and that even when the drug was discontinued in April, 1958, the polyneuritis progressed relentlessly until the full clinical picture of subacute combined degeneration of the cord was established by December, 1958. Moreover, this progression, despite treatment with a vitamin-B complex parenterally, suggested that malabsorption of these substances was not the primary cause of his neuropathy.

The skin lesions were believed to be those of pellagra, which is found in chronic deficiency of nicotinic acid and riboflavin (Sydenstricker, 1941). It is probable that the pellagra was caused by grossly impaired absorption of nicotinic acid, and this view is supported by the rapid response of the skin lesions to a parenteral vitamin-B complex. It is possible that isoniazid therapy, by interfering further with carbohydrate metabolism, contributed to the production of pellagra, since it is known that pellagra becomes worse during isoniazid therapy.

It is worth repeating that the neurological signs were unaffected by isoniazid withdrawal, by long-continued dosage of vitamin-B complex and folic acid, or by liver extract given parenterally for six weeks. This suggests that the primary cause was, in fact, a developing vitamin-B₁₂ deficiency, which liver extract was unable to prevent, presumably because of its low vitamin-B₁₂ content.

Summary

A case of non-Addisonian megaloblastic anaemia with subacute combined degeneration of the cord, associated with severe malabsorption in a structurally altered intestine, is presented. There was a history of tuberculosis treated with isoniazid.

It is suggested that before folic acid is given in the treatment of such cases deficiency of vitamin B₁₂ should be excluded, especially in the presence of early neurological involvement.

The possible relationship of vitamin-B₁₂ deficiency and isoniazid treatment to the neurological changes is briefly outlined.

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The 1959 edition of the Association of British Chemical Manufacturers' directory, *British Chemicals and their Manufacturers*, is now available. This new edition contains over 12,000 products named systematically and in accordance with British Standard 2474:1954—*Recommended Names for Chemicals Used in Industry*. Copies are available, free of charge, to all persons or firms genuinely interested in the manufacture or purchase of chemicals, from the association, Cecil Chambers, 86, Strand, London, W.C.2.

EXPERIMENTAL STUDIES ON BYSSINOSIS

BY

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Byssinosis is a disease occurring among cotton-mill workers (Schilling, 1956). Its main symptoms are dyspnoea and a feeling of tightness in the chest. These are usually most prominent when the workers return to the cotton-mill after absence from work for a few days, during the week-end, or a holiday. The respiratory symptoms are generally ascribed to the inhalation of the dust produced in the card-rooms of the mills. However, the way in which the dust produces the symptoms of byssinosis is not known. It has been shown that the symptoms are accompanied by a decrease of the maximal breathing capacity and an increase in airway resistance (McKerrow *et al.*, 1958). It has been suggested that histamine or some other active substance in the cotton dust is responsible for the dyspnoea of byssinosis. According to another hypothesis the symptoms are a manifestation of an allergic (antigen-antibody) reaction to the cotton dust (Haworth and Macdonald, 1937).

We have studied the effect of cotton dust on the lung ventilation in two men who had not previously been exposed to the dust in the cotton-mills. Extracts of cotton dust were inhaled in the form of an aerosol, and the changes in the lung ventilation produced by the extracts were studied with the nitrogen clearance method (Bouhuys *et al.*, 1956). This method involves continuous recording of the nitrogen concentration in expired gas during oxygen-breathing. The "lung-clearance index" (L.C.I.) (Becklake, 1952) is the amount of ventilation required to wash out the nitrogen from 1 litre of the lung volume down to 2% nitrogen in end-tidal gas. The clearance of nitrogen from the lungs is delayed, and the L.C.I. increased, in patients with asthma and in normal subjects after inhalation of histamine (Bouhuys *et al.*, 1960).

Experimental

The extracts were prepared from a sample of mixed cotton dust collected in a ventilator in a card-room. 3 g. of the dust was ground with sand in a mortar, 50 ml. of saline was added, and the sample was allowed to stand overnight at 4° C. The sample was filtered the next day and the filtrate used for the experiments. The activity of the extracts seemed to deteriorate with time, and for this reason fresh extracts were always used. The aerosol of the filtrate was produced in a nebulizer (Rooth, 1949) in the same way as histamine aerosols had been produced in a previous investigation (Bouhuys

et al., 1960). The subjects inhaled the extract from the nebulizer for 10 minutes. Immediately after this they started to breathe oxygen, the first inspiration being taken from the level of a normal expiration, and the elimination of nitrogen from the lungs was recorded. This wash-out procedure was repeated at intervals of 10 to 15 minutes during two to three hours, until the clearance of lung nitrogen had become normal again. Similar experiments were performed in the same subjects, using extracts of mixed house dust.

The subjects were both male laboratory workers. Subject B was 48 years of age and healthy; subject C was 33 and healthy at the time of investigation, but gave a history of bronchial asthma, which, however, had not caused more than occasional slight wheezing and dyspnoea for several years.

Results and Discussion

The results are summarized in the Table. Inhalation of cotton-dust extract (C.D.) increased the L.C.I. in these two subjects who had not been exposed to the dust in the cotton-mills previously. Inhalation of the house-dust extracts did not increase the L.C.I. In a previous investigation it was shown that inhalation of histamine aerosol increased the L.C.I. (Bouhuys *et al.*, 1960). The weakest histamine solution in the nebulizer that caused a measurable increase of the L.C.I. in subject C contained 5 mg. of histamine base per ml. The corresponding concentration for subject B was 0.05 mg. per ml. Thus B proved to be much more sensitive to inhaled histamine than C. In the present experiments B was found to be more sensitive also to the active agent in the C.D. However, the concentration of histamine in the C.D. was less than 0.001 mg. per ml. when determined with Code's (1937) method. Thus the increase of the L.C.I. caused by the C.D. could not be due to the histamine possibly contained in the C.D.

After inhalation of histamine the highest L.C.I. was usually recorded immediately after the inhalation, and the L.C.I. returned to normal within 15 to 45 minutes (Bouhuys *et al.*, 1960). The effect of the C.D. on the L.C.I. reached its maximum about 20 minutes after the

end of the C.D. inhalation, and it lasted for at least one hour. The dyspnoea caused by C.D. was accompanied by a feeling of general malaise.

The increase of the L.C.I. caused by histamine can be repeated on several consecutive days, but the effect of C.D. that had been obtained on first exposure to cotton dust did not occur after a second exposure on the following day. It could, however, be reproduced 5 and 60 days later. These findings are reminiscent of the symptom pattern in byssinosis.

These results of the inhalation of extracts of cotton dust, as well as some of the symptoms of byssinosis,

Blood-pressure records from two parallel experiments with cats weighing 2.5 kg. and anaesthetized with sodium pentobarbitone. The blood-pressure was recorded with a mercury manometer connected to a carotid artery. 1 γ H indicates intravenous injection of 1 γ histamine base, etc. 10 ml. saline and 10 ml. C.D. indicate intravenous injections of 10 ml. saline and cotton-dust extract respectively. N 3 mg. = intravenous injection of 3 mg. mepyramine maleate (neopyramine). 50 γ 48/80 = intravenous injection of 50 γ of compound 48/80.

might be explained if the cotton dust contained a substance capable of releasing histamine. We have performed some experiments with animal preparations which support the view that the C.D. used contains a histamine liberator.

When injected intravenously the C.D. caused a fall in blood-pressure in cats anaesthetized with sodium pentobarbitone (30 mg./kg.) (see Fig., upper curve). The fall in blood-pressure occurred after a latent period of about 30 seconds. A similar latent period was observed after injection of compound 48/80, a well-known histamine liberator (Dews *et al.*, 1953; Paton, 1957). The depressor response after injection of histamine, on the other hand, showed a latent period of about 12 seconds. When the same amount of C.D. was administered a second time to the same cat no fall in blood-pressure was observed. In another cat, pretreated with 3 mg. of mepyramine maleate per kg., the same C.D. did not cause any fall in blood-pressure (see Fig., lower curve).

Two isolated segments of guinea-pig ileum were suspended in separate baths, of about 5-ml. volume, containing oxygenated Tyrode solution (33° C.). Addition of 1 ml. of C.D. to the bath caused a slow contraction of the gut, quite different from the contraction elicited by histamine. The contraction reached its maximum after about seven minutes and persisted for

Lung-clearance Index After Inhalation of Cotton-dust and House-dust Extracts in Man

Subject	Date 1958	Inhaled Extract	Lung Clearance Index		Remarks
			Before Inhalation	Maximum Recorded after Inhalation	
C	10/10	C.D.	8.3	10.2*	Dyspnoea
C	11/10	C.D.	8.4	9.1	No complaints
C	10/12	C.D.	7.2	11.0*	Dyspnoea
B	10/10	C.D.	9.1	21.1*	"
B	11/10	C.D.	11.4	12.6	No complaints
B	15/10	C.D.	9.7	16.5*	Dyspnoea
C	14/10	H.D.	8.4	9.2	No complaints
B	14/10	H.D.	11.4	11.2	" "

C.D. = 10 minutes' inhalation of cotton-dust extract. H.D. = 10 minutes' inhalation of house-dust extract.

* Values outside the subject's normal range of L.C.I. (mean $\pm$ 2 S.D.), based on 21 control experiments in subject C (mean L.C.I. = 8.2; S.D. = 0.7; S.E. = 0.15) and on 18 controls in B (mean L.C.I. = 10.2; S.D. = 1.6; S.E. = 0.4).

a long time, even though the gut was washed repeatedly with fresh Tyrode solution. The contraction caused by 1 ml. of C.D. could be antagonized completely by mepyramine maleate (0.02 γ /ml. in the bath).

We have thus obtained some evidence that our C.D. contained a histamine liberator, and we should like to advance the hypothesis that some of the symptoms of byssinosis are caused by a histamine liberator in the cotton dust inhaled by card-room workers. Our evidence indicates that the histamine release can take place without a preceding antigen-antibody reaction.

Summary

Inhalation of an extract of cotton dust caused a delay in the clearance of nitrogen from the lungs during oxygen-breathing.

This effect, which presumably is due to bronchial obstruction, was obtained in two men who had not previously been exposed to the dust in cotton-mills.

The effect was not caused by histamine present in the extract.

The results of our experiments, as well as some of the symptoms of byssinosis, may be explained by the assumption that the cotton dust contains a histamine liberator.

Some evidence was obtained, from animal preparations, that the cotton-dust extract used here contained a substance capable of releasing histamine.

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In America six deaths from rabies occurred in 1958 and five in 1959 up to November 27. Of the 11 cases, five are attributed to dog bites, three to bites from bats, one to a bite from a fox, one to a bite from a skunk, and one unknown. While in the U.S.A. the animal mainly responsible for transmission is the dog, more and more evidence has been brought forward to show the importance of the bat in maintaining the infection in wild-life and causing infection in man. Since the first U.S. report of bat rabies was made in Florida in 1953, 359 cases of bat rabies have been reported in the U.S.A.; rabies in wild animals is found most frequently in the skunk, 1,005 cases being recorded in 1958. In Germany the bat appears not to be important in maintaining the infection in nature. The main reservoir is the fox: in 1958 1,017 cases of rabies in foxes were recorded in the Federal Republic. In Iran, rabid wolves are the greatest danger. The Iran Pasteur Institute reports, from 1949 to 1958, 443 persons bitten by wolves, with 39 deaths. Elsewhere, the dog plays the most important role. The complexities of the situation are, however, considerable, as exemplified by the Institut Pasteur of Algeria, which reports the following rabid animals in 1958: 915 dogs, 91 cats, 27 rats, 13 head of cattle, 10 donkeys, 9 jackals, 4 monkeys, 2 mice, 1 fox, and 1 rabbit. (W.H.O./55.)

EFFECT OF MENSTRUATION ON SCHOOLGIRLS' WEEKLY WORK

BY

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Menstruation has from the earliest times been regarded as an evil omen. Primitive and civilized people have made it the subject of endless taboos. Slowly and painstakingly evidence is accumulating which reveals the effect of menstruation on the different aspects of a woman's life (Morton *et al.*, 1953; Cooke, 1945; Bickers and Woods, 1951; MacKinnon *et al.*, 1959; Dalton, 1959). The more this knowledge is appreciated the more sympathetically can we regard the vagaries of womanhood, with the inequalities thrust upon her by hormonal variations of the menstrual cycle. This investigation was prompted by observing the mental dullness of many women when interviewed during the premenstruum.

In this study an analysis of data supplied by a girls' school is collated to show the effect of menstruation on general schoolwork, and, secondly, personal observations at another school suggesting its possible correlation with the behaviour of the schoolgirl.

Method

The data were collected from a public boarding-school for girls in south-east England during the autumn term. It is the custom at this school for each subject of the girls' work to be marked from 10 to 0 and these marks to be averaged each week, giving a weekly mark. The form mistresses of 15 forms supplied details of the weekly marks of 352 girls, aged between 11 and 17 years inclusive, and the matron supplied the dates of the girls' menstruations, which each girl entered in the usual book when collecting sanitary towels. The data were obtained without the knowledge of the teachers or girls. Bearing in mind that the weekly mark represents the average of 7 to 12 different subjects, marked by as many different teachers and covering 15 forms, it will be appreciated that the effect of an exceptionally difficult piece of work in one form in one subject or the inconsistent marking by a teacher due to her menstrual variation will be lost in the average of the weekly mark. In the analysis the weekly mark of each girl is compared with her mark in the week immediately preceding it to note if a rise or fall in grade has occurred; this necessitates the exclusion of the first week of term, the week following half-term holiday, and the week following any absences, as there is no weekly mark during the week immediately preceding it with which to compare.

Difficulties of definition arise because the school week has only five working days. The most marked symptoms of the premenstruum occur within the five days immediately preceding menstruation (Greene and Dalton, 1953), so for the purposes of this investigation the "premenstruum" was defined as the five days immediately preceding menstruation, and the "premenstrual" week as the week which contained at least three premenstrual days during the five-day school week. Similarly, the "menstrual" week was defined as