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PULMONARY ACARIASIS: A POSSIBLE CAUSE OF ASTHMA

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During the past two years we have observed a remarkably heavy incidence of bronchial asthma among patients admitted to this hospital. Investigation resulted in the following preliminary observations:

1. A certain proportion of asthmatic patients showed a high degree of eosinophilia, ranging from 40% to over 80%.

2. These cases rarely gave a previous history or family history of asthma or other allergic manifestation.

3. The existence of alimentary parasitism, a common tropical cause of eosinophilia, was excluded by the usual pathological tests.

4. The response to treatment by antispasmodics, vasodilators, iodides, opiates, and other sedatives, autohaemotherapy, and, in severe cases, oxygen by inhalation and by subcutaneous administration, intravenous adrenaline, lumbar puncture—if of temporary benefit to the patient, and even dramatic in status asthmaticus—was unsatisfactory as regards more permanent control of the condition.

Despite relief from symptoms, the eosinophilia persisted, and the patients were returned to duty, sometimes in a lower medical category, but mostly to be referred back again and again to hospital with recurrences of asthma, until their ultimate disposal was decided by a medical board who pronounced them unfit for further military service. For the period June, 1942, to June, 1944, bronchial asthma was responsible for 48% of respiratory cases and 21% of all cases invalidated out of the Army through the medical division of this hospital.

There seemed no alternative disposal for these cases at the time, and when the subject was discussed at a meeting of the Clinical Society of this hospital about ten months ago, Major T. R. Jansen, C.M.C., drew our attention to a refractory case of asthma in a civilian patient with massive eosinophilic leucocytosis which had been investigated by the Civil Medical Entomological Department. This case had shown the presence of mites in the sputum, and the patient had made a remarkable recovery on treatment by administration of pentavalent arsenic. This brought to our notice the research being carried out at the Ceylon Entomological Department by Carter, Wedd, and D'Abrera, who have since (1944) published an important paper on their preliminary observations on the occurrence of mites in human sputum and their possible significance. These observers have recovered from the sputum of 17 out of 28 patients suffering from respiratory complaints various types of mites, including species of the genera *Tyroglyphus*, *Tarsonemus*, *Carpoglyphus*, *Glyciphagus*, and *Cheyletus*. These mites were species commonly present in stored products, dust and debris of houses, shops, and stores, etc. Arsenical treatment was found to reduce the numbers of mites in the sputum and, in three cases with eosinophil counts of 38%, 42%, and 66%, to decrease the eosinophilia, with improvement in the respiratory condition. That the work of Carter, Wedd, and D'Abrera constitutes a significant advance in the study of the pathogenesis of certain respiratory disorders seems evident to us from their preliminary report and from the application of their methods of investigation to the

study of a series of cases of asthma with marked eosinophilia among soldiers under our observation.

Investigations

Our own investigations, which make no claim to completeness in scope or detail, were prompted by a search for some effective means of control over the number of asthmatic cases being invalidated out of the Army, and were directed chiefly towards the aetiological significance, if any, of occupation and environment in relation to the precipitation of this asthmatic syndrome, and towards the therapeutic merits of arsenic in effecting a durable degree of recovery that might enable these asthmatic soldiers to be returned as fit for duty. Our series of cases comprises, up to the present, Ceylonese soldiers from various regimental units who were admitted to hospital with asthma associated with an eosinophilia of over 4,000 per c.mm. The patients were kept under observation in a special ward with facilities for careful supervision of the examination and treatment carried out during this investigation. Discharge from hospital was decided, not by the clearing up of the asthmatic condition alone, but by the return of the eosinophil count to a satisfactory level.

Each patient's history was carefully scrutinized with special reference to any pre-existing personal or familial tendency to allergic diathesis as might be indicated by manifestations of hay-fever, urticaria, eczema, or migraine, in addition to asthma itself; pulmonary tuberculosis and other respiratory diseases; cutaneous and intestinal affections attributable to parasitic infestation; and blood diseases. Special attention was directed towards the patient's occupation and environment in a search for such factors as might expose him to inhalation of a mite-laden atmosphere.

Pathological data were collected from investigations which included the following: (1) Examination of blood for leucocytosis, eosinophilia, and alterations in the erythrocyte sedimentation rate. Differential counts were carried out daily by the method of 1,000-cell counts. (2) Examination of faeces repeatedly for ova, cysts, parasites, and Charcot-Leyden crystals that might indicate intestinal infection or infestation. (3) Examination of sputum for *B. tuberculosis* repeatedly, and by special technique for mites.

The examination of sputum for mites is a prolonged and tedious procedure involving special methods of preparation of the specimens and rigid precautions against contamination of the material by mites from extraneous sources. Twenty-four-hour specimens of sputum were collected direct in rubber-stoppered flasks and large test-tubes which had been specially prepared by thorough washing and flushing in running water to ensure adequate decontamination; the stoppers, which had been similarly decontaminated, were removed by the patient and held in his hand just long enough to permit the expectorated sputum to be discharged into the vessel, which was immediately re-stoppered tightly. The preparation of the sputum for examination was carried out according to the method described by Carter, Wedd, and D'Abrera.

"The fresh sputum was treated in the first place with an equal quantity of 1% potassium hydroxide; this was shaken and allowed to stand until the muco-purulent material had disintegrated. After a few hours, when the mixture had become more or less clear,

from 5 to 10 drops of Loeffler's alkaline methylene blue were added and the solution again shaken. Formalin sufficient to give a 10% concentration was then introduced and the mixture left until next morning (18 to 24 hours). The mixture was then centrifuged and the supernatant fluid drawn off; the deposit was examined under a binocular microscope."

Throughout this entire procedure scrupulous precautions have to be adopted against contamination of the sputum with mites from outside sources. The material has to be systematically searched under the microscope for the presence of mites, and the examination of a few smears, as for tubercle bacilli, is not sufficient for this purpose. The amount of labour and time involved in this procedure will be evident.

For radiological study of the course of the cases, skiagrams of the lungs were taken on admission of each case to the ward and

imposed during treatment, the "ordinary diet" of the hospital regime being allowed in every case except during febrile periods, when "milk diet" was substituted.

Case Records

Our present series comprises 30 patients, representing various military units: Army Service (10), Engineers (5), Artillery (6), Infantry (2), Medical Corps (3), Signal Corps (1), Military Police (2), Pioneers (1). For considerations of space detailed case histories are not reproduced here, but a tabulated analysis of the more significant positive findings is appended instead, together with notes on the aetiological, clinical, pathological, and therapeutic observations recorded during our investigation.

Tabular Analysis of Cases

Case No.	Age (Years)	Service (Mths.)	Duration of Asthma (Prior to Admission)	Occupation, Duties, Environment (Prior to Onset of Asthma)	Leucocyte Count		Eosinophil Count				Sputum Report	Treatment	
					Initial	Final	Initial		Final			Routine (Days)	Arsenical (Days)
							Per c.mm.	Per c.mm.	Per cent.	Per c.mm.			
1	18	3	3 weeks	Ration store sentry	37,000	7,000	73	27,010	4	280	Mites +	24	10
2	38	16	8 months	Quartermaster's store clerk	28,000	8,000	62	17,360	3	240	" "	30	16
3	28	18	3 weeks	Grocery store salesman	15,000	7,400	48	7,200	9	666	" "	11	28
4	32	18	3 months	Ration store steward	13,200	6,400	81	10,692	9	576	Mites not seen	30	14
5	42	19	2 weeks	Ration truck driver	17,000	6,800	63	10,710	11	748	Not examined	21	10
6	26	11	8 "	Ration store orderly	16,000	7,000	70	11,200	8	560	Mites +	30	18
7	26	24	3 years	General store salesman	15,000	6,800	56	8,400	5	340	Not examined	33	9
8	29	6	2 weeks	Tinker, petrol service depot	16,000	7,000	70	11,200	5	350	Mites not seen	40	18
9	24	12	2 years	Ration truck driver	14,000	7,600	56	7,840	3	228	Mites +	14	26
10	20	22	6 weeks	Quartered in hut near ration store	14,200	6,800	58	8,236	5	340	" "	12	25
11	26	3	2 "	Quartered in hut near ration store	15,400	8,100	80	12,320	4	324	Mites + +	15	20
12	19	27	3 months	Ration store sentry	10,600	8,800	59	6,254	10	889	Not examined	16	24
13	26	26	6 weeks	Quartered in disused ration store	19,200	6,400	38	7,296	6	384	Mites not seen	31	22
14	19	24	7 months	Ration orderly in cookhouse	16,400	6,500	54	8,856	7	455	" "	33	26
15	18	12	5 "	Ration-loading orderly	20,000	7,000	46	9,200	5	350	" "	20	33
16	26	20	4 "	Carpenter	17,000	6,400	54	10,880	5	320	Not examined	19	30
17	23	30	18 "	Ration-loading orderly	10,200	6,400	56	5,712	6	384	Mites +	11	17
18	27	18	4 weeks	Ration store and cookhouse orderly	15,400	6,400	54	8,316	2	128	Not examined	18	17
19	21	42	1 year	Pack and linen store orderly	16,000	7,800	46	7,360	4	312	Mites +	14	20
20	27	60	3 weeks	Ration truck duty	18,000	8,000	57	10,260	5	400	Mites not seen	10	17
21	29	24	5 months	Quartered in hut near ration store	28,000	7,600	62	17,360	3	228	Not examined	24	6
22	23	30	2 years	Quartered in hut near ration store	17,200	7,100	33	5,676	3	213	Mites +	24	27
23	29	48	1 month	Ration store orderly	11,000	6,900	50	5,500	4	276	" "	10	19
24	38	22	2 weeks	Quartered in hut near ration store	27,000	8,000	76	20,520	7	560	Mites not seen	13	10
25	32	24	1 month	Ration store and cookhouse orderly	24,200	7,600	70	16,940	4	304	Not examined	8	20
26	32	24	2 weeks	Ration transport orderly	18,600	7,000	38	7,068	5	350	Mites not seen	10	23
27	23	11	1 year	Grocery store salesman	14,800	7,000	72	10,656	7	490	Not examined	13	20
28	30	28	2 months	Ration-loading orderly	23,000	7,200	62	14,260	6	432	" "	8	20
29	20	24	6 "	Quartered in hut near ration store	25,000	7,000	70	17,500	7	490	Mites not seen	14	18
30	30	42	9 "	Ration store orderly	11,800	6,800	38	4,484	3	204	" "	14	8

repeated before discharge. Some of the patients were similarly examined during the course of treatment and the progress of their pulmonary condition observed by means of the altering appearances of the serial skiagrams.

A daily clinical check was maintained on the patients throughout the period of observation with the object of noting any relation between the degree of intensity of the asthmatic condition and that of the eosinophil count. While such clinical features as temperature, pulse rate, or eosinophil count could be accurately measured and charted, signs and symptoms of the nature of expiratory dyspnoea, prolonged expiration, or sibilant and sonorous rhonchi obviously do not lend themselves to similar methods of recording. However, an attempt was made to record the variations in the clinical course of each case by means of a block graph which served to provide a rough chart of the relative severity of the asthmatic condition from day to day.

Treatment was carried out in two stages: first, with routine anti-asthmatic remedies, and thereafter with specific therapy, the variations in response being recorded by means of the eosinophil chart and the clinical block graph. Routine treatment consisted of the pharmacopoeial "mist. asthmatica," comprising the usual remedies—potassium iodide, tincture of belladonna, and tincture of stramonium—but excluding any arsenical preparation. Additional measures for relieving severe dyspnoeic attacks—e.g., ephedrine, adrenaline, pituitrin—were employed whenever necessary, particularly when sleep was disturbed by nocturnal paroxysms. Specific treatment consisted in the oral administration of pentavalent arsenic. Stovarsol was the drug used at first, in the form of 0.26-g. tablets containing 27% arsenic. At an early stage of the investigation supplies of this drug ran out, and we decided to substitute carbarsone until it was again available. Carbarsone was administered in 0.25-g. tablets containing 28.85% arsenic. The daily dosage employed was one tablet twice daily of one or other of these preparations. No special dietary restrictions were

Aetiological Observations

The ages of the patients ranged between 18 and 42 years, and their periods of military service varied from 3 months to 5 years. With the exception of Nos. 14 and 19, who had suffered from lobar pneumonia, none of the patients gave a history of having been affected by any respiratory ailment other than that under investigation. Two patients (Cases 5 and 21) had been treated for mild attacks of dysentery of unspecified nature. None of the others gave a history of any intestinal infestation or of any cutaneous affection that might be associated with eosinophilia. Malaria figured in the past histories of 7 patients (Cases 5, 11, 12, 14, 16, 20, 22), but not in any prominent degree. There was no evidence of any tendency to an allergic state prior to the onset of asthma, which in all cases but three (Cases 7, 9, 27) had occurred after enlistment in the Army. The interval between enlistment and the onset of asthma in the other cases varied from 2½ to 35 months.

There was no indication of any familial tendency to allergic diathesis or to any respiratory disease or blood disorder in the case histories, with the exception of that of Case 19, where it was stated that one brother suffered from chronic bronchial asthma and another from early pulmonary tuberculosis, and that of Case 13, where a sister was said to be tuberculous.

Significant aetiological information was collected from an inquiry into the nature of the occupation and environment of the patients before the onset of asthma. No fewer than 25 of these 30 patients either had been engaged in orderly or sentry duties in ration stores, in loading or transporting rations, or had been quartered in the neighbourhood of ration stores. Of the remaining cases Nos. 2, 7, and 19 had worked in other dusty stores where linen, clothing, boots, pack articles, and miscellaneous goods of various descriptions were handled, while the carpenter (Case 16) had obviously been exposed to inhalation of sawdust

and the tinker (Case 8) had worked in a dusty petrol service store.

Clinical Observations

The onset of the condition was invariably slow and insidious, with an intermittent dry cough which became progressively more frequent and troublesome, particularly at night. Gradually the patients began to suffer from spells of expiratory dyspnoea with wheezing. These attacks, though generally mild and intermittent at first, became more and more frequent, causing increasing loss of sleep with a feeling of lassitude, malaise, and asthenia in the mornings, leading to a gradual impairment of general health and physical fitness. The duration of the asthmatic condition varied from 2 weeks to 3 years, and the constitutional symptoms rarely troubled the patient before his asthma had lasted about a month.

On admission to hospital the clinical picture was that of the usual symptom-complex of asthmatic bronchitis—cough with expiratory dyspnoea, hyperresonance of the lungs, prolonged expiration with sibilant and sonorous rhonchi audible all over the chest, and occasional leathery rales at the pulmonary bases. The sputum in most cases was scanty and viscid and never blood-stained; in a few cases there was no expectoration at all. One patient (Case 1) coughed up fairly copious quantities of stringy, tenacious mucus during the early stages, and felt considerably exhausted by his frequent and strenuous efforts at expectoration. Only 5 patients (Cases 3, 5, 7, 12, 28) showed a febrile temperature; but pyrexia was not a prominent feature of these cases, the temperature ranging from 99 to 101° F. and lasting from two to five days.

None of the patients showed signs of any cardiovascular disorder, enlargement of the spleen or liver, or cutaneous affection, such as psoriasis, scabies, etc. Appetite, digestion, and alimentary function were generally unimpaired, except for a mild attack of intercurrent enteritis in Case 3. No such allergic manifestation as hay-fever, urticaria, eczema, or migraine occurred in the clinical course of any of the cases.

Pathological Observations

Haematological examination showed a remarkably constant eosinophilic leucocytosis in the series of cases, with massive eosinophilia in many of them. The total leucocyte count ranged from 10,200 to 37,000 per c.mm., while the eosinophil concentration varied between 33% and 81%. It is from the absolute leucocyte count that the blood picture can best be appreciated. While there was no appreciable alteration in the total numbers of polymorphonuclear cells and lymphocytes, there was an enormous increase in the number of eosinophils, ranging from 4,484 to the massive concentration of 27,010 per c.mm. In assessing the degree of eosinophilia, therefore, the absolute count was used as the criterion of our initial and final records, but a percentage calculation based on daily 1,000-cell counts was employed for charting the course of each case. The eosinophils were mature cells that stained well and showed no abnormality. In a few cases the eosinophil count showed a sudden drop to a relatively low level without any special treatment, but only to rise after a brief remission. A good example of such a spontaneous temporary remission was patient No. 22, who on a previous admission to hospital recovered from his asthma with a sharp drop in his eosinophil count from 65% to 5% and was discharged, but was readmitted later with a recurrence of asthma and an eosinophilia of 33%. This case taught us the need for keeping such patients long enough under observation to decide whether the remission is temporary or not. In a few cases we found that asthmatic signs and symptoms were mild, or even temporarily in abeyance, while massive eosinophilia persisted. But in general there was a recognizable parallelism between the eosinophil content of the blood and the intensity of the asthmatic condition.

With the exception of a mild degree of secondary anaemia in a few cases there was no abnormality in the erythrocyte count or haemoglobin content of the blood. The erythrocyte sedimentation rate generally showed no appreciable deviation from the normal, apart from a few recordings of a slightly accelerated rate that was attributable to associated bronchitis.

The sputum did not show red blood cells, acid-fast bacilli, or any specific organisms on routine microscopical examination, but eosinophil leucocytes were sometimes observed. Mites of

either *Tyroglyphus* or *Tarsonemus* were found in 11 out of 21 cases whose sputum was examined by the special technique described by Carter, Wedd, and D'Abrera. This procedure—a tedious one involving prolonged and patient searching through a comparatively large mass of material in which the mites may rarely be present in more than scanty numbers—was a limited application in the circumstances. Some of the examinations lasted as long as five days (besides the two days or more needed for collecting and preparing the specimens) before mites were detected. Search was abandoned in cases in which no mites were seen within this period. There was rarely time for the examination of more than a single specimen of sputum from each patient. It was found that the chances of detecting mites seemed most favourable within three or four days of starting arsenical therapy. The scanty numbers of mites observed in our cases—rarely more than one or two—may be partly due to the fact that search was rarely continued after the first mite was detected in each specimen of sputum. In Case 11, however, about 14 mites were found in a specimen collected on the third day of carbarsone treatment.

Repeated examination of faeces showed mild infestation with *Ancylostoma duodenale* in Case 5; *Ascaris lumbricoides* in Cases 18 and 19; *Trichuris trichiura* in Cases 11, 12, and 18; *Blastocystis hominis* in Cases 4, 6, and 9; and *Trichomonas faecalis* in Case 12. Appropriate anthelmintic treatment was administered, but this produced no reduction in the eosinophil count, which in one of the roundworm cases actually rose afterwards. The urine showed no abnormality to routine chemical and microscopical tests, and there were no clinical indications for any special investigations such as for detection of mites in the urine.

Radiological Observations

Analysis of the radiological findings before treatment showed the frequent appearance of a pronounced catarrhal reaction of the finer lung markings, resulting in diffuse linear striations of a strikingly even and symmetrical distribution in both lung fields; this was suggestive of an acute inflammatory process resulting in a bronchitic or bronchiolitic reaction rather than of tuberculous infiltration. In addition there was a remarkable mottled effect produced by small, discrete, ill-defined spots disseminated throughout both lung fields; they were usually more evident in number and size in the hilar and basal zones. The hilar shadows often showed increased density. The combined effect of the shadows produced by the accentuated finer lung markings and by the mottling resulted in a hazy, ground-glass appearance, which proved to be so characteristic of the condition that several of the later cases received the concise radiological diagnosis, "Appearances of eosinophil lung present." These appearances seemed to be displayed best in the earlier cases, but were evident even where the asthma had lasted from 1 to 3 years (Cases 19, 9, 7). The chronic cases, however, more often showed appearances of certain associated changes such as chronic bronchitis, pleural thickening, emphysema, or prominence of the pulmonary artery. The mottling was not evident in a few cases the clinical condition of which was mild.

Re-examination of the lungs after arsenical treatment showed a remarkable change in the lung picture. The nodular opacities causing the mottling had disappeared and the linear striations had similarly disappeared or had subsided in intensity. The clearness of the lung parenchyma was in striking contrast to its original hazy appearance.

Therapeutic Observations

Each patient acted as his own therapeutic control by undergoing a course of routine treatment for asthma before being given arsenic. This stage of treatment varied from 10 to 50 days, some of the patients having already been under such treatment in other wards of the hospital before being referred to us. During routine treatment the eosinophil count dropped in Cases 4, 5, 11, 12, 14, 16, 18, and 21, and rose in Cases 1, 2, 7, 8, 13, 15, and 20, remaining at a relatively stationary level in the others. The most marked fluctuations were a sharp drop from 80% to 18%, with a subsequent rise to 52%, in Case 11; a drop from 60% to 28%, with a rise to 50%, in Case 12; a rise from 35% to 70% in Case 15; and a rise from 25% to 60% in Case 20. The clinical response to routine treatment was generally unsatisfactory, most of the patients showing

no improvement, others obtaining only temporary relief from their asthma. In Cases 2, 8, 10, 16, and 18 adrenaline injections were required to alleviate severe asthmatic paroxysms, mostly nocturnal; 8 injections of adrenaline m. vii with pituitrin 0.5 c.cm. had to be given in Case 16. Only Cases 9 and 12 showed any appreciable relief from routine treatment.

The stage of arsenical treatment varied in duration from 6 to 33 days, two tablets of carbarsone or stovarsol being administered daily. The response to arsenic was uniformly good and sometimes dramatic. Patient No. 7, who had suffered from asthma for 3 years, obtained no relief during 48 days of routine treatment, while his eosinophilia rose from 56% to 65%; from the very start of carbarsone treatment his eosinophil count dropped rapidly, and he was free from asthma in 3 days; he needed only 9 days' treatment with 18 tablets of carbarsone to complete his cure. Equally dramatic was the response in Case 21, in which the eosinophils dropped from 62% to 3%, with complete relief from asthma and restoration of pulmonary radiolucency, after 12 tablets of carbarsone in 6 days. Cases 1 and 5 completed treatment in 10 days with 20 tablets—of stovarsol in the former, and of carbarsone in the latter. Most of the patients showed a gradual haematological response to arsenic, Case 2 being a typical example; but alleviation of clinical symptoms was comparatively rapid in all cases. Several patients had exacerbation of symptoms between the third and sixth days of arsenical treatment. Cases 2 and 8 developed status asthmaticus on the fifth and fourth days respectively; the former was relieved by the continuous adrenaline injection technique of Hurst, but the second was more refractory and required lumbar puncture, which resulted in almost instantaneous control of the condition. The alarming manifestations in these two cases led to some diffidence about arsenical treatment on the part of other patients in the ward, and one was found secreting his tablets in a hollow tooth; thereafter the drug was administered in solution to prevent patients shirking treatment, which might have accounted for the delayed response in some of the cases. The criterion of cure was not the control of the clinical condition (which was generally effected in 7 to 10 days) but the reduction of the eosinophil count to a satisfactory level, and arsenic therapy was continued accordingly. There was no appreciable difference between carbarsone and stovarsol as regards the clinical response and control of asthmatic symptoms; but the former generally produced a more satisfactory and prompt haematological response, while the delayed reaction of the latter drug in this respect entailed a more prolonged period of medication. Both drugs were well tolerated, considering that several patients were under treatment for over 20 days.

Up to the present (over 9 months since the first patient was discharged from hospital) no recurrence of asthma has been reported in any of these patients by their regimental medical officers, while several who have been re-examined have shown a normal haematological picture.

Conclusions

This series represents a distinct group of asthmatic cases with marked eosinophilic leucocytosis and characteristic radiological appearances of the lungs. They showed no familial or pre-existing susceptibility to the disease. The response to orthodox methods of treatment was strikingly unsatisfactory in comparison with the remarkable control produced by pentavalent arsenical therapy.

The syndrome appears to correspond with that described in India by Frimodt-Møller and Barton (1940) as "a pseudo-tuberculous condition associated with eosinophilia," by Weingarten (1943) as "tropical eosinophilia," by Treu (1943) as "pseudo-tuberculosis of the lungs with eosinophilia," by Simeons (1943) as "benign eosinophile leukaemia," and by Chaudhuri (1943) as "eosinophil lung." Similar cases had been reported from Ceylon by Carter, Wedd, and D'Abrera (1944), from Egypt by Parsons-Smith (1944), and from the United States (in an ensign eight months after his return from India) by Emerson (1944).

The duration of asthmatic symptoms in our cases varied between 2 weeks and 3 years. The symptomatology differed

from some of the cases reported by previous observers in the absence of splenic enlargement and the infrequency of pyrexia, while the occurrence of bronchial asthma in every one of our patients was due to the fact that the investigation was particularly directed towards this condition.

Diagnosis.—The differential diagnosis involves the exclusion of pulmonary tuberculosis, pneumoconiosis, and bronchomycosis as causes of the respiratory manifestations, and of helminthiasis, cutaneous infestations, and certain haematological disorders in relation to the eosinophilia.

Pulmonary tuberculosis is negated by the absence of *B. tuberculosis* in the sputum, by the haematological findings, by the lack of clinical evidence, and by the remarkable response to arsenic therapy. The diffuse and symmetrical infiltration seen in the skiagrams of the lungs is alien to tuberculosis, though the mottled appearance due to the disseminated nodular opacities may simulate miliary tuberculosis; but the spots are smaller and less clearly defined, and the linear striations more accentuated, than in miliary tuberculosis.

Pneumoconiosis was a not unlikely possibility in our patients, whose lungs showed a suggestive radiological picture after a definite history of exposure to a dusty environment. But the mottled effect and the absence of diffuse fibrotic changes in the skiagrams, the rapid restoration of normal pulmonary radiolucency after arsenic therapy, together with the fact that eosinophilia is not pathognomonic of pneumoconiosis, serve to eliminate this condition from the diagnosis.

Bronchomycosis, which might have been suggested by some of the skiagrams, was excluded by the absence of fungal hyphae or blood in the sputum, and by the therapeutic response, not to potassium iodide, but to arsenic.

Helminthiasis might play a part in the production of eosinophilia and even in producing transient localized pulmonary infiltrations as in Loeffler's syndrome, where it has been presumed that the migration of helminth larvae through the lungs may be responsible for these changes. Negative evidence of any significant helminth infestation precluded these factors in our cases.

The possibility of cutaneous infestation, psoriasis, and eczematous and other dermatoses as causative factors in eosinophilia did not arise in any of our cases.

Eosinophilic leukaemia—a rare blood disorder associated with massive eosinophilia in which the leucocytes show evidence of immaturity in size and form—was excluded by the absence of any such abnormality in the cells seen in our cases, and by the absence of splenomegaly. Simeons has remarked that many of the eosinophils show evidence of having reached a more advanced stage of development in nucleation and lobulation.

Such anomalies as "idiopathic eosinophilia" and "hereditary eosinophilia" can be excluded on aetiological, clinical, and radiological grounds. Mite infestation might provide a satisfactory explanation of the former condition where haematological changes might be the sole reaction.

Spirochaetal agency might be suggested by the specific response to arsenic. The pre-eminent virtues of arsenic as a spirochaeticide need not preclude its therapeutic efficiency in other conditions any more than in the case of potassium iodide, mercury, or bismuth. Syphilis is not suggested in this condition by the clinical, radiological, or haematological findings. Serological tests by previous workers have provided no evidence of a syphilitic pathology in this syndrome, apart from coincidental infection in a few cases. Postulation of some obscure spirochaetal agency on grounds of the therapeutic reaction must await satisfactory confirmation. Meanwhile, the discovery of mites in the sputum of these patients is a positive factor upon which further inquiry and investigation can be based.

Treatment.—The eminently successful and often dramatic response of this syndrome to arsenical therapy is now well established. This was first observed by Weingarten in 1936, through one of his cases contracting syphilis; after four injections of neoarsphenamine the patient's subjective symptoms vanished and his eosinophilia showed a remarkable drop. In 1941 Treu obtained similar results by the trial of acetylarsan intramuscularly. Simeons used mapharside in 10% calcium gluconate with equal success. Since then other observers have confirmed the excellent therapeutic response—clinical, haematological, and radiological—to arsenic in this condition. Our present series of cases was treated by oral administration of carbarsone or stovarsol with a view to determining the value of such measures under circumstances in which facilities for parenteral therapy are not readily available, and our results justify the view that, even if the haematological response be sometimes delayed, oral treatment provides a very satisfactory means of dealing with this condition. From our experience

the period of treatment would seem to be appreciably curtailed by the use of carbarsone. Arsenic is not a new drug in the therapy of asthma. Aromatic arsenicals empirically added to asthma mixtures have given good results in the hands of the older practitioners, while more prominent success has followed the use of arsenic in organic form in recent times. The effect of this well-known parasiticide in an asthmatic syndrome associated with mite infestation may well provide a possible explanation of its long-standing merits in bronchial asthma.

Pathogenesis.—The demonstration of *Tyroglyphus* and *Tarsonemus* mites in the sputum of some of our cases lends support to the discovery of Carter, Wedd, and D'Abrera already referred to. The collection and examination of sputum specimens in our series were subjected to all possible precautions against contamination by mites from extraneous sources. One other case, referred from another ward of the hospital with a mite-positive sputum report, is not included in the present series as the precautions against extraneous contamination of the sputum seemed to be of doubtful efficiency. Carter, Wedd, and D'Abrera have eliminated the possibility of the mites being derived from the mouth or nasal passages of the patients by examining several specimens of saliva and nasal washings, none of which showed mites. Controls, using distilled water without precautionary measures, were carried out at times when specimens of sputum were being collected; and vessels containing distilled water were exposed overnight in the vicinity of mite-infested patients. No mites were found in any of these controls. In all patients whose sputum contained mites the findings were confirmed by subsequent examination, while in 11 negative cases no mites were found at any time. The evidence collected by these observers strongly points to the inference that mites invade, and even breed in, the lungs and bronchi of patients, obtaining access by inhalation. We have adduced evidence to justify the inference that our patients had acquired their disability after the inhalation of mite-laden air. The majority of our cases had been exposed to dust emanating from rice and other cereals, pulses, flour, sugar, tea, coffee, cheese, dried fish, dehydrated vegetables, spices and other condiments, and various other dry rations and grocery products such as are issued in bulk through ration stores. A few patients had worked in depots where military equipment and miscellaneous articles such as linen and leather goods were stored. The frequent existence of tyroglyphid and tarsonemid mites in stores and stored products being recognized, all these patients must be regarded as having been exposed to the risk of inhalation of these mites, which were later recovered from their sputum in certain cases. Chronic respiratory disabilities are known to occur in workers exposed to inhalation of wood dust; this material is sometimes infested with fungi of various types, particularly when derived from decaying timber in dilapidated houses subject to "dry rot," and from sawdust from unseasoned woods. Mites of the genus *Glyciphagus* have been known to occur in sawdust, and this may explain the case of one of our patients, a carpenter, who had been exposed to inhalation of sawdust, chiefly from immature and unseasoned timber. In this connexion it would appear that the possibility of a similar causation in the condition that has been recently described as "bagassosis"—a respiratory affection occurring among workers in bagasse or the residue from crushed sugar-cane—deserves investigation in view of the fact that tarsonemid mites are known to occur on sugar-cane, causing serious damage to crops, while the frequency of tyroglyphid mites in sugar is notorious. In bagassosis, however, eosinophilia does not seem to occur, while spontaneous recovery from the clinical and radiological changes appears to be common. The pathogenic significance of acarine mites seems, so far, to have received but scant attention in the literature. Certain references to this subject cited by Carter, Wedd, and D'Abrera are of interest:

"Invasion of the human alimentary and urinary tracts by tyroglyphid and tarsonemid mites has been held responsible for certain pathological effects. Various forms of dermatitis have been known to occur through mite infestation—e.g., 'grocer's itch' in workers in shops and stores where *Tyroglyphus* mites abound; 'grain itch' and 'straw itch' among those handling certain crops infested with *Tarsonemus* mites—rice and other grains, tea, sugar-cane, pine-apples, etc. Cutaneous and asthmatic symptoms in mill-workers have been attributed to their handling of grain infested with the mite *Pediculoides ventricosus*. Horses fed on maize infested with

Tyroglyphus and other mites have been reported to have sickened and died as a consequence of respiratory and alimentary disorders. Monkeys are known to harbour parasitic mites of the genera *Pneumonyssus* and *Pneumotuber* in their respiratory organs, and these mites are stated to be capable of causing serious pathological conditions."

The pathological changes underlying the present syndrome remain obscure owing to lack of knowledge as to its morbid anatomy. The condition is essentially benign, though it may run a chronic course if untreated, and the possibility of a case going to necropsy is remote, except through some fatal intercurrent complication. The views of previous observers on the possible pathogenesis of this condition have been based on certain interpretations of the haematological and radiological findings:

Frimodt-Möller and Barton have expressed the view that an allergic origin is implied by the fact that eosinophilia dominates the syndrome. Weingarten at first favoured an allergic explanation of the condition, but later decided that such an interpretation is not acceptable, and emphasized the unquestionable influence of environment as an aetiological factor. This observer has also drawn attention to the striking similarity between the distribution of the radiological mottling of the lungs and that of the bronchial tree, and considers that the mottling represents bronchopneumonic infiltration of groups of alveoli, probably caused by peribronchial lymphatic spread. Chaudhuri has suggested that a widespread pulmonary infiltration by eosinophils with large granules might explain these radiological appearances. Treu has made the observation, in reporting one of his cases in which an intercurrent pneumonia interfered with arsenical therapy but was followed by complete cure of the original condition, that the pneumonic infection might be assumed to have acted as a severe protein-shock therapy. Simeons considered that eosinophilia with the changes he has noted in the nuclei and lobulation of these cells is pathognomonic of the disease, while radiological changes in the lungs are inconstant. He has also found that injections of liver extract increase the haematological abnormality. He considers the condition identical with the "grande éosinophilie sanguinaire" of French authors.

Eosinophilia being regarded generally as the prominent feature of this syndrome, it is interesting to note that Osler has mentioned that the eosinophil count may rise as high as 53% in asthmatic patients. The view that the mottling of the lungs seen on radiological examination may be due to focal eosinophilic infiltrations obtains support from two observations—the frequent expectoration of eosinophil cells, and the concurrent disappearance of both the radiological and the haematological abnormalities after treatment. Although massive eosinophilia and radiological mottling of the lungs are frequent and dominant features in this syndrome, the view that they are essential characters of the condition remains open to question, for atypical variations lacking one or both of these features would seem possible:

In 5 of the mite-positive cases examined by Carter, Wedd, and D'Abrera the blood picture was normal; in 5 others eosinophilia of 6% to 12% was observed. We have seen spontaneous remission of the clinical and haematological condition in 3 patients, one of whom (Case 22) later returned with a recurrence, the others (not included in the present series) being still under observation. Weingarten has remarked that radiography in chronic cases shows only pulmonary changes identical with chronic catarrhal bronchitis. This was also evident in a few of our cases, particularly among patients with mild clinical manifestations. Since our investigations were started several asthmatic patients admitted to other wards of this hospital with eosinophil counts of from 3% to 15% and no characteristic radiological appearances, who have failed to respond to routine treatment, have been successfully treated with arsenic. The number of asthmatic patients discharged cured from this hospital has shown an appreciable rise, while the number of men invalided out of the Army for this condition has correspondingly declined, since the introduction of pentavalent arsenic therapy.

If the view advanced by Carter, Wedd, and D'Abrera that this syndrome may, in part at least, be explained on the basis of mite infestation of the respiratory system be accepted, the question that next arises concerns the role of the mites in the pathogenesis of the condition. Even if the asthmatic symptoms be interpreted as due to reflex irritation of a hypersensitive bronchial system, the eosinophilia does not bear explanation in these terms, and an allergic causation would seem to be the more likely explanation. German authorities, cited by Carter, Wedd, and D'Abrera, have expressed the opinion that alimentary, respiratory, and cutaneous disorders may result as allergic

reactions to infestation with tyroglyphid mites. Further research is necessary, and doubtless will be forthcoming, to ascertain whether the mites occurring in the sputum of patients suffering from this syndrome are capable of producing a respiratory allergen—as, for example, some exotoxin or other secretion.

In the light of present knowledge this syndrome, which has hitherto been recognized as a fairly common tropical respiratory disease of obscure aetiology and pathology, would appear to be due, in some cases at least, to pulmonary acariasis caused by the inhalation of a mite-laden atmosphere and possibly inducing allergic reactions in the respiratory system. Although our investigations have so far concerned patients who have lived or worked in obviously mite-infested surroundings, such as ration stores, the liability to pulmonary acariasis from less evident and unsuspected sources must not be overlooked, for mites are widely distributed.

While living in an old house in Colombo, long ago, one of us (E. S.) developed asthma, which cleared up with a change of residence. Another occupant of that house was badly affected with asthma for many years. About thirty years later a medical colleague went to live in the same house, and he, too, developed asthma, which left him when he moved from there. This seems more than mere coincidence, and some obscure factor in the environment of that house—e.g., some constituent in the house dust or some particular flowers in its garden—must have been responsible for the asthma. Flowers have borne their share of blame for causing asthma over many decades. Mites are recognized pests of various cultivated plants and flowers; orchids, grown so freely in tropical gardens, and certain fragrant flowers much in vogue for personal adornment, household decoration, and temple offerings, are notable examples of this. The inducement offered by flowers to inhale their perfume has no doubt enhanced the reputation of their pollen as an asthmogenic agent. May it not be likely that mites harbouring in flowers are justly entitled to some share of this reputation?

The possible coexistence of pulmonary acariasis with other lung affections cannot be overlooked. Three cases of asthmatic bronchitis now under observation in this hospital, but not included in our present series, have shown eosinophilia with radiological evidence suggestive of tuberculous infiltration of the lungs; in one case the presence of both *B. tuberculosis* and *Tyroglyphus* mites in the sputum has been demonstrated. Mites have been found in the sputum of two cases of pulmonary tuberculosis recently examined at the Civil Medical Entomological Department of Ceylon.

In conclusion, the possibility that pulmonary acariasis may be responsible for other respiratory disorders besides asthma should not be ignored. Though our present investigations, for reasons already stated, were restricted to patients suffering from asthma, some of the cases described by previous observers as “pseudo-tuberculosis,” “tropical eosinophilia,” “eosinophil lung,” etc., have not been typical of bronchial asthma. Such cases, particularly when associated with a suspicious aetiology and resistance to orthodox therapeutic measures, might well be manifestations of pulmonary acariasis. The treatment of all such cases, whether asthmatic or otherwise, by the administration of pentavalent arsenicals is eminently worthy of consideration not only in the Tropics but anywhere that mites exist.

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THE URINARY ELIMINATION OF NICOTINAMIDE METHOCHLORIDE IN SUBJECTS WITH NORMAL GUMS AND WITH ACUTE AND CHRONIC GINGIVITIS

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The apparent similarity of acute ulcero-membranous gingivitis to pellagrous lesions of the mouth led Platt (cf. King, 1940) to suggest that nicotinic acid deficiency might play a part in the aetiology of the former condition. Subsequently King (1940, 1943, 1944) investigated the therapeutic effect of nicotinic acid and its amide on both acute and chronic gingivitis, and found that these compounds were highly beneficial. Other workers, however, have been unable to confirm these findings (Miller, Greenhut, and Roth, 1940; Ungley and Horton, 1943).

It was noted by Najjar and co-workers (1940, 1941a, 1941b, 1942) that a fluorescent pigment, “F₂,” could be obtained from the urine of normal dogs and normal human beings. The amount obtained was increased after the ingestion of nicotinic acid and several related compounds, but the pigment was absent from the urine of pellagrins and from that of dogs suffering from black-tongue. Further work (Huff and Perlzweig, 1943) suggested that “F₂” was nicotinamide methochloride, but two of us (Ellinger and Coulson, 1943; Coulson and Ellinger, 1943) have shown that nicotinamide methochloride in aqueous solution was non-fluorescent, that the substance present in the urine was also non-fluorescent, that this urinary substance was identical with nicotinamide methochloride, which gave rise to fluorescent “F₂” after alkalization and transfer to isobutanol, and that fluorescent “F₂” is probably a mixture of the *p*- and *o*-carbinol of N-methyl-dihydro-nicotinamide.

Before the nature of the compound had been established a method of assay for “F₂” in urine which gave relative but not absolute results was developed (Coulson, Ellinger, and Platt, 1942; Coulson, Ellinger, Glock, and Platt, 1942). Recently Coulson, Ellinger, and Holden (1944) have developed a quantitative method of assay for urinary nicotinamide methochloride. This method of assay forms the basis of a convenient test to indicate the nicotinamide level of the body.

This paper, which reports part of an investigation into gingivitis in the Royal Air Force initiated by Air Marshal Sir H. E. Whittingham, Director-General of Medical Services, presents the results obtained from the estimation of nicotinamide methochloride in the urine of subjects with gingivitis and those with normal gums.

Methods

Chemical.—(a) During the earlier part of the investigation, the composition of “F₂” or its precursor not having been determined, the method of assay which was used gave results in arbitrary units comparable with each other. (b) Subsequent to the identification of the precursor of “F₂” the quantitative method developed by Coulson, Ellinger, and Holden (1944) was used for the assay of urinary nicotinamide methochloride. The results of the first method cannot be converted into absolute values, since other factors, such as urinary electrolyte content, which were found to influence the assay, were controlled in the second method but not in the first.

The principle of both methods of assay is as follows. Aliquot portions of urine, the excretion rate of which was known, were absorbed on a Decalso column, which was subsequently washed with water and eluted with potassium chloride. The eluate was divided into two halves, both of which were extracted with isobutanol, one after alkalization with sodium hydroxide. The alkaline extracts were fluorimetrically compared with standards, while the neutral extracts served as reagent blanks.