DIETHYLCARBAMAZINE THERAPY IN TROPICAL EOSINOPHILIA

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Recently diethylcarbamazine has shown promising results in the treatment of tropical eosinophilia. The drug was used for the first time in this ailment by Ganatra and Lewis (1955). Since then reports have appeared in the literature showing that it is safe, and as effective as arsenic, in the treatment of the condition. Chaudhuri (1956) used daily doses of 12 to 16 tablets of diethylcarbamazine (50 mg. each) for 7 to 10 days and found it fairly effective in 10 out of 12 patients. Danaraj (1956) corroborated the work of Chaudhuri in 10 patients. Danaraj (1958) used diethylcarbamazine in the treatment of 100 cases of eosinophilic lung and obtained good results, comparing favourably with those obtained in treatment with organic arsenicals. Raheja (1958) treated 34 cases with oral diethylcarbamazine and cured 32 of them in 4 to 16 days.

Ganatra *et al.* (1958) treated 94 consecutive cases of tropical eosinophilia with different doses of diethylcarbamazine dihydrogen citrate ("hetrazan"). The drug was tried in the dosage schedules of 13 mg./kg. daily for four days, 13 mg./kg. daily for eight days, 6 mg./kg. daily for four days, 6 mg./kg. daily for eight days, 3 mg./kg. for eight days, and 26 mg./kg. for one day. Almost all the dosage schedules tried were found to be effective, but minor variations were seen in the degree of effectiveness. Shah and Sheth (1958) treated 25 cases of tropical eosinophilia with diethylcarbamazine citrate parenterally, and 23 showed clinical and haematological improvement. Viswanathan (1958) treated 20 cases with a single injection of diethylcarbamazine, 750 mg. The response was very good in 18 cases. In one case response was delayed. Only one patient needed a second injection, which brought about complete clinical and haematological relief. In a previous study of 32 cases in which oral therapy was given Misra *et al.* (1958) observed favourable results in 31. In seven out of eight cases parenteral therapy failed to effect complete cure. Six of them later responded to oral diethylcarbamazine.

In the present series 44 patients (34 males, 10 females) have been studied. The age distribution was:

Age	No. of Cases
15-19 years	10 (22.7%)
20-29 "	17 (38.6%)
30-39 "	9 (20.4%)
40-49 "	7 (16%)
50+ "	1 (2.3%)

Children were not included in this study, as there is a separate unit for children's diseases in our department. Among the adults, maximum incidence was in the 20-29 age-group. The youngest patient was 16 and the oldest 75.

Material and Methods

Selection of Cases.—The 44 cases of tropical eosinophilia were chosen serially. They either were

admitted into the wards of Medical Unit II or attended the medical out-patients department of Gandhi Memorial and Associated Hospitals. Most of the patients gave a typical history of dry cough, breathlessness, and pulmonary wheeze, but six were without pulmonary symptoms. The physical signs in those patients who presented with pulmonary symptoms varied from case to case, and consisted of harsh vesicular breathing with crepitations and rhonchi and varying degrees of bronchial spasm. One case was admitted with status asthmaticus. There was no correlation between the severity of the symptoms and the degree of physical signs or the increase in absolute eosinophil count. A skiagram of the chest or routine examination by fluoroscopy before the beginning of treatment showed increased striations or mottling in the lung fields in most cases. All cases had an eosinophil count of more than 4,000 per c.mm. The possibility of filariasis was excluded both clinically and on examination of night blood film for microfilaria. Stool and sputum examinations were performed in order to exclude any parasitic infection.

Plan of Work.—A careful history was taken and a thorough physical examination made in every case. In addition the following investigations were carried out: (1) total and differential W.B.C. count, (2) absolute eosinophil count, (3) night blood film for *Microfilaria bancrofti* on three consecutive nights, (4) fluoroscopy or a skiagram of the chest at the beginning and the end of treatment, and (5) stool, urine, and sputum examination. A thorough physical examination was done daily. Total and differential W.B.C. counts were made on alternate days in the beginning of the treatment and subsequently as often as necessary until the counts were within normal limit.

Dosage Schedule.—Diethylcarbamazine was used in the form of hetrazan tablets. It was given in daily doses of 8 mg. per kg. of body weight. Most adults received 12 50-mg. tablets a day in three or four divided doses; underweight adults were given 8-9 tablets daily in similar divided doses. The treatment was stopped as soon as adequate clinical and haematological response had been obtained. No other drug known to have eosinopenic action or known to cause alleviation of symptoms in eosinophilia was used in conjunction with diethylcarbamazine.

Criteria for Assessment of Results.—A patient was regarded as cured when all the symptoms and signs disappeared completely and the absolute eosinophil count came down to 1,000 per c.mm. or below. Symptomatic relief was assessed by asking the patient about the degree of relief in his condition in terms of annas in a rupee. A relief of + + + + was expressed when the patient said that he was relieved 16 annas in a rupee, + + + when relief was 12 annas, + + when the improvement was 8 annas, and + relief when improvement was 4 annas in a rupee. If there was no relief at all or it was less than 4 annas, it was concluded that no improvement has occurred. (A rupee is divided into sixteen annas.) The improvement in physical signs was taken as +, + +, and + + +, depending on the degree of diminution in rhonchi, crepitations, and change in the character of breathing. The relief was taken as + + + when there was complete absence of physical signs. At the end of treatment fluoroscopy was repeated in every case in order to see if radiological findings in the lungs had diminished or disappeared.

Results

Cure Rate.—Out of 44 cases treated by diethylcarbamazine 40 were cured (91%). In four cases the haematological response was only partial and there was no marked symptomatic relief.

Symptomatic Relief.—By the fourth day of treatment there was either complete or some relief in 40 cases (91%). No marked symptomatic relief occurred in four resistant cases. On further analysis it was found that even by the fourth day there was complete symptomatic relief in 6 cases (13.6%), +++ relief in 18 cases (40.9%), and ++ relief in 16 cases (36.4%). At the end of two weeks all the cases, except the four who were resistant, had complete symptomatic relief. Fig. 1 shows a typical case of response to treatment.

Fig. 1.—A typical case of response to diethylcarbamazine (hetrazan) therapy. ●—●, eosinophil count. Cross-hatching represents symptoms and signs.

Improvement in Physical Signs.—Coincident with symptomatic improvement there was general clearing of the physical signs, and at the end of treatment 40 cases (91%) showed complete remission of physical signs. In four cases in which the eosinophil count did not reach the normal level, the physical signs also persisted. By the fourth day of therapy +++ relief in signs was found in 18 cases (40.9%).

Eosinophil Counts.—Within four days of treatment the eosinophil count showed a definite fall in 24 cases (54.5%). In the rest of the cases the diminution in count was not significant, though clinical improvement was quite well marked. However, as the days passed the count fell to within normal limits in 40 cases (91%). The Table shows the mean absolute eosinophil count at the beginning and end of treatment.

Duration of Therapy.—Most of the cases (81.8%) were cured in two weeks. Four days were required for one case. Between four and six days were required for three cases, and treatment continued for more than two weeks in eight cases. These eight cases included

Mean Absolute Eosinophil Counts at Beginning and End of Treatment

Count Before Treatment	No. of Cases	Mean Count Before Treatment	Mean Count After Treatment
Below 5,000	8	3,675	707
5,000–10,000	18	5,334	800
10,000–15,000	6	10,200	860
15,000–20,000	4	16,720	918
Above 20,000	4	41,095	980

Note: Four cases were resistant to treatment.

the resistant cases, and these responded to oxophenarsine hydrochloride injections; in the other four cases cure was achieved in three weeks.

Toxicity.—The drug was administered for three to four weeks in some cases, and even then no marked toxic symptoms were encountered. The drug was fairly well tolerated. Only a small percentage of patients complained of nausea and loss of appetite. In two cases vomiting was also present.

Duration of Illness.—Close scrutiny of the data did not reveal any relation between the period of therapy and duration of the complaints.

Diethylcarbamazine-resistant Cases.—Four of the 44 cases did not respond well to diethylcarbamazine. One had responded to the drug six months previously, but on the second admission the response was poor even though treatment was continued for one month. There was an initial slight improvement in symptoms, but the absolute eosinophil count did not show any appreciable change. This patient responded to oxophenarsine injections and there was complete clinical and haematological cure. In the second case there was a slight fall in absolute eosinophil count from 15,000 to 12,000 by four weeks of diethylcarbamazine therapy, but there was no symptomatic relief. Three injections of oxophenarsine brought the count down to 640; symptomatic relief was complete after these injections. The third case was interesting in that he was relieved by oxophenarsine in 1953. In 1956 he was relieved by diethylcarbamazine. In 1959 the count

showed no change and there was no symptomatic relief after four weeks of diethylcarbamazine therapy. Four injections of oxophenarsine (0.02 g., 0.03 g., 0.03 g., and 0.04 g.) produced complete clinical and haematological relief (Fig. 2). In the fourth case the absolute eosinophil count was 15,250. Diethylcarbamazine was given for four weeks without any symptomatic improvement, and the eosinophil count was still 10,000 at the end of treatment. Four injections of oxophenarsine brought the count down to 600, and the symptoms also disappeared completely.

Discussion

Organic arsenicals were being used in the treatment of asthma with eosinophilia even before the classical

Fig. 2.—Chart of a diethylcarbamazine-resistant case which responded to oxophenarsine (mapharside) injections. ●—●, eosinophil count. Cross-hatching represents symptoms and signs.

description of the syndrome by Frimodt-Møller and Barton in 1940 (Roy and Bose, 1918; Ghosh, 1918; Treu, 1944). Since the chance discovery of the effectiveness of organic arsenicals in tropical eosinophilia by Weingarten (1943), many papers have appeared proving their efficacy in this ailment (Simeons, 1943; Heilig and Visveswar, 1943; Emerson, 1944; Patel, 1945; Viswanathan, 1945, 1948; Jhatakia, 1946; Joseph, 1946; Wilson, 1947; Soysa, 1949; Danaraj, 1951; Misra and Hameed, 1953; Prakash, 1955; Chaudhuri, 1956). Though results have been good with arsenicals, dangerous side-effects in terms of encephalopathy, myelopathy, exfoliative dermatitis, agranulocytic angina, and exacerbation of symptoms have been reported (Patel, 1945; Jhatakia, 1946; Viswanathan, 1947; Singh, 1948; Pundit, 1949; Danaraj, 1951; Mehta, 1955; Prakash, 1955; Manchanda, 1956; Misra *et al.*, 1959).

Other agents, such as antimony (D'Abrera, 1946), sulphonamides (Chaudhuri *et al.*, 1954; Joseph, 1946; Lal, 1945), chloroquine (Ganatra and Lewis, 1955), "mantomide" (Ganatra and Lewis, 1955), chlortetracycline and other antibiotics (Chaudhuri, 1950; Prasada Rao and Krishnan, 1952; Dias-Rivera *et al.*, 1950; Reeder and Goodrich, 1952; Misra *et al.*, 1958), corticotrophin and cortisone (Chaudhuri, 1951; Chaudhuri *et al.*, 1954; Coutinho, 1956; Dias-Rivera *et al.*, 1954; Misra *et al.*, 1958), and aminopterin (Ganatra and Lewis, 1955) have not given good results.

Analysis of the present work proves beyond doubt the efficacy of oral diethylcarbamazine in the treatment of tropical eosinophilia: 40 out of 44 (91%) cases were completely cured. No aggravation of symptoms was noted in any case and there was no initial rise in eosinophil count. Both the haematological and the clinical improvement were maximal within 10 days of therapy. No serious toxic effects were noted even when treatment was continued for two to four weeks. It is obvious, therefore, that diethylcarbamazine is definitely superior to arsenic because of its ease of administration, the high cure rate in a relatively small period of time, and the complete absence of dangerous toxic manifestations. Mild toxic symptoms in the form of giddiness and vomiting have been reported by Raheja (1958) and Danaraj (1958).

Diethylcarbamazine has been found to be equally good in those cases of tropical eosinophilia which had extrapulmonary symptoms and signs in addition to pulmonary ones, and also in those which presented aberrant manifestations of the disease—in the form of dry pleurisy in one, pleural effusion in another, pyrexia with lymphadenopathy in a third, and hepatomegaly with abdominal pain in a fourth. In four cases liver and in one case splenic enlargement regressed with clinical improvement in pulmonary symptomatology. Haematological improvement was observed in all cases.

In a previous study Misra *et al.* (1959) reported two cases that were resistant to arsenotherapy but responded to diethylcarbamazine. One of these patients was a medical student of this college who had developed exfoliative dermatitis twice with arsenic therapy. He became desperate with life and was forced to abandon his medical studies. Diethylcarbamazine produced a dramatic response in this patient, and he later resumed his studies. Those authors also reported one case which was resistant to diethylcarbamazine therapy.

In the present series four cases were found resistant to diethylcarbamazine therapy. Two of these had responded very well to diethylcarbamazine when the drug was administered in previous attacks, while in the other two diethylcarbamazine was given for the first time for tropical eosinophilia. However, all four cases responded to oxophenarsine injections. These cases show that some subjects might become resistant to diethylcarbamazine after one or more courses of treatment and that some may be resistant to the drug from the very beginning. In these cases arsenicals may be tried.

The cause of tropical eosinophilia still remains obscure. The view expressed by Carter *et al.* (1944) and Soysa *et al.* (1945) that tropical eosinophilia may be a manifestation of pulmonary ascariasis has not been able to stand the test of time. The remarkable therapeutic response of tropical eosinophilia to diethylcarbamazine, a drug known to be specific in filariasis and ascariasis, tends to the belief that the cause of this common condition may be parasitic infection. The work of Beaver *et al.* (1952) on the aetiology of visceral larva migrans has raised the possibility that a similar mechanism may be responsible for tropical eosinophilia. The parasitic theory finds further support from the works of Danaraj *et al.* (1957) and Gault and Webb (1957), from Vellore, India, and the evidence is gaining ground that the syndrome of tropical eosinophilia may be an allergic response to home helminthic infection.

Summary

Oral diethylcarbamazine therapy was tried in 44 cases of tropical eosinophilia and was found effective in 40 cases (91%). Four cases were resistant to diethylcarbamazine therapy. Two of these had responded very well to this drug when it was given in previous attacks, while in the other two it was given for the first time. All these cases responded to oxophenarsine injections. Diethylcarbamazine was found equally effective in relieving extrapulmonary manifestations of the disease—for example, dry pleurisy, pleurisy with effusion, lymphadenopathy, pain in the abdomen, splenomegaly, and hepatomegaly. No toxic reactions to it were observed in any of our cases, even when the therapy was continued for three to four weeks. No aggravation of symptoms was noted in any case, nor was there any initial rise in the eosinophil count. Both clinical and haematological response were maximal within 10 days of therapy. Diethylcarbamazine appears to be superior to arsenic because of its ease of administration, the high cure rate in a relatively small period of time, and the complete absence of dangerous toxic reactions.

The problem of the aetiology of tropical eosinophilia is discussed, and it seems that the syndrome may be an allergic response to some helminthic infection.

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"The future depends largely on our ability successfully to develop and market new products in response to a steadily changing incidence of disease. Some of these changes are due to factors beyond our control; others are influenced by our own activities. . . . These considerations help to explain the vital part played by technical, as distinct from economic, competition in our industry. However efficient we may be in producing and selling our existing products, the discovery of an effective new medicament or, for example, a more economical synthesis of an existing medicament, can render obsolete a product or group of products that may have taken us years to perfect and may have involved the investment of large sums in providing specialized plant and the skilled personnel necessary to its operation. Against such a background of technical competition we must view with considerable concern the relatively small expenditure on medical and pharmaceutical research in the United Kingdom compared with the weight of effort now being put into such research overseas, particularly in the United States, the Common Market countries, and Japan." (Sir Harry Jephcott, 25th Annual General Meeting, Glaxo Laboratories, Ltd.)

SEDIMENTATION RATE OF STORED BLOOD, USING SEQUESTRENE AS THE ANTICOAGULANT

BY

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It has been shown that a modification of Westergren's method for the estimation of the erythrocyte sedimentation rate (E.S.R.), using blood treated with sequestrene, gives results similar to those of the customary method, whether the E.S.R. is estimated immediately after the withdrawal of the blood or when the blood has been stored in the refrigerator for 24 hours (Melville and Rifkind, 1959).

Further work has been carried out to find the effect on the E.S.R. of longer storage of blood samples in the cold, and of storage of samples at room temperature for various periods.

Material and Methods

Blood samples were taken from patients in medical wards of a general hospital. Some samples were taken deliberately from patients known to have raised E.S.R.s. The sequestrene used as anticoagulant was the disodium salt of ethylenediamine tetra-acetic acid, at a concentration of 1 mg. per ml. of blood. Blood so treated is here termed "sequestrene blood."

For the estimation of the E.S.R. the modified Westergren method (Melville and Rifkind, 1959) was used. Mixing of the sequestrene blood and of the citrate-blood suspensions was carried out for at least two minutes. Whenever possible the E.S.R. estimations were made in duplicate, but in some cases when a prolonged study was to be made, only one estimation was done so that blood could be conserved. The readings were taken to the nearest millimetre after one hour. The room temperature of the laboratory was measured at intervals, and was usually in the range of 18 to 20° C. Blood from the refrigerator was always allowed to warm up to room temperature before the E.S.R. estimations were made.

Experiments

The E.S.R. of sequestrene blood measured immediately after withdrawal of the blood will be termed the "immediate E.S.R." Experiments were designed to compare the immediate E.S.R. of a number of samples with their E.S.R.s after they had been stored for various times, as follows: experiment 1, storage for 48 hours at 4° C.; experiment 2, storage for 24 hours at room temperature; experiment 3, storage for six hours at room temperature. In these three experiments the blood was not disturbed during the storage.

Experiment 4 was designed to find if there was a significant change of the E.S.R. of a sample during the