(Ahrens and Kunkel, 1949), and it has therefore been inferred that an increase in the ratio of phospholipids to cholesterol helps to prevent atherosclerosis. This view has been supported by the observation that the phospholipid:cholesterol ratio is smaller in atherosclerosis than in age-matched controls (Görtler *et al.*, 1950; Oliver and Boyd, 1953). The published studies on the relation between serum lipids and smoking do not include reports concerning serum phospholipids. In the present study phospholipids show no trend paralleling the smoking habits.

Attempts have been made to relate the rise in serum lipids observed in the previous studies in smokers to differences in the diet possibly due to smoking. Krut *et al.* (1961) have noted a difference in the perception of bitter taste between smokers and non-smokers. According to those authors this could lead to smokers having a preference for some special foods. The same group of investigators (Perrin *et al.*, 1961) have observed that smokers consumed more fat than non-smokers, but the difference was too small to explain the difference in serum lipids, and in Finland S. Punsar (unpublished data) could not detect any difference between the diet of smokers and that of non-smokers. Even the greater amount of fat consumed by smokers does not necessarily signify that all this fat is absorbed, for a recent study (Konttinen and Rajasalmi, to be published) has shown that the rise in serum triglycerides after a fatty meal is less in heavy smokers than in non-smokers.

The effect of giving up smoking should throw further light on the correlation between cigarette smoking and serum lipids, but in the only relevant report I found in the literature no change in serum cholesterol was detected in the six subjects studied (Thomas and Eisenberg, 1959).

The possibility has also been discussed that smoking could be another manifestation of the disturbance responsible for the rise in the serum cholesterol level, and in this connexion mental tension was incriminated as the cholesterol-elevating factor (Thomas and Murphy, 1958; Wertlake *et al.*, 1958; Grundy and Griffin, 1959; Dreyfuss and Czaczkes, 1959; Peterson *et al.*, 1960). It should be remembered, however, that mental tension cannot be measured but only estimated.

It is evident that further investigations of the relationship of smoking to the serum lipids are required.

Summary

Serum total cholesterol and the cholesterol content of the α - and β -lipoprotein fraction and serum phospholipids have been determined in a series of 314 healthy young men (range 18–25 years) starting military service, grouped according to smoking habits. There were no differences relating to smoking habits in any of the lipids studied.

Addendum.—Since the present study was made Acheson and Jessop (1961) have published their work on serum lipids in old men grouped according to smoking habits. They could find no association between cigarette or pipe smoking and serum cholesterol or β : α -lipoprotein ratio.

REFERENCES

- Acheson, R. M., and Jessop, W. J. E. (1961). *Brit. med. J.*, **2**, 1108.
 Ahrens, E. H., jun., and Kunkel, H. G. (1949). *J. exp. Med.*, **90**, 409.
 Anderson, J. T., and Keys, A. (1956). *Clin. Chem.*, **2**, 145.
 Blackburn, H., Brozek, J., Taylor, H. L., and Keys, A. (1960). *Ann. N.Y. Acad. Sci.*, **90**, 277.
 Bronte-Stewart, B. (1961). *Brit. med. J.*, **1**, 379.
 Dawber, T. R., Kannel, W. B., Revotskie, N., Stokes, J., Kagan, A., and Gordon, T. (1959). *Amer. J. publ. Hlth*, **49**, 1349.
 Doll, R., and Hill, A. B. (1956). *Brit. med. J.*, **2**, 1071.
 Dreyfuss, F., and Czaczkes, J. W. (1959). *Arch. intern. Med.*, **103**, 708.
 Fiske, C. H., and Subbarow, Y. (1925). *J. biol. Med.*, **66**, 375.
 Gertler, M. M., Garn, S. M., and Lerman, J. (1950). *Circulation*, **2**, 205.
 Gofman, J. W., Lindgren, F. T., Strisower, B., deLalla, O., Glazier, F., and Tamplin, A. (1955). *Geriatrics*, **10**, 349.
 Grundy, S. M., and Griffin, A. C. (1959). *Circulation*, **19**, 496.
 Hammond, E. C., and Horn, D. (1954). *J. Amer. med. Ass.*, **155**, 1316.
 — (1958). *Ibid.*, **166**, 1159.
 Jencks, W. P., Hyatt, M. R., Jetton, M. R., Mattingly, T. W., and Durrum, E. L. (1956). *J. clin. Invest.*, **35**, 980.
 Karvonen, M., Orma, E., Keys, A., Fidanza, F., and Brozek, J. (1959). *Lancet*, **1**, 492.
 Konttinen, A. (1959). *Ann. Med. exp. Fenn.*, **37**, Suppl. 7.
 Krut, L. H., Perrin, M. J., and Bronte-Stewart, B. (1961). *Brit. med. J.*, **1**, 384.
 Metropolitan Life Insurance Company (1943). *Statist. Bull.*, **24**, 6.
 Nikkilä, E. (1953). *Scand. J. clin. Lab. Invest.*, **5**, Suppl. 8.
 Oliver, M. F., and Boyd, G. S. (1953). *Brit. Heart J.*, **15**, 387.
 — (1955). *Ibid.*, **17**, 299.
 Perrin, M. J., Krut, L. H., and Bronte-Stewart, B. (1961). *Brit. med. J.*, **1**, 387.
 Peterson, J. E., Wilcox, A. A., Haley, M. I., and Keith, R. A. (1960). *Circulation*, **22**, 247.
 Thomas, C. B. (1958). *J. chron. Dis.*, **7**, 198.
 — (1960). *Ann. intern. Med.*, **53**, 697.
 — and Eisenberg, F. F. (1959). *Bull. Johns Hopk. Hosp.*, **105**, 14.
 — and Murphy, E. A. (1958). *J. chron. Dis.*, **8**, 661.
 Wertlake, P. T., Wilcox, A. A., Haley, M. I., and Peterson, J. E. (1958). *Proc. Soc. exp. Biol. (N.Y.)*, **97**, 163.

ALLERGIC REACTIONS TO TETANUS TOXOID

A REPORT OF FOUR CASES

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Tetanus is caused by the absorption of the toxins of *Clostridium tetani*. Established tetanus carries a poor prognosis, and among the 200 or so cases that occurred in England and Wales in 1959 there were 25 deaths (Registrar-General, 1961). Two substances are available for prophylactic treatment—tetanus antitoxin and tetanus toxoid. The former is a short-term prophylactic given at the time of wounding to effect passive immunization. Tetanus toxoid, a long-term prophylactic, is available as either alum-precipitated toxoid, used in the United States, or formol toxoid (Tet/Vac/FT), used in this country for active immunization. A primary course consists of three subcutaneous or intramuscular injections of 1 ml. The interval between the first and second injections is 6 to 12 weeks and that between the second and third injections 6 to 12 months. A reinforcing dose of 1 ml. every five years maintains an effective antitoxin titre.

Tetanus antitoxin may cause allergic reactions (Clarke, 1960); in comparison, tetanus toxoid is regarded as a safe and effective method of immunization. However, it is not generally realized that tetanus toxoid can also produce allergic reactions. Four such reactions are reported below.

Case Histories

Case 1.—A youth aged 19 had his first injection of Tet/Vac/FT in June, 1960, without a reaction. In August a second injection was followed within five minutes by generalized pruritus, angioneurotic oedema of the lips, and an urticarial rash on the trunk. Adrenaline (0.5 ml. of 1:1,000 subcutaneously), given immediately, brought considerable improvement. Promethazine hydrochloride ("phenegan") was given orally for the next two days (25 mg. eight-hourly). There was no personal or family history of allergy.

Case 2.—A young man aged 20 had his first injection of Tet/Vac/FT in June, 1960, with no ill effect. A further 1 ml. was given in August. Ten minutes after the second injection he had oedema of the eyelids and lips. Adrenaline (0.5 ml. of 1:1,000 subcutaneously) was given immediately with promethazine (50 mg. orally). Twenty minutes later he was free of symptoms and signs. He had no personal history of allergy; one sister is an asthmatic.

Case 3.—A man aged 30 had three injections of Tet/Vac/FT in 1953 at the correct intervals and no reaction occurred. In October, 1960, a further 1 ml. was given as a reinforcing dose and was followed within 10 minutes by a generalized urticaria. He was given adrenaline (0.5 ml. of 1:1,000 subcutaneously); no antihistamines were required. The patient gave a history of similar reactions after yellow-fever inoculation and T.A.B., but, unfortunately, no details were obtainable. There was no other personal history, or any family history, of allergy.

Case 4.—This patient, aged 40, had his first two injections of Tet/Vac/FT in January and March, 1953, but there was no record of a third. In November, 1960, a new course was started by giving a further 1 ml. Six days later he returned complaining of a sore arm; he was found to have considerable swelling at the site of the injection; no treatment was given. A further two days later he returned with general malaise and pruritus. On examination the swelling of his arm had increased, he had oedema of the eyelids and lips, and an urticarial rash on the upper half of his body. This reaction subsided rapidly after the administration of adrenaline (0.5 ml. of 1:1,000 subcutaneously). Chlorpheniramine hydrogen maleate ("piriton") was given orally for the next two days (4 mg. four-hourly). There was no family history of allergy, but the patient did suffer from mild eczema of his hands and forearms, probably associated with his job as a radiographer.

The same batch of Tet/Vac/FT was used in Cases 1 and 2; two different batches were used in Case 3 and Case 4.

Investigations

Scratch tests were performed in the following manner. About 0.1 ml. of Tet/Vac/FT was dropped on to the volar surface of the forearm and the skin scratched with a sterile needle, hard enough to break the skin without causing any bleeding. The site was observed for 30 minutes and the width of any weal then recorded. A normal saline control was used. The test was performed on the four cases and on 27 unselected volunteers, all of whom had had a full course of tetanus F.T. without a reaction. Of these controls, seven (26%) gave a personal history of allergy and three (11%) gave a family history of allergy. In all four of the cases there was a significantly larger reaction to the toxoid than to the saline (see Table). In the control group,

Width of Weal in Reactors

	Case 1	Case 2	Case 3	Case 4
Tet/Vac/FT	6 mm.	5 mm.	3 mm.	8 mm.
Saline	0 "	1 "	0.5 "	4 "

D

most (75%) reacted to neither the toxoid nor the saline, and none had a weal wider than 1 mm.

Discussion

In 1927 Ramon and Zoeller showed that tetanus toxoid stimulated active immunity in man, but it was not available in quantity for human immunization until 1938. Although early workers recorded very few reactions, there was in 1941 a sudden appearance of reports of anaphylaxis. These reactions occurred with both formol and alum-precipitated toxoid, and were seen after first, second, or subsequent injections. Investigations showed that the reaction was caused by the Witte peptone in culture broth. The problem was solved at that time when the medium was changed.

Since then most reports of reactions have come from the United States, where alum-precipitated toxoid has caused a large number of local reactions and a few general allergic ones. We could find no record of an anaphylactic reaction to Tet/Vac/FT since the 1941 episode. Indeed, in the literature accompanying the products of two firms it is stated categorically that there is no risk of producing an anaphylactic reaction (Beecham Research Laboratories Ltd., Form No. 6637; Parke, Davis & Co., Form No. 2109). These firms and some authors admit that general sensitivity reactions may occur (Stafford, 1960; Parish and Cannon, 1961). They emphasize, however, that these are rare. Parish and Cannon also state that the possibility is greater in those with a history of asthma, hay-fever, or other allergy. It is of interest, therefore, that only one patient had any personal history and only one any family history of allergy.

No exact figures of the incidence of reactions can be given. During the period covered by this investigation (six months) about 800 injections were given at the two establishments concerned (R.N. Hospital, Haslar, and H.M.S. *Collingwood*), suggesting an incidence of 0.5%. This estimate is probably too high.

The important point, however, is that allergic reactions to tetanus toxoid do occasionally occur. Therefore it would seem prudent to keep under observation for at least 10 minutes all those who have received an injection of tetanus toxoid.

These cases also emphasize the wisdom of keeping adrenaline available for instant use whenever inoculations are being done.

Summary

Four cases of allergic reactions to tetanus toxoid are noted. The significance of these reactions is discussed. It is emphasized that all those receiving tetanus toxoid should be observed for a short time after their injection.

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REFERENCES

- Clarke, C. A. (1960). *Practitioner*, **185**, 399.
 Parish, H. J., and Cannon, D. A. (1961). *Antisera, Toxoids, Vaccines, and Tuberculin, in Prophylaxis and Treatment*, 5th ed., p. 123. Livingstone, Edinburgh and London.
 Ramon, G., and Zoeller, C. (1927). *Ann. Inst. Pasteur*, **41**, 803.
 Registrar-General (1961). *Statistical Review of England and Wales for the Year 1959*. H.M.S.O., London.
 Stafford, E. S. (1960). *J. Amer. med. Ass.*, **173**, 541.