in untreated cases. The association between lympho-proliferative disorders and the prominence of these regions of the chromosomes which are peculiarly sensitive to alteration by the action of certain chemical agents may have some relevance to the choice of drugs to be used in treatment.

Summary

The characteristics of the circulating lymphocytes in Hodgkin's disease have been investigated in 20 patients. The methods used were (1) in vitro response to phytohaemagglutinin and (2) chromosome analysis.

Transformation Studies.—The percentage of the lymphocytes that transformed morphologically after stimulation with phytohaemagglutinin varied between less than 1 and 56 (normal controls 36–60%). The depression of response was correlated to some extent with the severity of the disease. In some instances a low transformation score was associated with total lymphopenia. The depression of response did not appear to depend on current or previous treatment. It was concluded that the deficiency in response is one of the manifestations of the disease.

Chromosome Studies.—Mitotic yields were often low, but better results were obtained with suspension cultures than with microcultures. Most of the aneuploid cells, or cells with anomalous chromosomes, which we observed could be attributed to the effects of treatment. The frequency of radiation damage was within expected limits as compared with patients irradiated for other diseases. An increased frequency of constrictions in the C9 chromosome and the occasional exaggeration of this constriction was observed. This represents a modification of a feature present in normal cells and is by no means specific to Hodgkin's disease, since it has been observed in lymphoid cells in cases of other malignant lymphomas and in plasmocytoma.

The studies gave no indication of the circulation of a population of chromosomally abnormal lymphocytes, the majority of cells analysed having a normal chromosome complement.

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Mushroom-worker's Lung

ALEX SAKULA,* M.D., M.R.C.P.

[WITH SPECIAL PLATE BETWEEN PAGES 708 AND 709]

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In recent years the increased demand for mushrooms as a table delicacy has led to the development of intensive methods of cultivation in mushroom-growing farms. Many workers are at present involved in mushroom growing, and are therefore exposed to any potential hazard which might be associated with the process

Mushroom growers have themselves been aware of the occasional development of various symptoms during the course of their work, but the only medical report of these was by Bringhurst *et al.* (1959), who described a respiratory disease among 16 immigrant Puerto Ricans working in the "Chester" County area of Pennsylvania, where 90% of the mushrooms consumed in the United States are cultivated. No special reports of similar cases have appeared since then.

In this paper four cases are described of mushroom workers in Sussex (where 50% of English mushrooms are cultivated) who developed respiratory disorders thought to be related directly to their occupation.

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Mushroom Cultivation

The common edible mushroom, *Agaricus hortensis* (or *Psalliota bispora*), is grown on natural compost, consisting of a mixture of wheat straw and fresh horse manure, which is allowed to become partially decomposed or composted. This composting takes place in two phases.

In phase 1, carried on outdoors, stacks of compost are exposed to the atmosphere for three weeks. In phase 2 the compost is placed on to large wooden trays, introduced into closed chambers, and subjected for several days to a peak heat of 55–60° C., and 100% humidity, produced by blowing live steam into the chambers. This pasteurizing process kills off the pests and organisms which would interfere with the growth of the mushrooms. Various thermotolerant and thermophilic actinomycetes find the conditions of both phases of the composting process conducive to their growth.

The compost is then cooled to 25° C., and planted with specially prepared mushroom mycelium grown on manure or grain (known as spawn). This spawning process is usually

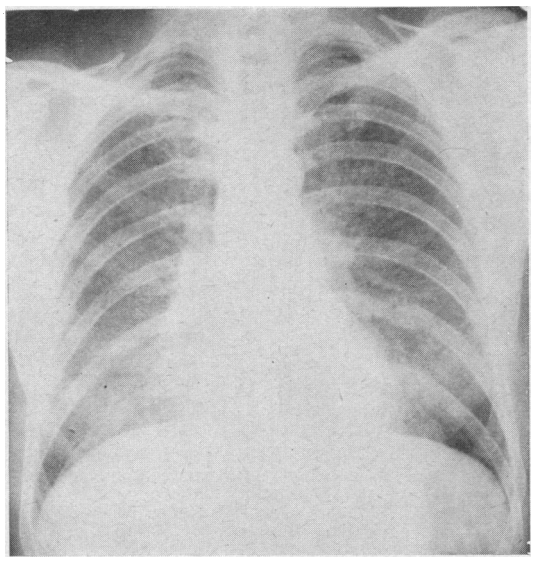

FIG. 1. — Case 1. Chest radiograph showing generalized mottling in both lungs and prominent hila.

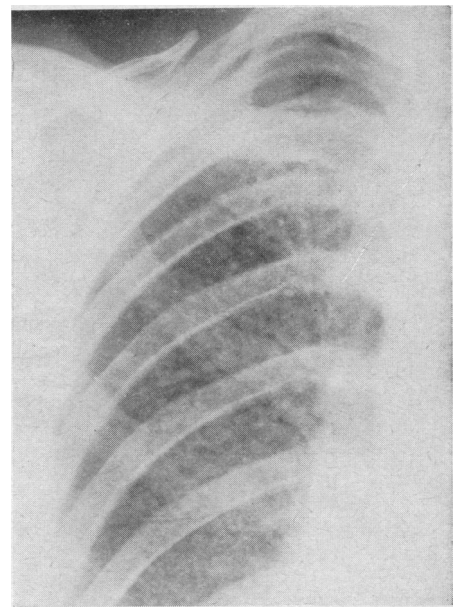

FIG. 2. — Case 1. Enlarged view of right upper zone of Fig. 1.

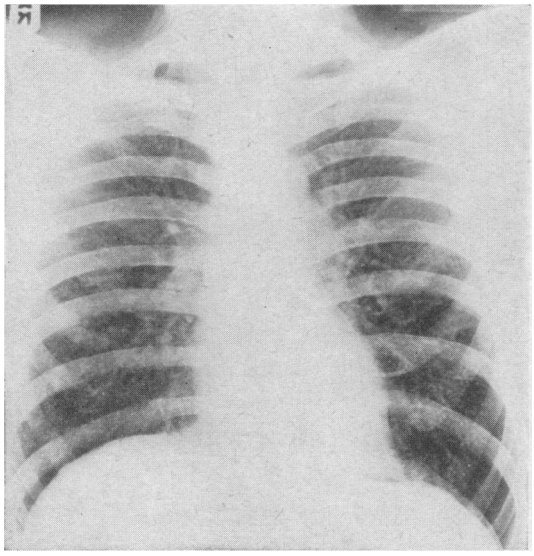

FIG. 3. — Case 2. Chest radiograph showing generalized mottling in both lungs.

FIG. 4. — Case 2. Enlarged view of right lower zone of Fig. 3.

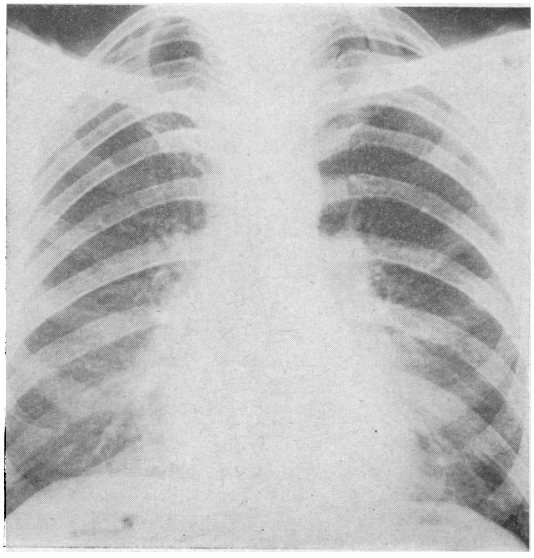

FIG. 5. — Case 3. Chest radiograph showing prominent hila and confluent mottling in both lungs, chiefly in lower zones.

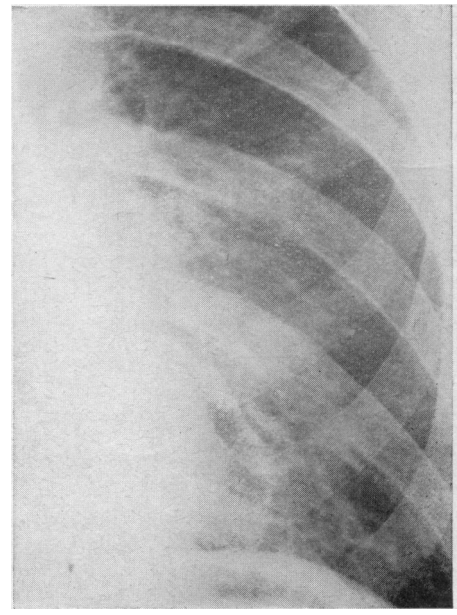

FIG. 6. — Case 3. Enlarged view of left lower zone of Fig. 5.

*

carried out by hand, either direct into the compost or by broadcasting the spawn on to the trays. The spawn is then mixed mechanically with the compost (through spawning), this process producing some disturbance of the compost with liberation of dust. Spawn running then occurs, the temperature being maintained at 20–25° C., with 90% humidity.

The compost in the trays is then covered or cased with a thin layer of peat-chalk mixture, which has previously been sterilized by heat or chemicals. This casing is necessary to encourage the fruiting of the mushrooms. The trays are then placed in the mushroom sheds, where the temperature is kept steady at 15° C. and the humidity at 80–90%, careful ventilation being maintained. The first growth or cropping will usually take place three weeks later, and the picking and packing of the mushrooms begins. Fresh flushes of mushrooms appear at weekly intervals, usually for six weeks. To prevent various parasitic diseases which might damage the mushrooms, various bactericides and fungicides—for example, formaldehyde—and pesticides and insecticides—for example, D.D.T.—are sprayed into the mushroom sheds. After the final picking the mushroom sheds are cooked out at 60° C., and the trays are emptied of the compost, which is dumped in a field.

It is during the spawning operation and when the mushroom sheds are emptied that most dust is liberated.

Case 1

A man aged 44 started work at a mushroom farm in November 1965 and was chiefly concerned with the spawning process. A month later he began to feel dizzy, developed headache and generalized muscle aches, and vomited. Cough and sputum ensued, and he became dyspnoeic on effort, with pain in the chest. When first seen in December 1965 he had ceased work, his symptoms were already subsiding, and there were no abnormal physical signs detectable in the chest. The chest radiograph showed a diffuse miliary mottling throughout both lung fields, the hilar shadows looking prominent (Special Plate, Figs. 1 and 2). Sputum culture produced a mixed growth of organisms; *Myobacterium tuberculosis* was not isolated. The tuberculin test was positive. W.B.C. was 8,000/cu. mm. (neutrophils 63%, lymphocytes 31%, monocytes 5%, eosinophils 1%); E.S.R. 8; serum proteins 6.4 g./100 ml. (albumin 4.1 g., globulin 2.3 g.). Skin allergy tests (including *Aspergillus fumigatus*) were negative. Serum precipitin tests were positive to *Micromonospora vulgaris* and negative to *Thermopolyspora polyspora* and to *A. fumigatus*.

During the ensuing month his symptoms cleared completely and the chest radiograph returned to normal. He ceased work on the mushroom farm, but when seen a year later, in April 1967, he was still bothered at times by undue dyspnoea and chest pain. A repeat of the serum precipitin test was negative to *T. polyspora*.

Case 2

A man aged 49 started work at a mushroom farm in February 1965. In December 1966 he became unduly dyspnoeic on effort, and developed cough and purulent sputum, these symptoms tending usually to be worse on Wednesdays, when he was engaged on spawning. The symptoms generally cleared by the week-end, only to return on the following Wesdnesday, when he needed to perform the spawning process again. His dyspnoea became so marked that he required to be admitted to hospital for one month, by the end of which time his condition had improved. On return to his former work, however, the respiratory symptoms at once occurred.

When first seen in February 1967 there were no abnormal physical signs in the chest. Chest radiographs showed a diffuse mottling in both lung fields, chiefly in the lower halves, but the hila were not prominent (Special Plate, Figs. 3 and 4). Sputum culture produced a light mixed normal growth. Culture for fungi was negative. *M. tuberculosis* was not isolated. The tuberculin test was negative. W.B.C. was 8,700/cu. mm. (neutrophils 67%, lymphocytes 29%, monocytes 4%); E.S.R. 13. Pulmonary function tests showed peak flow rate 415 litres per minute, forced vital capacity 4.05 litres, and forced expiratory volume in one second 3.25 litres (77% of F.V.C.). The serum precipitin test was positive to *T. polyspora*.

He remained away from his work and soon lost his respiratory symptoms; within two months the chest radiographs showed the lung mottling to have cleared completely.

Case 3

A man aged 47 was first seen in October 1960. He had been working at a mushroom farm for six months, being chiefly involved with the spawning process. He gave a six-weeks history of dyspnoea, this developing after what he had thought to be an "influenzal" illness. He was troubled by a spasmodic cough, little sputum, and attacks of dyspnoea several times daily. He felt weaker, had night sweats, and his weight dropped by 10 kg. Crepitations were audible over both lung bases. Chest radiographs showed a marked diffuse fine mottling, chiefly of the lung bases, to the extent that there was a "ground glass" effect, and the hilar shadows were prominent (Special Plate, Figs. 5 and 6). Sputum culture produced a mixed growth of organisms. *M. tuberculosis* was not isolated. W.B.C. was 4,500/cu. mm. (neutrophils 64%, lymphocytes 30%, monocytes 3%, eosinophils 3%); E.S.R. 18. The tuberculin test was positive. Skin allergy tests (including moulds and mushrooms) were negative.

After receiving penicillin and streptomycin by injection for one day he was remarkably improved. The antibiotics were discontinued, as it was thought that the rapid recovery suggested the subsidence of some sensitivity reaction rather than an infection. He returned to his former work, but was immediately troubled by bouts of dyspnoea, especially at night. Chest radiographs continued to show the mottled appearance at the lung bases. Treatment with prednisone was therefore started, and when seen a month later he had improved.

He returned to work at the mushroom farm, but was taken off the spawning process, though he remained in contact with the compost when emptying the trays and disposing of the used compost. When seen some years later, in April 1967, he was still bothered by undue dyspnoea and occasional chest tightness. Chest radiographs showed clearing of the mottling, though the right lung base looked fibrotic. Serum precipitin tests were negative to *T. polyspora* and *A. fumigatus*.

Case 4

A girl aged 17 was first seen in August 1960. She had been employed as a picker and packer in the mushroom sheds since leaving school at the age of 15. She had become subject to episodes of dizziness and cough for several months, but one week before being seen she developed anorexia and nausea, after which she became dizzy and more easily dyspnoeic, and chest pains developed. She had a cough, with purulent sputum, at times blood-stained. In addition, an irritating maculopapular rash appeared on the trunk and limbs. These symptoms developed within a few hours of entering the mushroom sheds, and cleared spontaneously after 48 hours' avoidance of the sheds. Clinical examination of the chest did not reveal any abnormal physical signs, and the chest radiograph looked normal. At first she was thought to have a simple bronchitis and and was treated with tetracycline, with improvement.

A month later she returned to her former work, but on re-entering the mushroom sheds she fainted on two occasions. Further investigation showed the chest radiograph to remain normal. Sputum culture grew normal flora. Culture for fungi was negative. *M. tuberculosis* was not isolated. The tuberculin test was negative. W.B.C. was 4,800/cu. mm. (neutrophils 62%, lymphocytes 31%, monocytes 7%). Bronchoscopy showed the bronchial mucosa to be pale and oedematous, and biopsy revealed normal histology. Skin allergy tests showed a positive reaction to moulds (including *A. fumigatus*), negative to mushrooms. Serum precipitin tests for moulds (including *A. fumigatus*) were negative. Cultures of specimens of the compost, the casing (peat and chalk), and sweepings of dust from the floor of the mushroom sheds all grew *A. fumigatus*. The serum precipitin test against *A. fumigatus* was negative.

The circumstantial evidence was strong enough to justify advising the girl to change her occupation. When seen six months later she had lost all her former symptoms. In April 1967 she was followed up, and was found to be quite fit; a chest radiograph appeared to be normal, and the serum precipitin test was negative to *T. polyspora*.

Discussion

In all four cases there was a definite occupational history of exposure to one of the mushroom-growing processes, the first three being definitely related to spawning. Usually some hours after exposure the initial symptoms of pyrexia, headache, dizziness, nausea, vomiting, or generalized muscle aches gave way to symptoms of acute respiratory distress, with cough, chest pain, dyspnoea, but not asthmatic wheezing. The radiological appearance of diffuse mottling seen in three of the cases could be easily confused with, for example, tuberculosis or sarcoidosis. In none of the cases was there a family or previous personal history of allergic illness, and skin tests were negative, with the exception of one case, which showed a positive test to moulds (including *A. fumigatus*). There was no eosinophilia. The symptoms cleared spontaneously on removal from the environment of the mushroom farm, but some degree of residual chest tightness persisted in two cases. A corticosteroid helped the symptoms of one case to clear. In two of the four cases the serum gave positive precipitin reactions to the actinomycetes *T. polyspora* or *M. vulgaris* respectively. In the other two cases the serological precipitin tests were not carried out at the time of the original illness but some years later, by which time the precipitin antibodies may well have disappeared.

Nature of Mushroom-worker's Lung

Respiratory disorders due to dusts of vegetable fibre origin were first described by Ramazzini (1700) in flaxworkers in Italy. Since then many similar conditions have been recognized, the best known being byssinosis from cotton, and bagassosis from sugar cane. The condition called farmer's lung was first described by Campbell (1932) in Westmorland. In recent years farmer's lung has come to be recognized as a not infrequent condition occurring in agricultural workers exposed to the dust arising from disturbing mouldy hay and other vegetable matter, and to be due to hypersensitivity to an antigen present in the dust of mouldy hay. The exact nature of this antigen was for long a subject of speculation, but the work of Pepys *et al.* (1963) showed that the antigens involved were the spores of thermophilic actinomycetes growing in the heated hay, chiefly *T. polyspora*, and rarely *M. vulgaris*. By means of agar-gel diffusion and immunoelectrophoresis it was demonstrated that the serum of the majority of patients suffering from farmer's lung contained precipitins to these organisms. In farmer's lung the subject develops constitutional and respiratory symptoms, usually three to six hours after exposure to the offending dust. The symptoms are unlike those of bronchial asthma; thus there is no wheeze, there is no eosinophilia, skin allergy tests are negative, chest radiographs show a diffuse miliary mottling, pulmonary function tests demonstrate an "alveolar block" diffusion defect, and lung biopsy reveals granulomata resembling those of sarcoidosis (Dickie and Rankin, 1958).

The clinical and radiological features of the first three cases described above certainly bear a close resemblance to those seen in farmer's lung. The finding of precipitin antibodies in two of the four cases provides the final evidence that mushroom-worker's lung is merely a variant of farmer's lung. The heating of the compost to 60° C. favours the growth of the thermophilic actinomycetes, and the inhalation of their spores provides the antigenic stimulus for the sensitization process responsible for the symptoms of mushroom-worker's lung.

Other factors which might possibly have been concerned in the aetiology of mushroom-worker's lung may be considered. Sensitivity to the mushrooms themselves or their spores does not appear to be the cause. Though *A. fumigatus* was demonstrated in the dust from the mushroom sheds there was no evidence that inhalation of these contaminant spores was responsible for the respiratory symptoms in the four cases described above. These symptoms do not seem to be due to allergy to any of the pests or insects which plague the mushrooms. For example, the mushroom fly, *Aphiochaeta agaraci*, may produce a specific allergic asthma (Kern, 1938; Truitt, 1951), but this is a different condition from that described in the present paper. Nor can the fungicides or pesticides be held responsible.

Nitrogen dioxide emanating from the disturbed compost was suggested as a possible cause of mushroom-worker's lung by Bringhurst *et al.* (1959), as the condition was thought to bear a resemblance to silo-filler's disease. In silo-filler's disease (Delaney *et al.*, 1956; Lowry and Schuman, 1956) workers are overcome by the poisonous fumes of nitrogen dioxide arising from chemical changes in the decomposing grain stored in the silos. There is, however, no evidence that in the mushroom-growing process any significant concentration of nitrogen dioxide is produced which would be responsible for the symptoms of mushroom-worker's lung as described here.

Conclusion

It is not claimed that respiratory disorders are very common among workers at mushroom farms. Nevertheless, certain individuals do become sensitized to the organic dust containing actinomycetes arising from the compost in which the mushrooms are grown. Dust is liberated when the compost is disturbed, as in the spawning process or on emptying the mushroom sheds and trays. Every precaution should be taken to ensure that workers potentially exposed to these dusts are protected from them, either by personal masks being worn or by efficient ventilation being maintained. A rapid "cool down" after pasteurizing of the compost may also impede the growth of the offending actinomycetes.

Summary

Four cases are described of workers at mushroom-growing farms in Sussex who developed respiratory symptoms resembling those seen in farmer's lung. Chest radiographs in three showed a diffuse miliary mottling, which cleared on removal from the environment of the farm. The serum of one case contained precipitins to *Thermopolyspora polyspora*, and the serum of another case contained precipitins to *Micromonospora vulgaris*. Thermophilic actinomycetes play an important part in the causation of farmer's lung. The process of composting in mushroom-growing farms favours the growth of these thermophilic actinomycetes, and the inhalation of their spores is responsible for sensitizing certain mushroom workers and producing the condition described here as mushroom-worker's lung.

I am grateful to Dr. R. Pillman and Dr. E. C. T. Evans for allowing me to quote Cases 2 and 3. The serum precipitin tests were carried out in the laboratories of the London School of Hygiene and Tropical Medicine and the Brompton Hospital.

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