our first case of fatal anaphylactic shock following subcutaneous injection of allergen. Since this case is interesting and instructive from several points of view, we feel justified in presenting it in some detail.

B.S., born 1936 (Reg. no. 7682/1950).

The patient, a 13-year-old boy, was admitted to Södersjukhuset on May 31, 1950 for *asthma and allergic rhinitis*. His health had previously been good on the whole, but since the age of eight he had suffered increasingly from allergic rhinitis and asthma on coming into close contact with dogs and horses, but *only* then.—On admission he had mild asthma with fairly numerous sibilant râles, which completely subsided after two or three days. His condition was otherwise quite normal, and he was afebrile throughout, with a normal sedimentation rate. His skin tests are negative except for a two-plus reaction to unboiled milk.

In view of the anamnestic data, dog and horse extracts were especially tested. The results reproduced in Table 1 were obtained on titration (titer: 1:10,000—1:100,000, resp. 1:100,000—1:1 million). As will be seen from the table the patient also showed relatively slight cutaneous sensitivity to cow extract and more pronounced sensitivity to extracts of dust from his home.

TABLE 2

Skin Tests.

Nace-Carbol	—	Dust 1896	—
Lambswool	—	Dust 2265	+
Feather	—	Dust 418	+
Histamine (1:10,000)	++	Dust 588	—
Fish	—	Timothy pollen	—
Meat	—	Birch pollen	—
Vegetabilia	—	Ox-eye daisy pollen	—
Boiled milk	—	Tuberculin (1:1,000)	—
Unboiled milk	++	Orange juice	—
Egg yolk	—	Hazel nut	—
Egg white	—	Aspergillus	—
Lycopodium powder	—	Penicillium	—
Chocolate	—	Stemphyllin graminin	—
Banana	—	Cladosporium herbarum	—
Wheat	—	Tomato	—
Rye	—	Oats	—

Specific desensitization (Table 2) to horse was instituted, as Table 3 shows, on June 5, and parallel therewith to dog on June 12 (alternating). Meanwhile the patient was quite free from distress until June 15, when he had nocturnal rhinitis and labored breathing, which symptoms soon disappeared spontaneously. On June 16 after an interval of 24 hours, when he was again given horse extract, the dose was not increased; but since he showed no untoward reaction it was then raised in the usual way. In the early hours of June 20 he again had slight asthma symptoms, which subsided spontaneously, and the following morning he was quite symptom free. It is doubtful whether the nocturnal asthma had been due to the desensitization; but if so the reaction was presumably caused by the injection of dog extract (0.7 ml, 1:100) which he received at 5 p.m. on June 19. An identical dose of dog extract was therefore given with due care at 10.30 a.m. on June 20, without producing any symptoms.

According to statements made *subsequently* by his fellow patients, he had rhinitis and somewhat labored breathing around noon on June 20, and was urged to inform the nurse but failed to do so. At 1 p.m., when he received an injection of 0.6 ml horse extract 1:10, he showed no distress or symptoms. Half an hour later, when questioned, he said he felt well, and showed no signs of rhinitis or asthma. He had behaved quite normally during the day and, as late as 3.15 p.m., had been running and playing in the corridor with another patient. When we visited the ward on our round 15 minutes later he was on all fours

TABLE 3

Date	Time	Horse Extract		Dog Extract		Remarks
		Amount in cc.	Solution	Amount in cc.	Solution	
5/6	15.00	0.2	1 : 1,000,000			
	17.00	0.4				
6/6	08.10	0.6				
	10.20	0.8				
	12.30	1.0				
	15.00	0.2	1 : 100,000			
	17.00	0.4				
7/6	08.00	0.6				
	11.00	0.8				
	13.00	1.0				
	15.00	0.2	1 : 10,000			
	17.00	0.4				
8/6	08.00	0.6				
	10.00	0.8				
	13.00	1.0				
	15.00	0.2	1 : 1,000			
	17.00	0.4				
9/6	08.00	0.6				
	10.30	0.8				
	15.00	1.0				
	17.00	1.2				
10/6	08.15	0.2	1 : 100			
	12.30	0.4				
12/6	08.15	0.6				
	10.30	0.8				
	13.00	1.0				
	15.00			0.2	1 : 100,000	
	17.00			0.4		
13/6	08.15	1.2				
	10.30			0.6		
	15.00			0.8		
	17.00			1.0		
14/6	08.15	0.2	1 : 30			
	10.30			0.2	1 : 10,000	
	13.00	0.4				
	15.00			0.4		
	17.00	0.6				
15/6	08.15	0.8				

TABLE 3 (cont.)

Date	Time	Horse Extract		Dog Extract		Remarks
		Amount in cc.	Solution	Amount in cc.	Solution	
	10.30			0.6		Rhinitis and labored breathing; subsided spontaneously
	12.30			0.8		
	15.00			1.0		
	17.00			1.2		
16/6	08.00	0.8				
	10.30			0.2	1:1,000	
	12.45			0.4		
	15.00			0.6		
	17.00			0.8		
17/6	08.30	0.1	1:10			
	11.00			1.0		
	13.00			1.2		
19/6	08.15	0.2				
	10.30			0.2	1:100	
	13.00			0.3		
	15.00			0.5		
	17.00			0.7		Mild nocturnal asthma
20/6	08.30	0.4				
	10.30			0.7		
	13.00	0.6				
	15.30					Shock. Death

in bed, sneezing violently and complaining of pressure in the chest and itching on the body. After a few seconds severe dyspnea supervened. He was immediately laid on the bed and artificial respiration and oxygen treatment instituted, while 0.4 ml adrenaline (1:1,000) was administered subcutaneously in the thigh within about a minute. At the same time 10 ml Oxyphylline plus 5 ml Nicetamide was given intravenously—all without effect. Within a few minutes the boy lost consciousness, developed severe pallid cyanosis and swelling of the face, and showed very weak cardiac activity with scarcely audible sounds, wherefore 0.2 ml adrenaline was slowly administered intracardially. On renewed auscultation no heart sounds were audible, so that a further 1 ml adrenaline was administered intracardially, though no signs of life could be detected. Death probably occurred 15 minutes at the latest after the onset of the attack. The ampules which had contained the extracts, etc. were immediately confiscated and a thorough investigation instituted. It showed that no mistake had been made with regard to extract, dilution, dosage, etc.

AUTOPSY REPORT

Cadaver of 13-year-old boy of normal development. Well-developed musculature, thin build. Very pronounced cadaveric patches. Height 151 cm, weight 39.7 kg.

The brain was removed. It had a normal configuration and showed nothing of pathologic nature, either on the surface, with regard to the vessels, or in the parenchyma.

The cervical organs appeared normal. There was no edema of the glottis or epiglottis; no signs of upper respiratory tract infection; no foreign bodies in the trachea or esophagus. The tonsils were of normal size and showed no gross inflammatory changes.

The heart was of normal size and presented no pathologic changes. The musculature was well contracted. Nothing abnormal was found in the great vessels.

No fluid could be observed in the pleural cavities. The lungs were in maximum expansion and the thorax in the full inspiration position. Several punctate hemorrhages were present in the tracheal and bronchial mucosa, but otherwise it showed nothing pathologic. Section of the lungs showed fairly dry parenchyma without signs of inflammatory changes. Esophagus and mediastinum, N.A.D.

The abdominal cavity contained no fluid. The stomach was distended and contained a quantity of practically undigested food. No large particles of fruit could be observed in the gastric contents. Intestinal canal, N.A.D. The liver was sanguineous and apparently in a condition of acute stasis. Pancreas and spleen, N.A.D.

The kidneys were of normal size; the capsule could readily be dissected free and section showed fully normal conditions. Adrenals, N.A.D.

Microscopic examination of lung parenchyma.

Sections from the lungs showed strongly dilated parenchyma with no signs of inflammatory changes.

June 29, 1950

O. Möller.

Further findings.

Preserved specimens consisted of pieces of lung tissue; unfortunately no other specimens were retained.

Fairly pronounced changes could be observed in the sections, particularly with regard to the larger bronchial branches. These were often filled with mucus containing desquamated epithelium and eosinophilic granulated leukocytes. The mucosal epithelium showed signs of very copious secretion. The basement membrane of the epithelium was considerably thickened. In the bron-

chial walls were found edema and fairly pronounced inflammatory cell infiltration, including quite a large number of eosinophilic granulated leukocytes. In the bronchioles, on the other hand, the histologic changes were not so pronounced. Some parts of the lungs showed no pronounced changes of the alveolar septa, but in other parts the alveolar septa were markedly thickened and the site of severe hyperemia. Further, an increased content of leukocytes was observed, and in places, signs of exudation into the alveoli. The blood vessels observed in the sections were to a large extent congested.

The histologic changes described above resembled those usually observed in bronchial asthma.

November 10, 1950.

Wahlgren/C. Lundmark.

This case warrants a number of remarks. A study of Table 2 shows that the dosage of extracts conformed to the pattern used by us in thousands of cases without any fatal reaction. The only divergence to some extent from our practice is that the dog and horse extracts were, so to speak, crossed—a mode of procedure that we have used, however, without any untoward effect in a large number of cases.

Exceedingly remarkable was the sudden onset of shock as late as two hours after the injection. It is generally stated (*vide* Rackemann, Vaughan and Black, Cooke, and others) that constitutional reactions scarcely ever appear later than 20 to 30 minutes after percutaneous administration of allergens. As Salén has earlier (1) pointed out, we must reckon, however, with the occurrence even of severe *clinical* reactions after as much as three to four hours, even if they are exceedingly rare.

The present case shows, in conclusion, what a hopeless situation may arise so far as treatment is concerned: the whole thing develops so rapidly that there is simply no time to take effective counter measures¹.

¹ Salén has earlier pointed out that in threatening situations adrenaline should be administered continuously, *with control of the pulse*, until the symptoms of shock have subsided. In such a case 4.5 ml adrenaline was consumed in about two and a half hours. It was probably a case of transient shock caused by an injection of morphin. If any objection might be raised to the schedule of treatment in the present case, it would be that the dose of adrenaline given immediately at the onset of shock was limited to 0.4 ml.

As a general rule, control of a case for half an hour following the injection of allergen has been deemed sufficient to preclude shock, but this case—like a few (with severe clinical reactions) mentioned earlier—demonstrates that such a precaution occasionally will not suffice. In this connection we would draw attention to our view that specific desensitization should preferably be carried out at a hospital. The risk of severe clinical reaction or shock after a patient has left the doctor will be especially great because the physician handling the case may perhaps have no knowledge of the previous history and hence may not resort to adequate treatment (adrenaline, etc.).

Considering the shock cases reported in the literature as well as the present one, and in view of the aforementioned investigation of Furstenberg and Gay, it seems justified to assume that although allergic shock is fundamentally due to the administration of allergen and the biologic reactions to it, *the state of shock will be capable of developing only if the conditions in the organism are propitious. As Salén (1951), among others, was recently able to show, the tendency to shock in percutaneous administration of allergens will be completely abolished, even in excessively hypersensitive cases, if the patient during desensitization receives small amounts of ACTH (10 mg $\times$ 4).* Salén has emphasized too the advantage of carrying out specific desensitization under the protection of ACTH, and has suggested that it might be possible in this way to eliminate the risk of shock. In view of the foregoing *we might postulate the occurrence of shock solely or mainly in connection with a disturbance of the homeostatic balance (Selye), in a state of hypofunction, referable to the function of cortisone or ACTH.* Such an assumption would also presuppose the occurrence of spontaneous, possibly physiologic variations in this respect—an assumption which, to our knowledge, has not yet been satisfactory investigated, much less confirmed.

With this we have treated in part our fourth question, concerning possible preventive measures. Adequately stand-

ardized extracts, adequate dosage, proper intervals between injections, avoidance of mistakes with regard to extracts or doses, careful control of the patient for three to four hours after the injection—all these considerations are of fundamental importance and are calculated to justify the working procedure introduced at the Department of Allergic Diseases, Södersjukhuset. Other measures which might be termed preventive are those which should be taken—immediately—if symptoms of clinical reaction appear: adrenaline injected locally and in another part of the body. The blocking of absorption from the injection site by adrenaline is generally considered, it would seem, to be of importance. The advantage of administering the drug cutaneously and in a part of the body where an Esmarck's bandage (or blood-pressure cuff) can be applied proximally is manifest. In cases of this kind it has been our custom to administer theophyllamine intravenously in addition to adrenaline.

In specific desensitization we have long used parallel adrenaline treatment ($0.5 \text{ ml} \times 3$ to 4 subcutaneously) in cases showing a tendency to clinical reactions. Duke, Vaughan and others suggest mixing the allergen extract with adrenaline immediately before injection. In recent years we have sought in addition to utilize antihistaminics for preventive purposes. It is difficult to judge what benefit this may have, though experience hitherto is undoubtedly favorable. The excellent protection afforded by ACTH (and possibly cortisone) medication has earlier been pointed out. According to most recent experience of *oral* administration of cortone (cortisone), even small amounts (25 to 50 mg per day) might possibly be expected to afford effective protection against the occurrence of clinical reactions and shock.

The preventive measures described in the foregoing are largely identical with those that should be taken in existing shock or clinical reactions of severe nature. However, everything must be done at a faster rate, and perhaps the greatest danger here lies in proceeding too rapidly. The question as to what degree injection of ACTH or cortisone may change

the situation in the presence of allergic shock has not yet been elucidated. At the Department of Allergic Diseases, Södersjukhuset, we have constantly had ACTH at hand during the past year.

A large number of allergy patients undergoing specific desensitization have had to complete the long-term treatment in their home districts outside Stockholm. So far as we are aware, no case of fatal shock has occurred hitherto. As a rule, we recommend that an antihistaminic tablet be taken about half an hour before the injection, and that the injection dose be halved and administered in two stages with a thirty minute interval.

SUMMARY

1. Following a review of the relevant literature it is pointed out that the risk of *severe* clinical ("systemic") reactions and fatal allergic shock is relatively small provided all requisite precautionary measures are taken.

2. A case is described of death from shock in connection with specific desensitization, in which the state of shock developed rapidly about two hours after the allergen injection and led to death within a few minutes, notwithstanding immediate treatment (adrenaline, etc.).

3. Considerations are adduced which indicate that specific desensitization should preferably be carried out at a hospital.

4. *It is postulated that the occurrence of shock presupposes a (transient) disturbance of the homeostatic balance in the form of an ACTH-Cortisone hypofunction.*—In most known cases of death from shock (and non-fatal constitutional reactions) no external causes, methodologic errors, overdosage, etc., have been demonstrable (Furstenberg and Gay).

5. The importance of the fact that we are able to carry out desensitization under ACTH protection, and the possibility of using in its place oral administration of Cortone (cortisone), are emphasized.

REFERENCES

1. *Salén, E. B.*: Acta Allerg. I, 1948.
 2. - & *B. Arner*: Acta Allerg. I, 1948.
 3. - Svenska läkaretidn., 1937, 1946, 1948.
 4. *Vallery-Radot, P.*: Précis des maladies allergiques. Edit. Flammarion, Paris, 1949.
 5. *Bruun, E.*: Acta Allerg. I, 1948.
 6. *Rimington, Stilwell & Maunsell*: Brit. J. exp. Path. 28, 309, 1948.
 7. *Salén, E. B.*: Acta Allerg. III, 1950.
 8. *Vaughan & Black*: Practice of Allergy, The Mosby Comp., St. Louis, 1948.
 9. *Rost, G. A.*: Allergie und Praxis. Springer-Verlag, Berlin, 1950.
- For further references see Vaughan & Black⁸.

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