cyclocoumarol. The same patient received cyclocoumarol for a further myocardial infarction three months after his initial illness and showed similar sensitivity.

The two patients who were resistant to phenindione were also found to be resistant to cyclocoumarol. The first received 600 mg. of phenindione daily for two days without producing a therapeutic effect upon the prothrombin time. She was then given 200 mg. of cyclocoumarol daily for two days, but again with little appreciable effect. The second patient was given 350 mg. of phenindione daily for three days. When this failed to prolong the prothrombin time sufficiently he was given 150 mg. of cyclocoumarol without any effect on the prothrombin times of the subsequent three days. On the third day following the previous dose of cyclocoumarol a further 300 mg. was given, and this produced only a moderate increase in the prothrombin time to 32 seconds three days later. Our experience suggests that resistance to one oral anticoagulant implies resistance to another. Others have reported, however, that resistance to one anticoagulant does not of necessity mean that high doses of another will be required. Rotter and Meyer (1952) describe a patient in whom a therapeutic degree of prolongation of the prothrombin time was inadequately maintained on as much as 1,350 mg. of ethyl biscoumacetate a day. When therapy was changed to cyclocoumarol adequate therapeutic levels were produced on only 50 mg. a day.

Summary

The properties of cyclocoumarol as an anticoagulant are reviewed on the findings obtained in its use in 57 patients. The results are compared with those obtained in 125 patients given ethyl biscoumacetate and 179 given phenindione under similar conditions.

The following points of comparison are made: (1) A therapeutic degree of prolongation of the prothrombin time was effected more quickly with phenindione than with cyclocoumarol. For all practical purposes, phenindione was as rapid in its action as ethyl biscoumacetate. (2) Patients receiving cyclocoumarol and ethyl biscoumacetate showed greater and more frequent fluctuations in their prothrombin times during maintenance therapy than did those receiving phenindione. (3) The percentage incidence of haemorrhage was greatest in the cyclocoumarol series. (4) In the three series the response of the prothrombin time to vitamin K₁ was the same, but in some patients receiving the longer-acting drug cyclocoumarol the prothrombin time subsequently lengthened and necessitated repeated doses of the vitamin.

On the basis of these findings phenindione is a more satisfactory and more easily controlled anticoagulant than either ethyl biscoumacetate or cyclocoumarol.

We thank the many clinicians whose patients were treated with the above anticoagulants; Dr. J. Basil Rennie for his encouragement and assistance; and Drs. J. L. Markson and J. W. Chambers, clinical biochemists, in whose laboratory the prothrombin times were determined, for their helpful comments and advice.

REFERENCES

- Barker, N. W. (1952). *Transactions of 5th Conference on Blood Clotting and Allied Problems*. Corlies, Macey, New York.
 — Haason, H. H., and Mann, F. D. (1952). *J. Amer. med. Ass.*, **148**, 274.
 Battle, W. D., Capps, R. T., Orth, O. S., and Meyer, O. O. (1950). *J. Lab. clin. Med.*, **35**, 8.
 Brambel, C. J., Hunter, R. E., and Fitzpatrick, J. de P. (1950). *Bull. Sch. Med. Maryland*, **35**, 91.
 Covert, D. F. (1952). *Amer. J. med. Sci.*, **224**, 439.
 Rotter, R., and Meyer, O. O. (1951). *A.M.A. Arch. Intern. Med.*, **88**, 296.
 — (1952). *J. Amer. med. Ass.*, **150**, 1188.
 Stats, D., and Davison, S. (1949). *Amer. J. Med. Sci.*, **218**, 318.
 Toohey, M. (1950). *British Medical Journal*, **1**, 518.
 — (1953). *Ibid.*, **1**, 650.
 — (1954). *Ibid.*, **1**, 1020.

AN ASSOCIATION BETWEEN SOCIAL CIRCUMSTANCES AND APPENDICITIS IN YOUNG PEOPLE

BY

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The mortality from appendicitis is about 20% higher in men of social classes I and II (professional and managerial workers) than it is in social class V (unskilled labourers) (Registrar-General, 1954). There is also evidence that the forms of the disease severe enough to cause admission to hospital are commoner among those of higher social and economic status. Thus, Bailey (1951) showed that the proportion of undergraduates who had undergone the operation was higher in boys from the more expensive schools. Ferguson (1950a) found that, considering all the in-patient hospital treatment received by the people of Ayrshire, social classes IV and V had a disproportionately low number of admissions for appendicitis compared with the other social classes. Stewart, Webb, and Hewitt (1955) found the same trend in the proportions of men aged 30 to 44 years who had undergone the operation before being examined prior to military service in the 1939–45 war. However, they found no relationship between social class in a similar sample aged 17 to 29.

In the course of studies of the health of potential national service men, made by taking records of men examined before call-up by civilian medical boards of the Ministry of Labour and National Service, it was possible to study the frequency of the operation in different groups (Lee, 1955a, 1955b). The relevant results are given in Table I, and show that the proportion

TABLE I.—Proportion of Men who had Undergone Appendicectomy Before Their Pre-Service Medical Examination. Men Examined in 1953–4. By Type of School Attended*

Type of School:	Secondary Modern	Grammar, Independent
No. of men operated on for appendicitis ..	148	147
No. of men examined ..	4,352	2,419
Proportion operated on	3.40%	6.08%

$$\chi^2 = 8.49. \quad P < 0.01.$$

* Only data from centres in England have been used in this comparison, as the types of school in Scotland are different. The figures are reconstructed from a stratified sample—all the records of unfit men were taken, and one-quarter of the records of fit men. This selection was made in an effectively random manner. Because of the sampling procedure, the numbers in the cells of the contingency table are themselves estimates. χ^2 cannot therefore be calculated directly in the ordinary manner. The value of χ^2 quoted at the foot of the Table has been corrected by adding to the expectations in the denominators of the usual formula the variances of these estimates.

of men who had been operated on was much higher in those who had been educated at a grammar or independent school than it was among those who had been to a secondary modern or all-age school.

In these studies of men examined before national service, records were collected from a variety of centres. In view of most of the evidence given above, it was surprising to find that the proportion of men who had been operated on was much higher in a group of men drawn from Clydeside and the West of Scotland (Clydeside A in Table II) than it was in similar groups drawn from North-west London and the Home Counties. In my studies the rates found in North-west London and in the Home Counties agreed well with those found by Stewart (1955) in Southend, Northampton, and Leicester. These are also given in Table II. To check

TABLE II.—*Proportion of Men Who Had Undergone Appendicectomy Before Their Pre-Service Medical Examination. By Area*

Area:	Part of Home Counties (1)	North-west London (1)	Leicester (2)	Northampton (2)	Southend (2)	South-east Lancashire (1)	Clydeside A (1)	Clydeside B (3) (4)
Proportion of men who had undergone the operation ..	4.0%	4.8%	4.4%	4.0%	3.9%	5.0%	6.4%	7.2%
No. of men examined ..	1,823	460	4,870	4,387	4,424	602	271	587

(1) Previously unpublished data from studies of the findings of the medical boards that examined young men before military service in 1953-4. The numbers given refer to the actual examinations reported, and are not reconstructed populations. 63% of these men were aged 18, and almost all the rest were under 23.

(2) These figures are from Stewart (1955). The men were examined during the war, and were aged 17 to 19.

(3) These figures are from the special study made at the boards to check the high appendicectomy rate in young men found in this area. The men were aged 17½-18½ in 1955. This was a study specially directed towards appendicitis. This may explain the slightly higher value than Clydeside A, the data for which were taken from a general survey of all diseases. However, Webb (1955) showed that appendicectomy scars were reliably recorded by those boards.

(4) Because of the different conditions under which the various data used in the calculation of the different rates were collected, no formal tests of significance have been used. However, with samples of this size it is unlikely that the variations are entirely due to chance.

TABLE III.—*Death Rates from Appendicitis. Greater London and Glasgow Area.* Per 100,000 Per Annum Over the Period 1945-54*

Ages:		0-14	15-44	45-64	65 and Over	All Ages
<i>Males</i>						
Glasgow Area	Deaths	94	90	90	76	350
	Rate	3.5†	2.0	4.2	9.5	3.5
Greater London	Deaths	220	265	402	441	1,328
	Rate	2.5	1.5	4.3	12.7	4.4
<i>Females</i>						
Glasgow Area	Deaths	59	87	89	64	299
	Rate	2.2	1.8	3.6	6.3	2.7
Greater London	Deaths	169	187	270	419	1,045
	Rate	2.0	1.0	2.4	7.7	2.9

* As defined in the text.

† The excess of the Glasgow rate over the corresponding London rate is unlikely to be due to chance: $\chi^2=6.92$; $P<0.01$.

that the Scottish figures were reliable a further special study was made of the records. The figures are given in Table II as Clydeside B. Thus there seems to be, for young males, an operation rate substantially higher in Clydeside than in London.

Mortality from Appendicitis in Males

These variations in the geographical distribution of the operation in young men are not closely reflected by the total death rates from appendicitis, taking all ages together. This is not surprising, since in the latest series of hospital admissions published (collected in 1951) only 15% of the admissions of males were over the age of 44, while during the same period in this country 62% of the deaths in men from this condition occurred at greater ages than this (Registrar-General, 1953, 1955a). However, if the age-specific death rates are taken—here it has been done for Greater London and the Glasgow area*—we get a different pattern (Table III). There is a definite excess in Glasgow of deaths in the younger age groups.

Thus substantially higher operation and death rates from appendicitis have been demonstrated in the Glasgow area in

*A better comparison would be between the two conurbations of Greater London and Central Clydeside. This is not possible, as the figures have not been available for Clydeside for long enough to give stable rates. An approximation to this area has been made by taking the counties of Lanark, Renfrew, and Dunbarton, with their burghs, and adding their experience and population to that of Glasgow City. This was necessary as the boundaries of the conurbation cut across the older administrative units, in terms of which the figures are given. The population of this composite area was 2,103,000 in 1951. At the same census the population of the Central Clydeside Conurbation was 1,758,000.

young men. In view of the evidence that this disease is associated with high social and economic status, and that the proportion of people in social classes I and II is lower in Glasgow than it is in London (Registrar-General, 1952), this finding seems to indicate that there must be a further independent environmental factor in the causation of the disease, at least in the young.

The contrasted ways in which the appendicitis death rate behaves in young and old people are shown as we examine the rates for England, the Glasgow area, and the rest of Scotland. These are given in Table IV. The excess death rate of young people in the rest of Scotland is unlikely to be

TABLE IV.—*Death Rates from Appendicitis by Ages. England, the Glasgow Area, and the Rest of Scotland. Males. Per 100,000 Per Annum Over the Period 1945-54**

	England	Glasgow Area†	Rest of Scotland
<i>Ages under 15</i>			
Deaths	1,079	91	110
Rate	2.6	3.7	3.3
<i>Ages over 64</i>			
Deaths	1,667	68	130
Rate	10.1	9.5	10.7

* Excepting in each case 1950, the figures for which year for England have not been published in this form.

† As defined in the text.

the result of the distance that some of them live from surgical facilities, for it is also found in the Glasgow area. Further, this excess is not found in old people in the rest of Scotland. The excess death rate from appendicitis in males under 15 in the rest of Scotland suggests that the factor, whatever it is, is not confined to Glasgow. A similar excess is found in Wales.

Discussion

The operation of appendicectomy is performed both in the acute stage of the disease and when it is more chronic. There is controversy over the usefulness of the latter type of operation (*British Medical Journal*, 1955), and the practice of different surgeons varies widely. Thus it might be expected that substantial variations in the operation between different areas would not reflect real differences in the disease. But the differences demonstrated here apply to the death rates as well as to the operation rates. They are thus likely to reflect actual differences in the disease, and not in its treatment.

The geographical and social variations of the disease discussed here relate only to the fairly homogeneous population of this country. With greater differences in conditions—as when people in the West Indies or tropical Africa are compared among themselves or with Europeans—much greater differences in the prevalence of the disease emerge, which do not seem to be related to differences in the surgical care available (Leacock, 1952; Karn, 1952; Barker, 1952).

The geographical variation found in Britain seems to fit in with the evidence that there is a link between appendicitis and duodenal ulcer. The prevalence of duodenal ulcer seems to be high in young men in Glasgow (Doll, 1952), and “duodenal ulcer proved to be an important fallacy in the diagnosis of chronic appendicitis” in a series reported from Glasgow (McLennan and Watt, 1954). Further, the hospital admission rates among troops in the U.K. for these two conditions have moved in a similar way. From 1946 to 1952 both rates rose, at a time when the general level of sickness fell, and since then they have both fallen a little (War Office, 1954a, 1956).

No information is given by these inquiries about the distribution of the operation among females. It is known that the incidence of the operation is very high in young women (Ferguson, 1950b; War Office, 1954b; Ministry of Pensions and National Insurance, 1955). There is no rise in the death rate of young women, to correspond with this high operation rate (Table III). The mortality of females under the age of 15 is greater in the Glasgow area than it is in London, but the excess is not so great as for males.

The mortality from appendicitis is still far from negligible (969 deaths in 1954 in England and Wales) although it is falling. Allowing for changes in the age structure of the population, the mortality of the males is 27% of what it was in 1938 (Registrar-General, 1955b).

Age, sex, social class, and place of residence probably affect the incidence of the disease, and these and other factors certainly affect the incidence of appendicectomy and the death rate from appendicitis. The distinction between (a) the distribution of the disease, (b) the distribution of the operation, and (c) the mortality rate is necessary at the present time, as nothing is known about possible variations in the minor forms of the condition. The variety of factors that influence the operation and death rates, and interact in a complex way, seems to rule out the possibility of there being a single cause for the disease. At the present time we are almost entirely ignorant of what these causes may be. Fuller knowledge, while valuable for its own sake, might well lead to better treatment or rational prophylaxis. Thus the use of purgatives is still very common among young people—a problem to which Reid (1956) has recently drawn attention.

What is the geographical and social distribution of the use of these drugs? Is appendicitis related to their routine or sporadic use? The operation rate is very high in young women, while the death rate is very low. What proportion of these appendixes removed from young women show good evidence of inflammation? Is the severe disease commoner here, or do these young women have an excess of the minor forms of the disease? If they do, why is this so? Children and young people in certain areas seem unduly exposed to the disease. Is the disease process different from that found in old people, when the social distribution may be quite different? These and many other problems of the disease could be approached by epidemiological methods.

Summary

Young males are more likely to be operated on for appendicitis and to die of the disease in the Glasgow area than they are in London. This is an unexpected finding, in view of the association between appendicitis and high economic and social status. The existence of a further factor in the causation of the disease is postulated.

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REFERENCES

- Bailey, N. T. J. (1951). *J. Hyg. (Lond.)*, **49**, 81.
 Barker, E. A. (1952). *British Medical Journal*, **2**, 1045.
British Medical Journal, 1955, **1**, 776.
 Doll, R. (1952). In *Modern Trends in Gastroenterology*, edited by F. Avery Jones, p. 366. London.
 Ferguson, T. (1950a). *Hospital and Community. 11 Hospital-treated Sickness Amongst the People of Ayrshire*, p. 68. Nuffield Provincial Hospitals Trust, London.
 — (1950b). *Ibid.*, p. 66.
 Karn, H. M. (1952). *British Medical Journal*, **2**, 566.
 Leacock, A. (1952). *Ibid.*, **1**, 1347.
 Lee, J. A. H. (1955a). *Publ. Hlth (Lond.)*, **68**, 102.
 — (1955b). *Proc. roy. Soc. Med.*, **48**, 653.
 McLennan, I., and Watt, J. K. (1954). *British Medical Journal*, **2**, 736.
 Ministry of Pensions and National Insurance (1955). *Digest of Statistical Analysis of Certificates of Incapacity, 1953-4*. Table 7. Ministry of Pensions and National Insurance.
 Reid, J. J. A. (1956). *British Medical Journal*, **2**, 25.
 Registrar-General (1952). *Census of Great Britain, 1951. 1% Sample Tables Part I*, p. 83. H.M.S.O., London.
 — (1953). *Annual Statistical Review of England and Wales, 1951. Tables Part I (Medical)*, p. 158. H.M.S.O., London.
 — (1954). *Decennial Supplement, England and Wales (1951). Occupational Mortality*, p. 11. H.M.S.O., London.
 — (1955a). *Statistical Review of England and Wales, 1950-1951. Supplement on Hospital In-patient Statistics*, p. 66. H.M.S.O., London.
 — (1955b). *Statistical Review, England and Wales. 1954. Tables Part I (Medical)*, p. 58. H.M.S.O., London.
 Stewart, A. M. (1955). Personal communication.
 — Webb, J. W., and Hewitt, D. (1955). *Brit. J. Prev. Soc. Med.*, **9**, 147.
 War Office (1954a). *Report on the Health of the Army, 1951 and 1952*, p. 78.
 — (1954b). *Ibid.*, p. 79.
 — (1956). Personal communication of provisional figures.
 Webb, J. (1955). *Proc. roy. Soc. Med.*, **48**, 656.

INFLUENCE OF VITAMINS UPON SOME TERATOGENIC EFFECTS OF RADIATION

AN EXPERIMENTAL STUDY

BY

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Developmental malformations may readily be produced in the embryo by exposure of the dam to ionizing radiation during pregnancy (Hicks, 1953). Extensive investigations have been carried out upon chemical agents which either increase or diminish the radio-sensitivity of the tissues, but little attention has been paid as yet to the possibility that the teratogenic effects of radiation may be modified in a similar fashion. Wolff and Kirmann (1954), however, have shown that certain substances, such as cystamine, protect the developing tissues to some extent from the effects of x-radiation, and thus reduce the incidence of malformations in the offspring of dams exposed to x-radiation during pregnancy.

A large body of evidence has now accumulated which indicates that the induction of a maternal hypovitaminosis or hypervitaminosis is an effective method of producing a wide range of deformities in the embryo. The literature has recently been reviewed by Woollam and Millen (1956). Alteration of the maternal vitamin intake produces deformities in the young remarkably similar to those which occur when the dam is exposed to ionizing radiation during pregnancy. Defects of the eye and hydrocephalus which are readily produced by radiation (Hicks, 1953) also occur when the dam is subjected to the effects of hypovitaminosis or hypervitaminosis A (Giroud, 1955). The question naturally arises whether alteration of the vitamin intake of the dam during pregnancy might not have some effect in increasing or reducing the sensitivity of the young to the teratogenic action of radiation. The present communication deals with a group of experiments in which the effects of a combination of vitamins on the radiosensitivity of the foetus were studied.

Material and Methods

Preliminary Investigations.—It was considered necessary to concentrate on a single deformity, the presence or absence of which could be demonstrated unequivocally. Anophthalmia fulfilled this criterion satisfactorily. Preliminary experiments were therefore conducted to establish the time of administration and level of dosage of x-radiation which would produce a suitable standard incidence of anophthalmia.

Experimental Details.—Virgin female white rats of the Wistar strain were divided into four groups of 12 each as follows: Group 1 received radiation and vitamins; group 2 received radiation only; group 3 received vitamins only; and group 4 (controls) received neither radiation nor vitamins. Pregnancy was dated by vaginal smears taken daily at 9 a.m.; the day on which sperm was found in the smear was taken as Day 1. Animals in groups 1 and 3 received the following vitamins by parenteral injection at 2 p.m. on Day 1: vitamin A, 10,000 i.u.; vitamin D₂, 50,000 i.u.; α -tocopherol acetate, 60 mg.; aneurine hydrochloride B.P., 70 mg.; nicotinamide, B.P., 45 mg.; riboflavin B.P.,