obstruction of the bronchi, with distension of the peripheral alveoli. These distended alveoli might subsequently rupture direct through the visceral pleura or into the interstitial spaces. In the latter case the air may then track along intrapulmonary tissue planes to the mediastinum, or peripherally to the subpleural surface, when blebs may form and subsequently rupture.

The rare occurrence of spontaneous pneumothorax in association with metastatic tumours of the lung is somewhat surprising, as lung necrosis is a conspicuous feature in such cases, and pleural perforation might be expected more commonly. Certainly few such cases have been recorded.

I wish to thank Dr. Neville Oswald for permission to publish this case. For the reports on the pathological findings I am indebted to Dr. J. W. Clegg.

REFERENCES

- British Encyclopaedia of Medical Practice* (1949). Cumulative Supplement, p. 331, edited by Lord Horder. Butterworth, London.
- Golden, R. (1941). *Diagnostic Radiology*, p. 158. Nelson, New York.
- Lodmell, E. A., and Capps, S. C. (1949). *Radiology*, **52**, 88.
- Perry, K. M. A. (1939). *Quart. J. Med.*, **32** (n.s. 8), 1.
- Steiner, P. E. (1939). *Amer. J. Path.*, **15**, 89.
- Thornton, T. F., and Bigelow, R. R. (1944). *Arch. Path.*, **37**, 334.
- Twining, E. W. (1938). In *A Textbook of X-ray Diagnosis by British Authors*, edited by S. Cockrane Shanks, P. Kerley, and E. W. Twining, **1**, 401. Lewis, London.
- Willis, R. A. (1948). *The Pathology of Tumours*, p. 731. Butterworth, London.
- Young, Sir R. A. (1936). *British Medical Journal*, **2**, 699.

HAEMOLYTIC TRANSFUSION REACTION DUE TO AN ANTI-LEWIS^a AGGLUTININ

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In April, 1950, a blood sample was sent to our laboratory from a woman aged 25. She had been admitted to the surgical department of this hospital, where a cholecystectomy was performed by Professor Dr. I. Boerema. Two hours after the operation she developed a severe shock, which was treated with blood transfusions. The total amount of blood given, from three different donors, was 1,500 ml. During the infusion of the second bottle there was a mild transfusion reaction with chill and a rise of the temperature to 38.7° C. The transfusion, however, was not discontinued, and blood from the third donor was endured without further

reactions. Nevertheless this patient showed the typical signs of a haemolytic transfusion reaction—that is, oliguria with haemoglobinuria—but made an uneventful recovery on being treated in the usual way.

A recheck of the patient's and donors' blood was made. Tables I and II show the results of the blood grouping and cross-matching of the patient's serum with

TABLE I.—Blood Groups

Patient	..	..	..	A ₁	..	MN	..	cde
Donor I	..	..	..	A ₂	..	MN	..	cde
Donor II	..	..	..	A ₁	..	MM	..	cde

cell suspensions of donors I and II. An Rh or M or N antagonism could be excluded. The patient's serum contained a cold agglutinin which was still active at body temperature. Incomplete antibodies could not be detected by the indirect Coombs test. We could as well exclude an A₁ and A₂ antagonism, the patient's serum reacting with both A₁ and A₂ cell suspensions at different temperatures. Out of 27 cell suspensions six were agglutinated at 37° C. and five at 44° C.—that is, in about 20%.

On the basis of this frequency we excluded the possibility of an antagonism of the systems H, Jobbins, Kell, and Cellano, and thought a Lewis antagonism most probable, for the following reasons: (1) we were able to prove the connexion between the secreting properties of the patient and the intergroup reaction under discussion, the patient being a secretor, the first donor a non-secretor, and the second donor a secretor; and (2) no agglutination occurred if the patient's serum was mixed with saliva of a secretor and red cells of the first donor (saliva inhibition test).

On these observations we felt justified in concluding that it was a haemolytic transfusion reaction due to the presence of an anti-Lewis^a agglutinin. It is therefore the blood of the first donor that must have been responsible for the haemolytic reaction.

Dr. van Loghem kindly controlled the serological examination in his laboratory. He could exclude the factors C^w, S, P, and Duffy as eventual causes of the transfusion complication (Table III). He also compared our serum with a known anti-Lewis^a serum and found identical figures. Hence he could confirm our results.

The occurrence of anti-Lewis^a agglutinins in human sera has been described several times already. However, it seems to be the first time that this antibody has given rise to a haemolytic transfusion reaction.* Fortunately the consequences of this discovery do not seem to be serious from the clinician's point of view. We may easily believe that the frequency of these reactions will be extremely low. Yet the occurrence of even such rare reactions compels us to take the necessary precautionary measures.

*It was learnt from a personal communication that both Mr. I. Dunsford (Sheffield) and Dr. M. M. Pickles (Oxford) saw similar transfusion reactions. Neither case, however, has so far been published.

TABLE II.—Cross-matching

		37° C.			Room			3° C.			
		1:1	1:2	1:4	1:1	1:2	1:4	1:1	1:2	1:4	1:8
Serum patient	Saline	++	+	±	++	+	±	+++	+++	+	±
Cells donor I	Albumin	+	—	—	—	—	—	+	±	—	—
Serum patient	Saline	—	—	—	—	—	—	+	±	—	—
Cells donor II	Albumin	—	—	—	—	—	—	+	±	—	—

TABLE III.—*Blood Groups*

Patient	..	A ₁ , MNS, Le(a-), cde/cde, C ^w -, Duffy+
Donor I	..	A ₂ , MNS, Le(a+), cde/cde, C ^w -, Duffy-
Donor II	..	A ₁ , MMS, Le(a-), cde/cde, C ^w -, Duffy-

The advance of our knowledge of antigens in human blood is a serious hint to transfusion workers not to contemplate blood transfusion as a routine procedure, but as a medical treatment which needs the closest consideration. Though by that means all undesirable reactions cannot be avoided, it may help to lessen their incidence.

We wish to thank Dr. J. J. van Loghem, jun., for controlling our results in his laboratory.

[After submitting this article for publication we became aware of a paper by V. I. Krieger and R. T. Simmons (*Med. J. Aust.*, 1949, 1, 85), which deals with a similar transfusion reaction.]

BIBLIOGRAPHY

- Andresen, P. H. (1948). *Acta path. microbiol. scand.*, **24**, 616.
 — (1948). *Ibid.*, **25**, 728.
 — Andersen, A., Jordal, K., and Henningsen, K. (1950). *Rev. Hémat.*, **5**, 305.
 Diamond, L. K., and Allen, F. H. (1949). *New. Engl. J. Med.*, **241**, 867.
 Grubb, R. (1948). *Nature, Lond.*, **162**, 933.
 — and Morgan, W. T. J. (1949). *Brit. J. exp. Path.*, **30**, 198.
 Loghem, J. J. van (1950). *Ned. Tijdschr. Geneesk.*, **94**, 312.
 Mourant, A. E. (1946). *Nature, Lond.*, **158**, 237.

Medical Memoranda

Codeine Sensitivity

In spite of the widespread use of codeine in therapeutics, only 12 cases of idiosyncrasy have been recorded in the literature, including an earlier case I reported (Mackenzie, 1949). However, the similarity between the reaction to codeine and one of the exanthemata makes awareness of the possibility a matter of some clinical importance, especially in view of the increasing tendency of the laity to take codeine compounds for a "cold" or sore throat. Publication of the following two cases therefore seems justified.

Case 1

A motor mechanic took two "veganin" tablets one evening for a "cold." The next morning he noticed an irritation affecting the whole body, and in the evening, 28 hours after taking the tablets, a rash appeared on the trunk and thighs and around the angles of the mouth. Next morning the rash was follicular, with a surrounding erythema; it was most marked over pressure areas, particularly the anterior folds of the axillae, the groins, and the belt area, but was present over most of the trunk and around the left angle of the mouth. He had some general malaise, which he put down to the original "cold." By the next day, without any special therapy, the rash had faded and the irritation lessened, and two days later the rash disappeared, soon followed by the irritation. There remained a fine powdery desquamation, particularly on the anterior folds of the axillae and over the lower face. The patient now felt well. He had never taken veganin before.

The specific nature of the reaction was demonstrated a few weeks later by giving a test dose of codeine phosphate, $\frac{1}{4}$ gr. (16 mg.) at 3 p.m. Irritation appeared on the lower lip at 7 p.m., and by 9 p.m. had spread to the trunk and thighs. About 11 p.m. a follicular rash appeared all over the body. Both rash and irritation remained through the next day, when a blood count showed 120 eosinophils per c.mm., and on the following day the rash was fading and the more severely affected parts were peeling. Two days later all that remained was some irritation in the belt area and on the thighs. While the rash was present there was

general malaise, headache, and nausea. There was no pyrexia throughout, and there were no lesions in the mouth.

Some weeks later the patient was given morphine, $\frac{1}{4}$ gr.: no reaction of any kind developed. He was then given codeine phosphate, $\frac{1}{4}$ gr., as a single dose, followed by "benadryl," 50 mg. three times daily. The rash and general symptoms appeared as before, but on this occasion there was practically no irritation.

Case 2

This patient, a girl aged 12, had been given two veganin tablets for a headache and sore throat in the evening. The following morning her body was covered with an irritating rash, which the district nurse reported as scarlet fever. When seen the second morning, the rash was fading, but there was still some irritation present on the chest and arms. Her temperature was 99° F. (37.2° C.). The fauces were inflamed and the tongue was coated. On the following day the rash and irritation had disappeared, leaving only a fine branny scaling.

Further inquiry showed that the patient was not sensitive to aspirin, but she had not previously taken any codeine compounds. Accordingly, two weeks later, when all signs and symptoms had subsided, she was given one tab. codein. co. B.P. (codeine content, 8 mg.). Four hours later an itchy macular rash appeared on the face, backs of the hands, and flexures of the knees, spreading in two hours to the chest. Within 24 hours the rash involved the whole body, but was most marked in the waist area and the flexures of the knees. During the next 12 hours the rash faded and the irritation lessened, and in a further 12 hours the rash and irritation had disappeared. There remained only a fine powdery desquamation for a further two days. There was no fever or malaise.

Several weeks later the patient was given a pill containing codeine phosphate, $\frac{1}{4}$ gr. (8 mg.). A similar reaction followed, and took the same course as already described. Some time after this had subsided she was given a tablet of morphine sulphate, $\frac{1}{4}$ gr. Four hours later she noticed a slight irritation of the skin, but no rash appeared.

No other member of the family showed any reaction following ingestion of codeine.

Comment

Case 1 differs from the one I previously reported and from Case 2 in that general malaise accompanied the reaction, and the idiosyncrasy was confined to the single opium alkaloid—codeine. In both cases here reported a definite desquamation followed. Neither patient had previously shown any allergic manifestations.

The pruritus and the rash, which may be macular or follicular at the onset, are the features common to all the recorded cases. In addition, some have shown desquamation, eosinophilia, and malaise.

According to the literature, skin tests have been used with varying success to demonstrate codeine sensitivity. In view, however, of the apparent rarity of the condition, their practical value must be limited. As with other suspected drug eruptions, the easiest and best test is the effect of repeating a small dose of the drug.

The literature has been reviewed by Scheer and Keil (1934) and by Seidmann (1943), who also reported further cases.

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REFERENCES

- Mackenzie, G. K. (1949). *British Medical Journal*, **2**, 266.
 Scheer, M., and Keil, H. (1934). *J. Amer. med. Ass.*, **102**, 908.
 Seidmann, M. (1943). *Arch. Derm. Syph., Chicago*, **47**, 654.