signs. Chest radiography showed bilateral granular and nodular shadowing. A patch test for berylliosis was negative. Drill biopsy of the right lower lobe showed miliary granulomata, the outstanding feature of which was the presence of numerous conchoid bodies. The appearances were those of chronic berylliosis. A shallow right pneumothorax resulted from the drill biopsy but absorbed uneventfully. Treatment was started with corticosteroids, but without appreciable clinical or radiological improvement. He was awarded 20% industrial compensation.

Discussion

The first systematic approach to percutaneous lung biopsy was the needle aspiration method described by Martin and Ellis (1930). This technique produces a small specimen and has chiefly been used by investigators such as Lauby, Burnett, Rosemond, and Tyson (1965) for the differential diagnosis of pulmonary tumours.

In order to obtain a larger specimen for the study of diffuse lesions interest has recently centred on special needles incorporating a cutting mechanism. Manfredi, Rosenbaum, and Behnke (1963) published the results of 18 lung biopsies and advocated the use of a Franklin–Silverman needle. Smith (1964a) reviewed the literature and reported a series of 61 patients who had needle biopsy of the lung—39 with a Vim–Silverman and 22 with a Jack needle. In an addendum further experience with the Jack needle was mentioned, but he subsequently recorded one fatal pulmonary haemorrhage and recommended that the procedure should be performed in an operating theatre with a thoracic surgeon available (1964b). Krumholz and Weg (1966) obtained lung tissue in 56 out of 65 (86%) biopsies with a Franklin–Silverman needle on patients with diffuse lung lesions, chiefly sarcoidosis or interstitial fibrosis. Complications included 12 pneumothoraces, six of which required intubation, and two haemoptyses of 40–50 ml. Another patient with pulmonary hypertension, not included in the series, had a 750-ml. haemoptysis. A disadvantage of their method is that the patient has to hold his breath for 15–30 seconds.

Apart from the work of these authors, most of the reported techniques of needle biopsy have been directed towards a diagnosis of peripheral thoracic tumours, and biopsy of diffuse lung lesions has usually been performed by open thoracotomy according to the method described by Andrews and Klassen (1957). Although this ensures an adequate specimen of lung for histological examination, it entails a major surgical procedure and is subject to the usual complications of thoracotomy.

In our experience high-speed air-drill biopsy with the large trephine has proved successful in obtaining adequate specimens of diffuse lung lesions without the need for major surgery. It is performed at the bedside, thereby saving time in the operating theatre, although it is wise to arrange thoracic surgical cover. From the patient's point of view it is quick and painless, and breath-holding is not required. A further advantage is that the procedure can be repeated if an adequate specimen is not obtained or as a means of assessing the patient's progress.

Summary

One hundred biopsies of the lung or pleura have been performed with a high-speed air-drill over the last four years. A specially designed trephine, 2.1 mm. in bore, proved successful in obtaining adequate specimens from patients with diffuse lung lesions. With this trephine in its final form 33 out of 38 (87%) lung biopsies were successful. Conditions such as sarcoidosis, berylliosis, alveolar proteinosis, and eosinophilic vasculitis were successfully diagnosed. Complications were not serious and pneumothorax, which occurred in 15% of cases, was usually asymptomatic.

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Medical Memoranda

Agranulocytosis Coincident with Amodiaquine Therapy

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Agranulocytosis is recognized as a rare complication of amodiaquine therapy. Love, Foulk, Williams, and Mitchell (1953) reported two cases of leucopenia; Yates, Leeper, and Fishler (1955) reported a case of pancytopenia; and Kennedy (1955) described a case of absolute neutrophil leucopenia. Glick (1957) described fatal agranulocytosis following 200 mg. of amodiaquine daily for eight weeks, and Perry, Bartholomew, and Hanlon (1962) an almost fatal reaction with hepatitis and agranulocytosis after 200 mg. daily for seven days.

This paper reports four cases (one fatal) in which agranulocytosis occurred coincident with taking amodiaquine as a malaria suppressive.

Case 1

A previously healthy 20-year-old man, resident in Papua for only one week, was admitted to hospital with high fever, malaise, and a sore throat. He had taken 150 mg. of amodiaquine once or twice daily for three weeks, that dose having been prescribed in error as a malaria suppressive. He had never taken amodiaquine before, and was not taking any other drug. Haemoglobin was 14.1 g./100 ml., and the total leucocyte count 3,000/cu. mm., with no granulocytes. Bone-marrow aspiration showed an almost complete absence of developing granulocytes. Paul–Bunnell test was negative.

He was extremely ill from the onset, running a high fever and vomiting intermittently. A small blister on the knee developed into a spreading cellulitis from which *Pseudomonas pyocyanea* was isolated, the same organisms also being cultured from the blood stream. In spite of broad-spectrum antibiotics, digitalis, and corticosteroids he died on the fifth day in a state of "Gram-negative shock." Blood counts are shown in the Table.

CASE 2

A previously healthy man aged 30 was admitted to hospital with headache, fever, anorexia, joint pains, diarrhoea, and a sore throat. Haemoglobin was 14.4 g./100 ml., leucocyte count 2,000/cu. mm., with only 2% granulocytes. Thinking that he had malaria, the patient had taken 450 mg. of amodiaquine daily for five days. He had been in Papua for only four weeks, and had taken 300 mg. of amodiaquine twice weekly during this time. He was not taking other drugs, and had not had antimalarials before.

Being allergic to penicillin, he was treated with oxytetracycline, and later, when he developed a painful infected haemorrhoid, erythromycin and streptomycin were added. Fever persisted for 16 days and granulocytopenia for three weeks. He was discharged with a leucocyte count of 4,000/cu. mm., and 30% granulocytes (see Table).

CASE 3

A 57-year-old woman complained of pain in the back and epigastrium for one week and was thought to have cholecystitis. Haemoglobin was 11.7 g./100 ml., and there were 2,800 leucocytes/cu. mm., with 40% granulocytes. One week later, after a further attack of pain, the leucocyte count was 3,200/cu. mm., with an almost complete agranulocytosis. She had been in Papua for one month, and had taken 300 mg. of amodiaquine weekly. She had never taken this drug before, and was not having any other drugs.

She was admitted to hospital and treated with penicillin. On the third day her temperature was 103° F. (39.4° C.) and streptomycin was added. The agranulocytosis persisted, and on the fourth day prednisolone 15 mg. q.i.d. was begun. Two days later the percentage of granulocytes had increased, and by the third week the leucocytes showed a normal distribution (see Table). A Paul–Bunnell test performed in the third week was negative.

CASE 4

A 65-year-old man complained of severe sore throat, malaise, and earache. He was treated with penicillin, but three days later was unable to swallow because of pain. He was admitted to hospital, where haemoglobin was found to be 13.5 g./100 ml., leucocytes 1,100/cu. mm., with complete agranulocytosis. Pus from his inflamed ear gave a profuse growth of *Ps. pyocyanea*. He had been in Papua for 10 weeks, and had taken 300 mg. of amodiaquine weekly, but no other drugs.

He was treated with penicillin and oxytetracycline, but continued to run a fever of up to 104° F. (40° C.) for six days, after which his condition slowly improved. By the eleventh day his count had risen to 5,800/cu. mm., with 47% granulocytes (see Table), and he was then discharged.

Day of Illness	Case 1		Case 2		Case 3		Case 4	
	W.C.C.	G.	W.C.C.	G.	W.C.C.	G.	W.C.C.	G.
1	3,000	(0)	2,000	2%	2,800	40%	1,100	(0)
2	550	(1)	—	—			700	(0)
3	850	(0)	1,600	(2)				
4	600	(0)	—	—			800	(2)
5	650	(0)						
6			1,400	(2)			2,000	12%
8					3,200	(11)		
9								
10			1,300	(8)	3,500	(1)		
11					1,500	(10)	5,800	47%
12								
13			1,600	(2)				
14					1,000	15%		
15								
16			1,600	(5)	3,000	36%		
17								
18			1,600	(few)				
19					6,200	22%		
20			1,500	10%				
23					7,000	65%		
24			4,000	30%				

W.C.C. = Total leucocyte count. G. = Number of granulocytes either as a percentage of the total count or, where figure is in parentheses, total number found after a search for five minutes.

DISCUSSION

In all four cases amodiaquine was the only drug known to have been ingested in the month preceding the illness. In all four the granulocytes were the only elements of the blood to be affected, red cells, other leucocytes, and platelets remaining normal.

It has not been possible to prove that the agranulocytosis was caused directly by amodiaquine. In Cases 1 and 2 the possibility is strengthened by the fact that the drug was taken in excessive dosage (as in other fatal and near fatal cases reported). It is important for practitioners in temperate zones to familiarize themselves with correct dosage schedules for antimalarials.

The three non-fatal cases occurred in the same month, in European persons newly arrived in Papua. This suggests the possibility of an infectious disease or some other factor common to all three, either causing agranulocytosis or rendering them susceptible to the effect of amodiaquine. No such factor could be traced.

The amodiaquine taken by all four patients was Camoquin 150-mg. tablets. Tablets supplied in Cases 2 and 3 were referred to the manufacturer, and were reported to conform with official standards.

The cause of death in Case 1 appears to have been *Ps. pyocyanea* septicaemia, which was not recognized until the patient was in extremis. Corticosteroids did not seem to have a significant influence on the course of the illness, and were not given to two of the patients who recovered.

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ADDENDUM.—Since this report was written there has been a further fatal case of agranulocytosis in a 47-year-old Australian missionary at Wewak. He was admitted to hospital under the care of Dr. Vaughan with cellulitis of the foot, and had recently suffered from two boils and a paronychia. Bone-marrow and blood examination showed almost complete agranulocytosis, with thrombocytopenia. Despite intensive antibiotic treatment he developed acute gingivitis, pharyngitis, and otitis externa, and died after a few days. Cultures from blood, foot, throat, and ear all grew *Ps. pyocyanea*. He had taken 300 mg. of amodiaquine weekly since arrival in the Territory of Papua and New Guinea ten weeks previously, with an additional 2,100 mg. during the five days prior to admission. The only other drugs taken had been Aspro and tetracycline.

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