Asthma Induced by Antihistamines

The phenomenon of rapid alternation of clinical syndromes among allergic individuals has long been recognized—for instance, asthma and eczema in young children. It would appear that the antihistamines are capable of provoking such an alternation. Tomlinson (1948) and Harris (1948) cite cases in which eczema supervened when hay-fever was treated with diphenhydramine hydrochloride. Frankland (1949) refers to the onset of asthma towards the end of the pollen season in patients who have been treated with antihistamines.

The records of nine patients who exhibited this phenomenon are given below. They were seen during the course of investigation and treatment of 3,000 cases of allergic rhinopathy (including hay-fever) in the past four years. In each case cited antihistamine therapy produced relief of the symptom treated, coincidentally with the appearance of asthma. In most cases this effect was reversible, and cessation of this therapy restored the *status quo ante*. Pollen was usually but not invariably a major aetiological factor.

CASE REPORTS

Case 1.—A woman aged 37 had had intermittent vasomotor rhinitis for 13 years; it was perennial, but worse in the summer months. Skin sensitivity to house dust and pollens was demonstrated. A first and only attack of asthma occurred with great severity immediately after taking antazoline tablets. This has not recurred, and the patient has refused to take further antihistamines.

Case 2.—A girl aged 8 had had atopic eczema since infancy and seasonal hay-fever for the last three summers, but no asthma. In the summer of 1950 she took mepyramine maleate on two or three occasions, and each time an attack of asthma supervened. When the drug was discontinued no further asthma occurred. Skin sensitivity was demonstrated to pollens only.

Case 3.—A woman aged 29 had had vasomotor rhinitis and asthma for five years. After a course of hyposensitization treatment in 1948 and 1949 the asthma had practically disappeared, but the vasomotor rhinitis persisted though improved. In April, 1950, she took promethazine hydrochloride for the first time, with immediate improvement of the nasal condition, but severe asthma occurred within three days. Cessation of the drug brought about complete relief of asthma but recurrence of vasomotor rhinitis. She has repeated the test on four further occasions (using different antihistamines) with identical results each time—on the third night of treatment she develops asthma.

Case 4.—A woman aged 30 had had morning rhinorrhoea for many years which cleared completely during pregnancy three years ago but recurred with increased severity and frequency a year later. Mepyramine maleate relieved the nasal condition, but within a day or two produced moderately severe asthma for the first time. The asthma has persisted in a mild form though antihistamines have been discontinued. Pollen sensitivity was demonstrated.

Case 5.—A woman aged 50 had seasonal hay-fever at age 21 which was treated and relieved by cauterization. A severe recurrence in the summer of 1949 was treated with diphenhydramine hydrochloride. Her first attack of asthma occurred immediately thereafter and has persisted in spite of cessation of antihistamines. Although pollen sensitivity can be demonstrated the asthma is not purely of allergic origin, as there is an infective element superimposed.

Case 6.—A woman aged 40 had a ten-years history of vasomotor rhinitis. In 1950 she was given promethazine hydrochloride, which afforded relief. Asthma then appeared for the first time—possibly coincidental. Sensitivity to house dust was demonstrated but not to pollens.

Case 7.—A woman aged 39 had had seasonal hay-fever for seven years, increasing in severity each year. It was twice aggravated by pregnancy. Three years ago a course of diphenhydramine hydrochloride was followed by relief of hay-fever, but the immediate appearance of asthma for the first time. Since then the asthma has recurred with each pollen season. Pollen sensitivity was demonstrated.

Case 8.—A woman aged 64 had had atopic eczema of the wrist and shoulders for 10 years. There was a family history of a similar complaint. On two occasions in 1949 she was treated with antazoline, and on each occasion immediately developed moderately severe asthma—her only two attacks. The causative allergen has not been identified.

Case 9.—A man aged 40 had a two-years history of perennial rhinopathy and nasal polyposis. He had mild wheezing in 1949 while taking promethazine hydrochloride. He was aspirin-sensitive. Skin sensitivity to pollens was demonstrated. Chlorcyclizine hydrochloride produced quite an acute attack of asthma, which disappeared with cessation of treatment but returned again when a further dose was taken.

COMMENT

The antihistamine drugs vary considerably in the relief they afford to different allergic manifestations. Good results are obtained in allergic rhinopathy, poor or negligible results in asthma, although Herxheimer has shown that histamine-induced bronchospasm or mild asthma can be relieved to a measurable extent by large doses of aerosol antihistamines. The theory has been put forward that in these resistant manifestations the histamine or H substance is released in a more inaccessible fashion, and that the neutralizing effect of antihistamine drugs fails to reach the point of release in adequate amounts. The series of cases described above could be explained by postulating that, an antihistamine having been given in sufficient dosage to neutralize an allergen-reagin reaction in one tissue, the reaction appeared in another tissue which the dosage administered was inadequate to protect.

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Optimum Injection Volume for Intramuscular Streptomycin Sulphate

Streptomycin sulphate has recently appeared on the market in solution ready for intramuscular administration, .1 g. being available as a 2, 3, or 4-ml. injection.

Our investigation was undertaken to determine whether the volume of fluid had any bearing on the pain-producing qualities of the injection. Only if a larger volume can be shown to be less painful is there any point in using it, for the advantages of 2-ml. injections in convenience and lesser cost of syringes are obviously great, particularly in domiciliary work. The viscosity rises so rapidly with smaller volumes of solvent that anything less than 2 ml. is impracticable.

METHOD

To ensure that any difference found would be due to the volume used and not to variations in the streptomycin or the solvent, only one manufacturer's materials were employed, the solutions being prepared specifically for the trial to exclude batch variations, etc.

A new No. 1 serum needle was used for each injection, this being the smallest needle offering little resistance to the flow of the more viscous 2-ml. injection. So far as was possible these injections were given by the same nurse (80%), and in any case one nurse gave all the injections on any one day. The injections were given alternately in the lateral aspect of each thigh, and the patients were unable to see the size of the syringe used.

Two separate trials were held, with an interval of one month between them. The patients were unselected, all who were receiving one daily intramuscular injection of 1 g. of

streptomycin being included. The interval enabled a greater number of patients to be included, for only three were in hospital long enough to appear in both trials. In the first trial seven men and six women were given a total of 180 injections. In the second trial six men and seven women received 149 injections.

The nurse giving the injections worked strictly to a prearranged plan, allocating 2 ml. or 4 ml. on a random basis. Only she knew the type of injection the patient had received.

One of us (L. C. K.) investigated on the following day the pain reactions of all the patients. Like them, the observer did not know which injections had been given, whilst both results and injection volumes were so recorded that only later could they be fully correlated. On three occasions it was not possible to record the results because the patients concerned were not fit to give a true record of the pain experience.

Pain reactions were classified as "immediate" and "delayed," with three arbitrary grades in each group (1=nil or mild; 2=moderate; 3=severe).

RESULTS

The results are shown in the Table. It will be seen that there are many more moderate and severe delayed reactions associated with 4-ml. than with 2-ml. injections. The pattern

Results

	Size of Injection	Degree of Pain 1	2	3	Total
Trial I (180 *Patients*)					
Initial pain	4 ml.	70	12	6	88
	2 ml.	76	14	2	92
Delayed pain	4 ml.	67	14	7	88
	2 ml.	82	8	2	92
Trial II (149 *Patients*)					
Initial pain	4 ml.	64	10	3	77
	2 ml.	67	3	2	72
Delayed pain	4 ml.	58	12	7	77
	2 ml.	61	9	2	72

is the same in each trial, which adds further significance to the results. In both trials combined, 40 moderate and severe delayed reactions occurred with 4-ml. injections as compared with only 21 with the 2-ml. injections ($\chi^2=8.62$, $P<2\frac{1}{2}\%$). The results for initial pain, although showing a similar trend, are not statistically significant.

CONCLUSIONS

If 1 g. of streptomycin sulphate is administered intramuscularly as a 2-ml. injection, significantly less delayed pain can be expected compared with its administration as 4 ml. Rising viscosity prevents less than 2 ml. being used, but this volume is satisfactory when using a No. 1 serum needle.

Streptomycin sulphate, now marketed as a prepared 2-ml. injection, is thus the most convenient and satisfactory form available. At the same time this packing minimizes handling by the nursing staff, and, if the rubber-capped vials are used, enables the officially recommended precautions against skin sensitization to be carried out. (Packing in a glass ampoule makes this impossible.)

Our thanks are due to Mr. N. W. Please for examining the statistical validity of our results; to the nursing staff and patients for their willing co-operation; and to Glaxo Laboratories Ltd. for preparing and supplying the streptomycin solutions.

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Metastases from Carcinoma of Bronchus causing Enormous Enlargement of Liver

The following case is reported on account of the enormous enlargement of the liver produced by metastatic tumour deposits.

CASE REPORT

A man aged 68 attended the Bradford Royal Infirmary on April 20, 1953, with a complaint of dyspnoea, abdominal swelling, and pain in the right upper quadrant of the abdomen of several weeks' duration. There was a history of productive cough during the past year and haemoptysis on several occasions during the previous three weeks. On examination he was very dyspnoeic. Palpation of the abdomen revealed a greatly enlarged and hard liver which was thought to be malignant.

On July 13 he was admitted to St. Luke's Hospital, Bradford. On admission (temperature 97° F. (36.1° C.), pulse 110, respirations 24) he was confused and dyspnoeic; there was neither cyanosis nor jaundice. Oedema of both legs and of the scrotum, penis, and sacral region was present. The abdomen was greatly distended and tender, and the lower border of what was thought to be the liver was palpable in the lower extremity of the abdomen. The breath sounds on the right side of the chest were diminished. He became progressively more confused and died on July 18.

Post-mortem Examination.—The relevant findings were as follows. At the hilum of the right lung there was a firm grey-white neoplasm, about 2 in. (5 cm.) in diameter, which appeared to originate in the main bronchus of the right middle lobe. There was no pneumonic consolidation. The liver was enormous (weight 19 lb. 4 oz. or 8,730 g.), and contained numerous metastases, ranging in size up to 4 in. (10 cm.) in diameter. The mediastinal, aortic, and upper abdominal lymph-nodes showed obvious metastatic involvement. The supraclavicular and axillary glands were not enlarged. The peritoneum, omentum, spleen, pancreas, adrenal glands, kidneys, and brain showed no macroscopical evidence of metastatic involvement. In the gastro-intestinal tract there was no evidence of a neoplasm. Five small superficial ulcers were present in the mucosa of the stomach along the greater curvature.

The histological features of the bronchial neoplasm were those of an undifferentiated carcinoma of "oat-cell" or spindle-cell type. The appearances were uniform throughout the primary growth and the metastases. The ulcers in the stomach were not neoplastic.

COMMENT

The noteworthy feature of this case is the size (8,730 g., normal about 1,500 g.) of the liver. Cases in which livers with metastatic growths have attained great weights (13 between 5,000 and 10,000 g., and 7 exceeding 10,000 g.) are referred to by Willis (1952). The livers reported by Kikuth (1925) and Fried (1925) weighed 11,800 g. and 6,400 g. respectively, and were from cases of lung carcinoma.

In the above case the liver retained its normal shape despite extensive neoplastic involvement, and we are reminded that, next to local lymphatic spread, the liver is probably the most frequent site for metastases in carcinoma of the bronchus (Hadfield and Garrod, 1947; Willis, 1953).

I have to thank Mr. J. Dawson and Dr. C. L. Davidson for the clinical data relating to this case.

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