average being 59. Every patient was requested to attend for supervision at intervals of four weeks. Injections of 1,000 $\mu\text{g.}$ of vitamin B_{12} ("cytamen") were given once every 12 weeks. The haemoglobin and red-cell count were estimated at least every 12 weeks, and more often if the levels were not entirely satisfactory.

Serum vitamin B_{12} assays were performed on the majority of patients, using the method described by Ross (1952) modified by Hutner *et al.* (1956) using *Euglena gracilis* 3 strain as the test organism. Samples were obtained at 18 months at random intervals of one, two, or three months after vitamin- B_{12} administration.

Results

To determine whether or not there was any deterioration in the haematological values during the course of the trial the mean of the first three and the mean of the last three red-cell counts and haemoglobin estimations were compared. The haematological levels at which it was considered desirable to maintain patients were:—for men: haemoglobin 100%, red-cell count 5,000,000/c.mm.; for women: haemoglobin 90%, red-cell count 4,500,000/c.mm.

During the course of the trial three patients died from other diseases and nine were withdrawn owing to intercurrent illness or inability to attend.

Of the remaining 100, 87 were maintained in the trial throughout a two-year period of study and showed no deterioration in their red-cell counts or haemoglobin values. Seventeen of these, however, were maintained with red-cell counts slightly under the desired levels, and two required intermittent oral iron therapy to maintain their haemoglobin levels.

Thirteen patients were withdrawn from the trial at intervals varying from 9 to 16 months (mean 14 months) on account of unsatisfactory red-cell counts, though none were below 4,000,000/c.mm., and in these cases the dosage of vitamin B_{12} was increased to 1,000 $\mu\text{g.}$ monthly in an effort to determine whether or not an improvement might be obtained. Of this group, one patient had, after 12 months in the trial, developed paraesthesia of the hands and feet, which did not clear up until the dosage of vitamin B_{12} had been increased to fortnightly. Three patients were known to have other disease: one had mild rheumatoid arthritis, one had been under out-patient treatment for a year for pulmonary tuberculosis, and one had a probable bronchial carcinoma. These four patients had the lowest haematological values in the whole survey.

Eleven of these 13 cases showed a rise of the red-cell count of 100,000–400,000/c.mm. (mean 300,000/c.mm.) following the more intensive vitamin- B_{12} therapy. These must be accepted as failures of the regime.

Serum vitamin- B_{12} assays performed on the first group of 87 patients after 18 months showed satisfactory levels in all cases except in one performed three months after her last vitamin- B_{12} injection, which gave a borderline result though her haematological values were normal. Facilities were not available for carrying out assays on the 13 patients of the second group at the time at which they were withdrawn from the trial.

Summary and Conclusions

One hundred treated cases of pernicious anaemia were maintained on a two-year trial to assess the adequacy of the maintenance therapy of 1,000 $\mu\text{g.}$ of parenteral vitamin B_{12} every 12 weeks.

Throughout the period of study 87 patients showed no deterioration as judged by their haematological values (haemoglobin and red-cell count) and serum vitamin- B_{12} assays.

Thirteen patients showed unsatisfactory red-cell levels after 9 to 16 months, and in 11 of these improvement was obtained by increasing the vitamin B_{12} dosage to 1,000 $\mu\text{g.}$ monthly.

It is concluded that one injection of 1,000 $\mu\text{g.}$ of vitamin B_{12} every 12 weeks provides adequate maintenance therapy for most patients suffering from pernicious anaemia. However, as this dosage is inadequate in a small number of patients it cannot be recommended as a general routine measure.

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DIETHYLCARBAMAZINE IN TROPICAL PULMONARY EOSINOPHILIA

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Tropical pulmonary eosinophilia, which is widespread in India, is now recognized as a major cause of respiratory illnesses. It is increasingly regarded as an eosinophilic disorder in which bone-marrow, blood, lungs, liver, and probably other viscera may be involved. So far, its aetiology is mainly speculative, though allergy, parasitic infection, and viral infection have all been incriminated.

Until recently, arsenic was the sheet anchor in its treatment. Antimony and bismuth (D'Abrera, 1946), sulphonamides (Joseph, 1946; Chaudhuri *et al.*, 1954), chloroquine, and chlorbetamide ("mantomide") (Ganatra and Lewis, 1955) have all given disappointing results. Chaudhuri (1950) and Prasada Rao and Krishnan (1952) reported encouraging results with chlortetracycline, but antibiotics have not proved effective in the hands of Misra *et al.* (1958), Reeder and Goodrich (1952), and Diaz Rivera *et al.* (1950).

Antihistaminics have been widely used for symptomatic relief, but relief lasts only so long as the drug is continued and is unaccompanied by haematological or bone-marrow changes. Both corticotrophin and cortisone have been tried, but, despite an initially favourable response, relapse has been the rule and the bone-marrow changes have never been reversed. Ganatra and Lewis (1955) used aminopterin to depress the haemopoietic eosinophil activity in six cases, with marked clinical relief in five. The response was transitory, however, and compared poorly with that to arsenic. Ganatra *et al.* (1958) have also reported failure with mepacrine and chlorbetamide.

The recent discovery of the value of diethylcarbamazine in this disorder has led to arsenic rapidly losing ground to it. Diethylcarbamazine is now known to be non-toxic; it is equally effective and can be given orally. Ganatra and Lewis (1955) have reported their results with oral diethylcarbamazine ("hetrazan") for four days in 11 cases of pulmonary eosinophilia, and later (Ganatra *et al.*, 1958) in 94 cases, using different dose schedules and control groups. Here we record our impressions of 40 cases (32 cases on oral and 8 on parenteral diethylcarbamazine) studied by one of us (A.S.) at King George's Medical College, Lucknow,* and a further 18 cases studied by all of us at Bhopal.

Methods

Selection of Cases.—Only those patients were studied who showed an absolute eosinophil count of 4,000/c.mm. or more, whose stools and sputum were negative for any parasitic infection, and whose night blood-films were negative for *Microfilaria bancrofti* on three consecutive nights, in addition to there being no clinical evidence of filariasis. The clinical picture of dry cough, breathlessness, and pulmonary wheeze, so characteristic of pulmonary eosinophilia, was present in every case. On routine radioscopy the picture was usually of prominent reticulation and hilar shadows. There was no familial history of allergy.

Procedure.—After a careful history and clinical examination, the following investigations were done: total and differential W.B.C. count; absolute eosinophil count; and sternal smear examination. After four days' therapy the total and differential W.B.C. counts were repeated. A thorough clinical examination was made daily, and W.B.C. counts were carried out as often as necessary till the count came down to normal. At this stage an absolute eosinophil count was done, and sternal puncture was repeated in 14 cases.

Drug Therapy.—Diethylcarbamazine was administered in a daily dose of 8 mg./kg. body-weight. Most adults received 12 tablets (50 mg. each) daily in three or four divided doses; children or underweight adults had eight or nine tablets in similarly divided doses. In four cases, early in the series, the daily dosage was reduced gradually to prevent any possibility of relapse. With more experience, however, this seemed unnecessary, and it became our practice to stop the drug as soon as the haematological response was adequate. No other drug known to have eosinopenic action, or known to give symptomatic relief, was simultaneously administered. Diethylcarbamazine was also given parenterally in eight cases, as described below.

Follow-Up.—All the cases have been followed up fortnightly to detect any recurrence.

*In collaboration with Professor S. S. Misra, Dr. K. Nath, and Dr. S. Prakash; published separately (1959).

Criteria of Progress.—(a) **Cure:** Eosinophil count below 800/c.mm. and complete remission of all symptoms and signs. (b) **Symptomatic Relief:** Patients were interrogated about their symptomatic relief in terms of annas in a rupee.† Relief was ++++ if the patient said that he was relieved 16 annas in a rupee, +++ if improvement was 12 annas, ++ if improvement was 8 annas, and + if it was 4 annas. Lesser degrees of relief were recorded as no improvement. (c) **Improvement in Physical Signs:** This was arbitrarily recorded as +, ++, or +++, according to the severity of rhonchi, crepitations, and other signs of bronchospasms. If there were no physical signs, improvement was recorded as +++. (d) **Radiological Improvement:** All patients were examined radiologically on discharge, to confirm that the reticular shadows had diminished or disappeared. In most cases fluoroscopy was done, but in some of the Bhopal cases skiagrams were also taken.

Results of Oral Treatment

Cure Rate.—At Lucknow 31 out of 32 (97%) cases on oral therapy were completely cured. In only one case was there no haematological response, though some symptomatic relief occurred. Unfortunately this patient left the hospital against medical advice before any further observations could be made on him. All the 18 patients studied at Bhopal showed haematological cure, though in one case symptoms did not completely disappear. Thus the cure rate in the 50 cases studied was 98%. Ganatra *et al.* (1958) reported that 2 out of 13 patients did not respond to a daily dose of 13 mg. of diethylcarbamazine per kg. for four days, 7 out of 16 did not respond to 6 mg./kg. for four days, 3 out of 23 did not respond to 6 mg./kg. for eight days, 4 out of 17 did not respond to 3 mg./kg. for eight days, and 3 out of 19 patients did not respond to 26 mg./kg. for one day only. Thus, in all, 19 out of 94 of their patients did not respond. We feel that this lower rate of cure (80%) was due to inadequate treatment in many groups.

Symptomatic Relief.—Of the 32 Lucknow cases 31 experienced complete symptomatic relief by the end of treatment. By the fourth day of treatment there was complete symptomatic relief in four cases, +++ relief in 14, and ++ relief in 14. Only the one unsuccessful case shown little improvement by the fourth day. These results were confirmed in the 18 Bhopal patients. By the fourth day three cases had been completely cured and there was +++ relief in eight and ++ relief in seven. All except one of the Bhopal cases were symptom-free four to five days before the stage of cure was reached. The only patient who was not completely relieved symptomatically was treated for only four days; though his eosinophil count came down to normal, there was only ++ relief of symptoms. He was subsequently given arsenic, his symptoms then being completely relieved. Thus out of the total 50 cases, 7 (14%) showed ++++ relief, 22 (44%) +++ relief, and 21 (42%) ++ relief within four days of starting treatment. Only two patients were not completely relieved by the end of therapy—one was not cured and the other was subsequently given arsenic parenterally, though he had already shown a haematological response.

†The rupee, the standard Indian coin, is divided into 16 annas; so that improvement of 16 annas meant 100% relief, of 12 annas 75% relief, and so on. Most people, illiterate or otherwise, traditionally and correctly express their relief, gains, or losses in terms of annas in a rupee.

Improvement in Physical Signs.—Of the 32 Lucknow cases 31 showed a complete remission of physical signs at the end of treatment. Only the unresponsive case failed to show any improvement haematologically or in physical signs. After four days' therapy improvement in physical signs was +++ in 14 cases. In all the 18 Bhopal cases physical signs had completely disappeared by the end of treatment, and by the fourth day there was +++ improvement in eight cases. Thus of the 50 cases, 22 (44%) showed a +++ relief in physical signs within four days. The degree of symptomatic relief and the diminution in physical signs appear to run parallel. The physical signs had disappeared by the time a complete haematological response was obtained.

Reduction in Eosinophil Count.—Within four days of starting treatment a definite fall in eosinophil count occurred in 16 of the 32 Lucknow cases (50%); in the remainder there was either no fall or an unimpressive fall in spite of the early clinical improvement. However, eventually the count came down to normal in all but one case. Of the 18 Bhopal cases the eosinophil count fell to normal in three cases within four days and in another five there was a definite fall; in the remainder a fall occurred after one week's treatment.

Bone-marrow Response.—Bone-marrow was examined in 14 of the Lucknow cases. All showed hyperplasia, with many mature and immature eosinophil cells, at the start of therapy. Examination of the sternal smear after treatment ended showed only a few eosinophil cells, most of which were mature. Sternal-smear examination was not done subsequently in our work at Bhopal because we felt that the effect of diethylcarbamazine on the bone-marrow had been sufficiently studied in these 14 cases.

Duration of Oral Treatment

The longest duration of therapy (30 days) was in the second of the 32 Lucknow cases, and was, as explained above, to prevent possible relapse. After further experience it was realized that this was unnecessary, and in later cases treatment was discontinued as soon as haematological cure was achieved. Closer scrutiny of the 32 Lucknow cases showed that one case was cured in less than four days, three cases in four to six days, 13 in 7 to 10 days, three in 11 to 14 days, six in 15 to 16 days, and in six treatment was continued for more than 16 days. Of these six cases, one was resistant, in one treatment was deliberately prolonged as already stated, and in four a cure was effected within 23 days. In the 18 Bhopal cases three required treatment for four days, one for six days, eight for 7 to 10 days, two for 11 to 14 days, three for between 15 and 16 days, and one for 22 days. Out of the total 50 cases, 29 (58%) were cured within 10 days, 43 (86%) within 16 days, and almost all the responding cases by the 23rd day.

In a group of 13 patients treated with 13 mg. of diethylcarbamazine per kg. daily for four days only (a higher daily dose than we used) Ganatra *et al.* (1958) reported an unfavourable response in two cases. We feel that this treatment was inadequate and that if it had been continued the two unresponsive cases would probably have responded, for in their other group of six cases, in which the same daily dose was continued for eight days, all the patients responded. Similarly, Ganatra *et al.* treated 16 cases with 6 mg. of diethylcarbamazine

per kg. for four days and seven (44%) did not respond. Evidently treatment was again inadequate—obviously so in two cases which deteriorated when the drug was discontinued after initial improvement. When the same daily dose was continued for eight days in another 23 cases only three did not respond, the number of failures approximating to those in a group treated with 13 mg./kg. for four days. Ganatra *et al.* also treated a group of 17 patients with 3 mg./kg. for eight days and recorded failure in four cases, though two of these improved when further treatment was given. Again, on a single daily dose of 26 mg./kg., they had 3 failures out of 19 cases.

When their cure rate is related to the total dose of diethylcarbamazine, it is seen that with 104 mg./kg. in eight days 100% of six cases responded; with 52 mg./kg. in four days 84.6% of 13 cases responded; with 48 mg./kg. in eight days 87% of 23 cases responded; with 24 mg./kg. in four days 56% of 16 cases responded; with 24 mg./kg. in eight days 76.4% of 17 cases responded; and with 26 mg./kg. in one day 84% of 19 cases responded. Though the number of patients in each group was unfortunately not the same, these figures confirm our impression that the cure rate is proportional to the total dosage of drug given. A total dosage of 140 mg./kg. was administered by them to six cases in eight days, and all of them responded; in our series 104 mg./kg. had been administered by the 13th day, and by that time most of our cases also had either completely recovered or were well on their way to recovery. We consider that for a satisfactory and quick response free from side-effects the average case generally requires 8 mg./kg. daily for 8 to 15 days. This period is much shorter than about a month required with arsenic therapy.

Ganatra *et al.* stopped treatment arbitrarily after one, four, or eight days. We prefer to continue it until there is an adequate haematological response.

Dosage.—With 8 mg./kg. daily we obtained good results reasonably quickly without any side-effects. With the higher doses of 13 mg./kg. and 26 mg./kg. Ganatra *et al.* noted an initial aggravation of symptoms. A daily dose of less than 8 mg./kg. would unnecessarily delay cure.

Toxicity.—In our experience patients have tolerated the drug very well, and apart from anorexia and nausea in a few cases we have so far not encountered any serious side-effects. This is in marked contrast to arsenic therapy.

The duration of illness and the initial eosinophil count bore no relation to the duration of required therapy.

Cases Resistant or Sensitive to Arsenic.—One of us (A.S.) has used diethylcarbamazine successfully in two arsenic-resistant cases, and we have since seen a third. One of them was a medical student with tropical eosinophilia of 10 years' duration who twice developed exfoliative dermatitis after arsenic therapy, failed to respond to pyretotherapy, and showed only a very transitory response to cortisone. He obtained no relief from antihistaminics and other bronchodilators, and was forced to give up his medical studies. He responded well to diethylcarbamazine and has since resumed his studies.

Results of Parenteral Treatment

Misra, Nath, Shanker, and Prakash (1959) administered diethylcarbamazine intramuscularly to eight patients. Two were given 2 ml. (800 mg.) as a single dose—one

became unconscious within 30 minutes of administration, his condition later being successfully controlled with oral diethylcarbamazine, while the symptoms and the eosinophil count of the other returned to within normal limits within 11 days. A third patient failed to respond to thrice-repeated parenteral doses, but quickly improved with oral diethylcarbamazine. A fourth patient, given an initial dose of 800 mg., improved symptomatically within 24 hours, lung signs cleared up within two days, and the eosinophil count came down to normal within six days. He was subsequently given oral therapy to avoid a possible relapse. All these four patients, who received an initial dose of 800 mg., suffered from nausea, vomiting, and an intense desire to sleep. Other side-effects included giddiness, dryness of the mouth, and intense itching.

The other four patients were given three or four injections of 400 mg. at intervals varying from three to six days. All showed symptomatic improvement, with lessened physical signs, but their eosinophil count did not return to normal. In three normality was later achieved with oral diethylcarbamazine and in one with two injections of oxophenarsine hydrochloride. Side-effects in these four patients were minor, and included giddiness and drowsiness.

The conclusion was reached that diethylcarbamazine used parenterally was disappointing. It did not cure in seven out of eight cases. Six of the failures later responded to oral therapy, and one was cured with arsenic.

Conclusion

A cure rate of 98% with oral diethylcarbamazine compares favourably with that obtained with parenteral arsenic therapy. The series of Ganatra *et al.* (1958) showed a lower cure rate, but this was probably due to inadequate dosage and earlier withdrawal of the drug.

Unlike arsenic, which often worsens symptoms to begin with, oral diethylcarbamazine therapy gives quick symptomatic relief.

Both neoarsphenamine and oxophenarsine have been known to cause an initial rise in eosinophils, and, though Chaudhuri (1951) reported that there was no rise with aminarsin, this finding could not be confirmed by Misra *et al.* (1958). In no case has diethylcarbamazine in a daily dose of 8 mg./kg. caused an initial increase in eosinophils, and the count has rapidly returned to normal.

Toxic reactions have not been encountered with the recommended daily dose of 8 mg./kg. According to Ganatra *et al.* (1958) undesirable side-effects have been seen in cases treated with 13 mg./kg. and 26 mg./kg. a day.

Administration of diethylcarbamazine orally is an easy method. The oral arsenic preparation, carbarsone, is not nearly so effective. With carbarsone, Danaraj (1952) reported a cure rate of 74%, Misra *et al.* (1958) 50%, Ganatra *et al.* about 85% (27 cases), while Viswanathan (1948) condemned it as ineffective.

The average duration of treatment in arsenic-treated cases is 20 to 30 days. With oral diethylcarbamazine 58% were cured within 10 days and 86% within 16 days.

Usefulness in Arsenic-resistant Cases.—Not infrequently physicians have encountered patients who are resistant to arsenic therapy, and are at a loss to do anything for them. Misra *et al.* (1958) obtained a good response in such cases with pyrexia therapy, using

T.A.B. vaccine. Oral diethylcarbamazine offers an easy cure for such cases with none of the disadvantages of pyrexia therapy.

One of us had previously found that the results of parenteral therapy were disappointing. It is concluded that an initial injection of 800 mg. produces toxic reactions and causes marked respiratory depression. In addition to these drawbacks, and the disadvantages of the mode of administration, parenteral administration failed to cure seven out of eight cases and caused an initial symptomatic aggravation.

Summary

Experience with 58 cases of tropical eosinophilia is reviewed; 50 were given oral and 8 parenteral treatment.

The findings are compared with those of Ganatra *et al.* (1958).

The therapeutic efficiency of oral diethylcarbamazine is equal to that of parenteral arsenic therapy. Its advantages over parenteral arsenic are: (a) earlier symptomatic relief; (b) no initial eosinophilia; (c) a quicker cure; (d) no toxic side-effects with a daily dose of 8 mg./kg., no initial worsening of symptoms, and no intolerance by the patient; (e) it is given orally; (f) it is cheaper; and (g) it can effectively cure arsenic-resistant cases.

We suggest that an oral dosage of 8 mg./kg. is ideal, and conclude that treatment should be continued till an adequate haematological response is obtained.

Parenteral therapy with diethylcarbamazine has been disappointing, and an initial dose of 800 mg. causes toxic symptoms and is sometimes dangerous.

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