Papers and Originals

Investigation of Relation between Use of Oral Contraceptives and Thromboembolic Disease. A Further Report

M. P. VESSEY,* M.B., B.S.; RICHARD DOLL,† M.D., D.SC., F.R.C.P., F.R.S.

British Medical Journal, 1969, 2, 651-657

Summary: The results of a previous study of the use of oral contraceptives by married women discharged from hospital with a diagnosis of thromboembolic disease in the years 1964-6 were reported by us last year. The present paper adds results relating to patients discharged during 1967 and a few data, that could not be sought previously, for patients discharged with cerebral or coronary thrombosis from three of the hospitals in the earlier period.

Of 84 patients with deep-vein thrombosis or pulmonary embolism 42 (50%) had used oral contraceptives during the month preceding the onset of their illness, while only 23 of the 168 controls (14%) had done so. No differences in risk were found either for the types of preparation or for the duration of use. After allowance for age and height, the patients with venous thromboembolism were about 10 lb. (4,535 g.) heavier than the control patients, irrespective of whether they were using oral contraceptives or not. No appreciable difference was found between the smoking habits of patients with and without venous thromboembolism treated during 1967, nor between women who were using oral contraceptives and those who were not. The trend in hospital admissions for venous thromboembolism with time corresponded to the trend in the use of oral contraceptives, and there was no evidence to suggest that the number of admissions was affected by publicity about the risk of using the preparations. Of 19 patients with cerebral thrombosis 11 (58%) had been using oral contraceptives, compared with an expected figure of 3.5 from the experience of the control subjects. All the published data (clinical, angiographic, and post-mortem) show that the thrombosis affects the cerebral arteries rather than the cerebral veins. Of 17 patients with coronary thrombosis 2 (12%) had been using oral contraceptives, compared with an expected figure of 2.1. The patients with coronary thrombosis smoked more than the control patients and were, on average, 8.3 lb. (3,765 g.) heavier than control women of the same age and height.

The new evidence strengthens the belief that oral contraceptives are a cause of venous thromboembolism and cerebral thrombosis but does not indicate that they are a cause of coronary thrombosis.

Introduction

Last year we reported the results of a controlled investigation of the use of oral contraceptives by women admitted to hospital for a thromboembolic disorder (Vessey and Doll, 1968). From these and other data we concluded that the use of oral contraceptives was a cause of venous thrombosis, pulmonary embolism, and cerebral thrombosis, but not apparently of coronary thrombosis. Some important questions, however, could not be answered adequately, since too few patients had been investigated. We therefore extended the study for a further year and now report the consolidated results for patients admitted to hospital in the four-year period 1964-7.

Method

We used the procedure described in our previous report throughout. In brief, hospital diagnostic indexes were searched to identify women aged 16 to 40 years who had been discharged from any one of 19 large general hospitals in the North-west Metropolitan Regional Hospital Board area with a diagnosis of deep vein thrombosis, pulmonary embolism, cerebral thrombosis, or coronary thrombosis. All such women were included in the study unless they were single or widowed; had an evident reason for developing the disease; were pregnant, postmenopausal, or sterilized; or could not be interviewed because they had died during their stay in hospital. For each patient with

deep vein thrombosis or pulmonary embolism two control patients were selected who had suffered an acute surgical or medical condition, or had been admitted to hospital for elective surgery, and who matched the affected patient for age, parity, date of admission, and absence of any predisposing cause of thromboembolic disease. Affected and control patients were interviewed in their homes by the medical social worker who had interviewed the patients in the first part of the study (Miss Keena Jones). As before, a few patients who could not be interviewed answered our questions by post.

When there was any difficulty in deciding whether a patient met the criteria for inclusion, the case history was reviewed independently by a colleague, who made the decision without knowledge of the woman's use of contraceptives.

Patients Studied

Twenty-nine new patients were identified who met our criteria and had been treated for venous thromboembolism during 1967. Twenty-three were interviewed, four completed a postal questionnaire, one had returned to the United States, and one could not be traced.

For comparison with these 29 patients, 58 others were selected as controls. Of these, two were found to have emigrated and two others were substituted for them. Fifty patients were interviewed and seven completed postal questionnaires. The remaining patient was traced, but consistently refused to answer either the door bell or our letters. We thus obtained data for 26 more triads of patients, each consisting of one patient with venous thromboembolism and two matched

* Member of Scientific Staff.

† Director.

Medical Research Council's Statistical Research Unit, University College Hospital Medical School, London W.C.1.

controls, making a total of 84 completed triads for the whole period of the study. Two further patients were identified who met all the criteria, except that they had died in hospital; both were treated in 1967.

In the study of cerebral and coronary thrombosis we confined ourselves previously to patients who had been treated in the 16 hospitals which recorded the patient's age in their diagnostic indexes. We have since been able to examine the case notes for all the patients recorded as having been treated for these conditions at the three other hospitals and now have data for cerebral and coronary thrombosis from all 19 hospitals for the whole period, 1964–7. In this way we have identified 14 additional patients who meet the criteria for inclusion, 10 of whom were treated for cerebral thrombosis and 4 for coronary thrombosis. All were interviewed in their homes or completed a postal questionnaire.

The total numbers of women included, the numbers who replied to our questions, and the numbers who died in hospital are shown in Table I.

TABLE I.—Numbers of Women Investigated and Sources of Information

Diagnosis	Source of Information	No. of Women Treated in:		Total No. Investigated
		1964–6	1967	
Deep vein thrombosis or pulmonary embolism	Interview	57	23	80
	Postal questionnaire ..	3	4	7
	Case notes only:			
	Emigrated	1	1	2
	Untraced	0	1	1
	Died in hospital ..	0	2	2
	Total	61	31	92
Non-thromboembolic conditions (controls)	Matched with controls* ..	58	26	84
	Interview	111	50	161
	Postal questionnaire ..	9	7	16
	Case notes only:			
	Emigrated	5	2	7
	Untraced	1	0	1
	Interview refused ..	1	1	2
Cerebral thrombosis	Total	127	60	187
	Matched with patients* with thromboembolism	116	52	168
	Interview	6	7	13
Coronary thrombosis	Postal questionnaire ..	5	1	6
	Total	11†	8	19
	Interview	12	3	15
Coronary thrombosis	Postal questionnaire ..	1	1	2
	Case notes only:			
	Died in hospital ..	3	0	3
Coronary thrombosis	Total	16	4	20

* Including only patients for whom information was obtained by interview or postal questionnaire.

† Including two women identified since the first report (Vessey and Doll, 1968).

Results : (1) Deep Vein Thrombosis and Pulmonary Embolism

Use of Oral Contraceptives

Table II shows the proportion of patients who had been using oral contraceptives during the month before the episode which led to hospital admission (or during the month before admission for patients undergoing elective surgery).¹ In 1967, as in 1964–6, the proportion who had been using oral contraceptives was higher in women admitted for venous thromboembolism (62%) than in the control patients with whom they were matched (25%), and the difference was again statistically significant ($P < 0.001$).

The name of the preparation last in use was determined for all patients in the matched triads, except for one with thromboembolism and two in the control series. In Table III this information is compared with data for the supply of oral

contraceptives to retail pharmacies provided for each year 1964 to 1967 by Intercontinental Medical Statistics Limited. Two separate comparisons are given; the first is based on the chemical composition of the preparations, while the second is based on a classification of their clinical effects (*British Medical Journal*, 1968a), ranging from the most strongly progestogenic to the most strongly oestrogenic. To compute the expected distributions, calculations were made for each year separately and the results summed. In general, there is reasonable agreement between the numbers observed and the numbers that would have been expected if there was no difference between the risks associated with the different preparations. Inman and Vessey (1968) obtained a similar result in their analysis of the use of oral contraceptives by women who died from thromboembolism in 1966, and it seems likely that if there is any difference in the risk associated with the different types of oral contraceptive it is relatively small.

TABLE II.—Patients with Venous Thromboembolism and Matched Control Patients Classified by Use of Oral Contraceptives During the Month Before the Onset of Their Illness (or During the Month Before Hospital Admission for Control Patients Undergoing Elective Surgery). (Percentages Shown in Parentheses)

Year of Treatment	Diagnostic Group	No. of Patients		
		Oral Contraceptives		Total
		Used	Not Used	
1967*	Thromboembolism ..	16 (62)	10 (38)	26 (100)
	Control	13 (25)	39 (75)	52 (100)
1964–7†	Thromboembolism ..	42 (50)	42 (50)	84 (100)
	Control	23 (14)	145 (86)	168 (100)

* Pike's test for matched controls (Pike, 1969)
 $\chi^2 = 15.3$, $n = 1$, $P < 0.001$

† Pike's test for matched controls
 $\chi^2 = 66.8$, $n = 1$, $P < 0.001$

Note: The usual χ^2 test for a 2×2 table fails to take into account the way in which the affected and control patients were matched and is therefore likely to overestimate the probability of obtaining the observed results by chance. If the usual test is applied to the data in the table the values of $\chi^2_{(1)}$ obtained are 8.4 and 36.6 respectively.

TABLE III.—Types of Oral Contraceptive Last Used by Patients with Thromboembolism and Their Matched Controls Compared with Those Expected on the Basis of National Supply Figures (1964–7)

Oestrogen	Progestogen	No. of Patients with Thromboembolism		No. of Control Patients	
		Observed	Expected	Observed	Expected
Ethinylloestradiol	Norethisterone	12	13.6	5	7.4
Ethinylloestradiol	Megestrol	7	4.4	1	2.2
Mestranol ..	Norethisterone	3	2.2	1	1.2
Mestranol ..	Ethinodiol	10	8.4	8	4.6
Mestranol ..	Norethynodrel	1	5.4	1	2.4
Mestranol ..	Lyncoestrenol	6	4.2	5	2.8
Mestranol ..	Chlormadinone	0	0.8	0	0.6
Weak	Strong	13	13.9	5	7.4
Weak	Weak	7	4.0	1	1.9
Strong ..	Strong	18	14.4	14	8.4
Strong ..	Weak	1	5.1	1	2.2
Strong* ..	Weak—end of cycle only	0	1.6	0	1.1
All types ..	All types	39†	39.0	21	21.0

* Sequential formulations.

† 2 patients taking Metrolen-M (a mixture of mestranol and ethinodiol identical to Ovulen, but normally prescribed for gynaecological reasons and not represented in the supply figures) have been omitted.

The suggestion has been made that sequential preparations might be particularly dangerous because of the unopposed effect of the oestrogens (*British Medical Journal*, 1968b). None of the women with venous thromboembolism that we investigated had been using these preparations; but this was hardly surprising, as only about 3% of the oral contraceptives supplied during 1964–7 were sequential in type. The lack of observed cases does not exclude the existence of a greater risk with these preparations, but it should be noted that the data provide no support for the suggestion that the risk is greatest with the preparations that are inherently the most oestrogenic.

Data for the duration of use of the contraceptives at the time of onset of the disease (or before admission for control patients undergoing elective surgery) are shown in Table IV.

¹ It may be noted that of the eight patients with thromboembolism treated in 1964–7 who are not included in Table II, four are known to have been using oral contraceptives at the onset of their illness.

For each patient the duration was calculated as the sum of all periods of use, and thus represents the total exposure to oral contraceptives. Few patients, however, had interrupted the use of oral contraceptives once they had been started, and essentially the same results are obtained if only the last course is taken into account. The results do not suggest that the risk of venous thromboembolism is any greater early in the course of medication, as might be expected if the effect was an idiosyncratic reaction in a specially susceptible fraction of the population, nor that it increases with increasing duration of use.

TABLE IV.—Duration of Use of Oral Contraceptives: Patients with Thromboembolism and Controls (1964-7)

Total Duration of Use (Completed Months)	Patients with Thromboembolism		Control Patients	
	No.	%	No.	%
0-2	6	14	6	26
3-5	8	19	2	9
6-11	11	26	5	22
12-23	10	24	7	30
24 or more	7	17	3	13
All durations	42	100	23	100
Mean duration (months)	12.3		10.3	

Sources of Bias

In our earlier report we considered the possibility that the results might have been produced if doctors diagnosed thromboembolic disease more readily, or admitted patients to hospital more readily, when they obtained a history of the use of oral contraceptives than when they did not. If this had been so, it seemed probable that the association between thromboembolism and the use of oral contraceptives would be strongest in those patients for whom there was most opportunity for knowledge of the history to have influenced the decision—that is, in patients for whom the physical basis for the diagnosis was least certain. We therefore tested the hypothesis by asking a colleague (Dr. F. E. Speizer) to review abstracts of the case histories from which all reference to contraceptive practice had been omitted, and to classify them according to the reliability of the diagnosis. The results failed to confirm the hypothesis and, indeed, showed that the association with the use of oral contraceptives was strongest among those patients for whom the diagnosis was most firmly established.

Dr. Speizer was unable to review the new data, and we asked another colleague (Dr. P. Fraser) to review all the data, both old and new, without knowledge of the classification that had been made previously. The results were similar. Five of the 13 patients (38%) who were classified in the least certain category had been using oral contraceptives, while the numbers in the intermediate category and the most certain category were respectively 26 out of 57 (46%) and 15 out of 22 (68%).

A further test for bias in diagnosis and referral to hospital is provided by examining the trends in the number of admissions with time. These are illustrated in Figs. 1 and 2.

Fig. 1 shows the number of women with venous thromboembolism who were using oral contraceptives and were admitted to hospital in four-monthly periods from the beginning of 1964 to the end of 1967. As would be expected, the numbers show considerable variation, but the trend is upwards and the slope of the regression line closely parallels the increase in the use of oral contraceptives (from about 4% of non-pregnant married women in 1964 to about 14% in 1967). Fig. 2 shows the number of women with venous thromboembolism who were not using oral contraceptives and were admitted to hospital in the same periods. In contrast to Fig. 1 this shows a constant rate of admission.

The three arrows in Fig. 1 indicate times at which there was much publicity about the association between oral contraceptives and thromboembolism. The first arrow corresponds to the publication of a letter to the *British Medical Journal*

about the preliminary findings of the Committee on Safety of Drugs (Cahal, 1965). This letter was to some extent reassuring, but it pointed out that more cases of pulmonary embolism had occurred in women taking oral contraceptives than would have been expected. The second corresponds to the time of an answer to a question in Parliament about oral contraceptives and thromboembolism (*British Medical Journal*, 1967), and the third to the publication of the Medical Research Council's (1967) preliminary communication on this subject. Both these last events recorded the existence of a risk and received widespread publicity. Fig. 1 shows that none of this publicity produced any marked fluctuation in the number of women admitted to hospital. Since it also failed to have any appreciable effect on the sales of oral contraceptives (Intercontinental Medical Statistics Ltd., personal communication) this finding provides further support for the belief that the association is real and not due to a greater tendency to diagnose thromboembolism in women using the preparations.

FIG. 1.—Number of patients who were using oral contraceptives admitted to hospital with venous thromboembolism in successive four-monthly periods, 1964-7. Estimates of the oral contraceptives supplied in England and Wales in each year are also given (based on information provided by Intercontinental Medical Statistics Limited, the Family Planning Association, and other sources). FIG. 2.—Number of patients who were not using oral contraceptives admitted to hospital with venous thromboembolism in successive four-monthly periods, 1964-7.

Associated Factors

Comparisons were also made between the affected patients and their matched controls to see if they differed in any other respect that could account for their difference in contraceptive habits. The two groups were similar in age, marital status, parity, year of admission, and absence of many predisposing causes of thromboembolism, because the selection of the control patients had been limited by these considerations. They were also similar in regard to country of origin, religion, social class, interval since the birth of the last child, and (in those without a history of previous thromboembolism) the presence of varicose veins. Data for the first 58 triads of affected and control patients have been published previously (Vessey and Doll, 1968) and the later results are similar to the first.

For four other factors—a history of previous thromboembolism, the presence of obesity, the prevalence of cigarette smoking, and the family history—the previous results indicated

possible differences between the affected patients and their matched controls (Vessey and Doll, 1968).

In our previous report the proportion of affected patients who gave a history of a previous attack of thromboembolism was about the same, irrespective of the subsequent use of oral contraceptives—a finding that was regarded as unexpected because many doctors consider a history of thromboembolism as a contraindication to the use of these preparations. With the inclusion of the new data the similarity is less close, and Table V shows that the proportion of affected patients who gave a history of previous thromboembolism is now smaller among those who were using oral contraceptives (29%) than among those who were not (40%). In fact, it is impossible to interpret this finding without some further knowledge of the interaction between the use of oral contraceptives and the predisposing factors that are associated with a history of previous disease. To obtain this, much more information is needed than we now have about the contraceptive practices of control patients with a history of previous thromboembolism.

TABLE V.—History of Previous Venous Thrombosis or Pulmonary Embolism in Affected and Control Patients, 1964–7. (Percentages Shown in Parentheses)

Diagnostic Group	History of Previous Venous Thromboembolism	No. of Patients		
		Oral Contraceptives		Total
		Used	Not Used	
Thromboembolism	Present ..	12 (29)	17 (40)	29 (35)
	Absent ..	30 (71)	25 (60)	55 (65)
	Total ..	42 (100)	42 (100)	84 (100)
Control	Present ..	3 (13)	6 (4)	9 (5)
	Absent ..	20 (87)	139 (96)	159 (95)
	Total ..	23 (100)	145 (100)	168 (100)

This uncertainty does not affect the general conclusion, that the development of venous thromboembolism is associated with the use of oral contraceptives, as the association is just as pronounced when women who had never had a previous attack of thromboembolism are considered alone. Among these women the use of oral contraceptives was much greater in affected patients (30 out of 55, or 55%) than in the control group (20 out of 159, or 13%) and the difference is statistically highly significant ($P < 0.001$).

Hospital records were too incomplete to be used as a source of information about physical measurements, and information about height and weight was obtained from the women themselves. For each patient the stated weight was compared with the standard weight provided by Kemsley *et al.* (1962) for women of the same age and height. In our earlier report we found that women who developed thromboembolism while taking oral contraceptives were no more overweight than control women using these preparations. The results based on the larger numbers now available are shown in Table VI and

indicate that this is not so. Irrespective of whether or not they were using oral contraceptives, the women who suffered thromboembolism were about 10 lb. (4.5 kg.) heavier (after adjusting for age and height) than the controls, and the difference between the means of the two diagnostic groups was statistically significant ($P < 0.01$). These results confirm the belief that obesity is a factor in the development of thromboembolism but show that differences in weight could not account for the association between the use of oral contraceptives and the development of the disease.

TABLE VI.—Mean Deviations of Stated Weights from Standard Weights With Their Standard Errors. (Numbers of Patients Shown in Parentheses)

Diagnostic Group	Mean Deviation from Standard Weight (lb.)		
	Oral Contraceptives		All Women
	Used	Not Used	
Thromboembolism	11.0 ± 3.5 (49)	14.5 ± 4.4 (41)	12.8 ± 2.8 (81*)
Control ..	0.7 ± 4.3 (23)	4.8 ± 1.9 (142)	4.2 ± 1.7 (165*)

* Height or weight unknown for 3 patients with thromboembolism and 3 controls.

The size of the standard errors shown in Table VI provides an adequate explanation for the considerable differences observed between some of the data for 1964–6 and the corresponding data for 1967. Thus, to take the most extreme example, the mean deviation for the 10 control patients who were treated in 1964–6 and were using oral contraceptives was +7.1 lb. (3,220 g.), and the mean deviation for the 13 corresponding patients in 1967 was –4.3 lb. (1,950 g.), but the difference between these two means is not statistically significant ($P = 0.15$).

Data for smoking habits are given in Table VII. In our previous report we noted that the affected patients were, on average, heavier smokers than the controls. The later results provide no further indication of a similar effect, and the earlier difference between the smoking habits of the two groups can thus reasonably be attributed to chance ($P = 0.08$).

In our previous data the heavy smokers among the affected patients were predominantly those who were also using oral contraceptives, and on this basis Frederiksen and Ravenholt (1968) suggested that smoking and the use of oral contraceptives might interact in the pathogenesis of the disease. The data for patients admitted to hospital in 1967 provide no evidence of any such interaction, and it seems more probable that the original association was due either to an extreme effect of chance or to a sociological effect that is no longer present. For example, it is possible that oral contraceptives were more likely to be used by women who also smoked cigarettes, but that the association has disappeared as the use of the preparations has become more general.

To obtain some independent assessment of whether there is an increased risk of venous thromboembolism among smokers

TABLE VII.—Number of Patients Smoking Different Quantities of Cigarettes by Year of Treatment and Diagnostic Category. (Percentages Shown in Parentheses)

Year of Treatment	Diagnostic Group	Oral Contraceptives	No. of Cigarettes Smoked per Day at Onset of Episode			Total No. of Patients	Mean No. of Cigarettes Smoked per Day
			0	1–14	15+		
1967	Thromboembolism	Used ..	9 (56)	5 (31)	2 (13)	16 (100)	4
		Not used ..	6 (60)	2 (20)	2 (20)	10 (100)	9
		Total ..	15 (58)	7 (27)	4 (15)	26 (100)	6
	Control	Used ..	7 (54)	5 (38)	1 (8)	13 (100)	6
		Not used ..	24 (62)	11 (28)	4 (10)	39 (100)	4
		Total ..	31 (59)	16 (31)	5 (10)	52 (100)	5
1964–7	Thromboembolism	Used ..	17 (40)	9 (21)	16 (39)	42 (100)	11
		Not used ..	17 (40)	16 (39)	9 (21)	42 (100)	8
		Total ..	34 (40)	25 (30)	25 (30)	84 (100)	9
	Control	Used ..	10 (43)	10 (43)	3 (14)	23 (100)	6
		Not used ..	73 (50)	46 (32)	26 (18)	145 (100)	6
		Total ..	83 (50)	56 (33)	29 (17)	168 (100)	6

we examined the latest data available from a study of mortality in British doctors. Thirty-one deaths had been attributed to venous thromboembolism (*International List Numbers* 463–466) in 15 years, and the age-standardized mortality rates per 100,000 were 96 for non-smokers, 57 for cigarette smokers, and 71 for pipe and mixed smokers (Doll and Hill, 1964, and unpublished data).

Lastly, we noted in our previous report that a history of phlebitis was three times as common among the mothers and sisters of the affected women as among the mothers and sisters of the controls, and that it was equally common irrespective of whether the affected women had used oral contraceptives or not. The later results confirm these findings but add nothing which could show whether the results are due to familial differences in susceptibility or to preferential recall by the affected women.

Size of Risk

The magnitude of the risk attributable to the use of oral contraceptives can be estimated by relating the number of patients with venous thromboembolism to the number of women served by the hospitals to which the patients were admitted. This latter figure is not known with certainty, but it can be estimated from knowledge of the number of hospital beds in the region, the structure of the corresponding population, and figures for the supply of oral contraceptives in the country as a whole (Vessey and Doll, 1968). On this basis we estimated previously that the annual attack rate of venous thromboembolic disease, without evident cause but of sufficient severity to require admission to hospital, was about 5 per 100,000 among married women who were not using oral contraceptives and 47 per 100,000 among married women who were. Incorporating the results for 1967 leads to almost identical results—that is, rates of about 5 and 45 per 100,000 respectively.

In this comparison no allowance is made for differences in age (between 16 and 40 years) or parity, and this could be important, as these factors are closely related to the use of oral contraceptives. Inman and Vessey (1968), for example, estimated that in 1966 the proportion of married women who used oral contraceptives varied from 0% among nulliparous women aged 35 to 44 years to 44% among women who had already borne three or more children by 25 years of age. How far these factors affect the incidence of idiopathic venous thromboembolism is not known, but estimates can be made from our data for hospital admissions, census data for the distribution of parity by age (Registrar General, 1966), and data for the use of oral contraceptives by age and parity (Intercontinental Medical Statistics Ltd., personal communication; Inman and Vessey, 1968). These estimates, which require the assumption that women in the area served by the North-West Metropolitan Regional Hospital Board are typical of women in the country as a whole in respect of parity and contraceptive use, lead to the conclusion that the incidence of idiopathic venous thromboembolism does not vary greatly with either age or parity. Standardization for these factors has no material effect on the estimated risks of developing the disease (married women not using oral contraceptives, 5 per 100,000; married women using oral contraceptives 57 per 100,000).

The relative risk can also be derived in a simpler way by comparing the results for affected and control patients (Table II). This method has the advantage that the two series of patients are matched for marital status, age, parity, and, to a large extent, for state of health, so that these factors are unlikely to affect the comparison. It has the disadvantage, however, that it is directly dependent on the number of control patients who were using oral contraceptives. Even with the enlarged series this is a small number, so that the confidence limits of the ratio are wide. From these data it is estimated that the risk of hospital admission for idiopathic venous thromboembolism is increased by the use of oral contraceptives

from sixfold to sevenfold (42/42 divided by 23/145=6.3 to 1) with 95% confidence limits between 3.4 and 11.6 to one.

(2) Cerebral Thrombosis²

The total number of women who were identified as having been treated for cerebral thrombosis and who satisfied our criteria for investigation is shown in Table VIII, subdivided by year of treatment, certainty of diagnosis, and use of oral contraceptives. Eight patients were treated in 1967 and two additional patients were discovered who had been treated earlier in the three hospitals omitted from the first part of the study (see Table I and section on “Patients Studied”). Eleven of the 19 women (58%) had been using oral contraceptives when their illness began. If the control patients selected to match the women with venous thromboembolism are used for comparison and allowance is made for age, parity, and year of admission the expected number is estimated to be 3.5. Even with so few patients, this difference is statistically highly significant ($P<0.001$). From these data the risk of developing cerebral thrombosis, in the absence of any known predisposing cause, is estimated to be about six times higher when oral contraceptives are used than when they are not. Although this estimate is based on small numbers, it may be more accurate than would be supposed, as independent data for deaths in 1966 reported by Inman and Vessey (1968) lead to the same figure.

TABLE VIII.—Number of Patients with Cerebral Thrombosis Treated in Each Year, 1964–7

Oral Contraceptives	Diagnosis	No. of Patients Treated in:				
		1964	1965	1966	1967	All Years
Used	Certain*	0	1	1	1	3
	Not certain	0	3	2	3	8
	Total	0	4	3	4	11
Not used	Certain*	0	0	1	0	1
	Not certain	1	2	0	4	7
	Total	1	2	1	4	8

* Angiographic evidence of arterial occlusion at a site which could be related to the focal signs.

The number of patients is too small to justify any detailed examination of the types of oral contraceptive used, the duration of their use, trends in incidence, or of associated factors. It may be noted, however, that oral contraceptives were used by three out of the four patients in whom the diagnosis was proved by arteriography; that the mean duration of use of oral contraceptives at the time the illness occurred was 8.3 months (for comparison see Table IV); that the smoking habits of the women with cerebral thrombosis (non-smokers and ex-smokers, 9; smokers of 1 to 14 cigarettes a day, 6; smokers of 15 or more cigarettes a day, 4; mean consumption per day, 7) were similar to those of control patients (Table VII); and that their average weight deviated little from the national standard for their height and age (women with cerebral thrombosis +2.9 lb. (1,315 g.); control patients +4.2 lb. (1,905 g.), see Table VI).

(3) Coronary Thrombosis

The total number of women who were identified as having been treated for coronary thrombosis and who satisfied our criteria for investigation is shown in Table IX, subdivided by year of treatment, certainty of diagnosis, and use of oral contraceptives. Four patients were found to have been treated in 1967; but despite an intensive search no additional cases were found in the records of the three hospitals omitted from the first part of the study (see Table I and section on “Patients

² As before, we have used this term for the want of a better one. The diagnosis of cerebral thrombosis is difficult to establish with certainty, and it is possible that some patients in our series suffered from other intracranial conditions.

Studied"). Two only of the 17 women (12%) had been using oral contraceptives when their illness began, almost exactly the number expected from the experience of the control patients of similar age and parity (2:1). Three other patients died from coronary thrombosis while in hospital and were excluded from the special study because they could not be interviewed; none were recorded in the hospital case notes as having taken oral contraceptives.

TABLE IX.—Number of Patients with Coronary Thrombosis Treated in Each Year, 1964–7

Oral Contraceptives	Diagnosis	No. of Patients Treated in:				
		1964	1965	1966	1967	All Years
Used	Certain*	0	0	0	1	1
	Not certain	0	0	0	1	1
	Total	0	0	0	2	2
Not used	Certain*	2	1	1	2	6
	Not certain	5	1	3	0	9
	Total	7	2	4	2	15

* Fresh pathological Q waves in the electrocardiogram or S-T and T-wave changes accompanied by characteristic enzyme changes.

Three of the 17 patients who survived (18%) were non-smokers or ex-smokers, 8 (47%) smoked 1 to 14 cigarettes a day, and 6 (35%) smoked 15 or more cigarettes a day. These proportions and the mean amount smoked per day (12 cigarettes) differ from those recorded for the control patients (Table VII) and accord with many other observations indicating that cigarette smoking is an important factor in the development of coronary thrombosis in young adults.

The patients with coronary thrombosis were also somewhat overweight. The excess, +8.3 lb. (3,765 g.) on average in comparison with the standard weight for women of the same height and age, was intermediate between that recorded for control patients (+4.2 lb.; 1,905 g.) and that recorded for women with venous thromboembolism (+12.8 lb.; 5,805 g.).

Discussion

In our earlier report we gave reasons for believing that the sources of bias inherent in retrospective studies of hospital patients had not materially affected our results. These reasons are now strengthened by the trends in the number of hospital admissions for venous thromboembolism over the period 1964 to 1967 (Figs. 1 and 2) and by the demonstration that these trends were not distorted when the risks of oral contraceptives were given the greatest publicity.

Some other evidence has also been published. Firstly, Vessey and Weatherall (1968) showed that mortality statistics for venous thromboembolism in England and Wales were compatible with the increase in the use of oral contraceptives and with the small mortality which they are estimated to produce; and Markush and Seigel (1969) showed that this was also true for mortality statistics in the United States. Secondly, Jeffcoate *et al.* (1968) and Millar and Robertson (1968) confirmed that oestrogens, when used to suppress lactation, are associated with an increased risk of puerperal thromboembolism. Thirdly, Bergeron and Wood (1969) showed an increase in hospital admissions for cerebral thrombosis in New York which was confined to women who were using oral contraceptives. They reviewed the records of women aged 20 to 45 years who had cerebral angiograms performed at the Neurological Institute, and found that in 1960, when oral contraceptives were not in general use, 58 women had non-occlusive disease and two had occlusive disease, one of whom was pregnant. In 1966, 55 women had non-occlusive disease and nine had occlusive disease; none of the latter were pregnant, but eight had been using oral contraceptives.

Drill and Calhoun (1968) alone have published evidence opposed to the conclusion that oral contraceptives are a cause

of venous thromboembolism. They found that the incidence of "thrombophlebitis" recorded in the literature was much the same in certain large groups of women, some of which were local populations while others consisted of women who were under treatment with oral contraceptives. They noted also that the recorded incidence of thrombophlebitis during pregnancy (and before delivery) was unusually low. The value of these comparisons is, however, limited, because the series were compiled by different workers and the definitions of thrombophlebitis and the completeness of reporting are likely to have varied from one series to another. Such evidence does not weigh heavily against that obtained by personal investigation of groups of patients under controlled conditions.

The sum of the new evidence strengthens the belief that oral contraceptives are a cause of venous thromboembolism and cerebral thrombosis. It fails, however, to provide any indication that they also cause coronary thrombosis.

The magnitude of the risk cannot be estimated with precision from the present study. The best estimate of the risk of hospital admission for deep vein thrombosis or pulmonary embolism, in the absence of other predisposing cause, appears to be about six to seven times higher among married women who are using oral contraceptives than among those who are not, with a 95% probability of being between 3.4 and 11.6 times higher. Other evidence, derived from national data for contraceptive use by age and parity, suggests that the true risk is likely to be nearer the upper than the lower of these limits. This conclusion accords with the estimate derived by Inman and Vessey (1968) from mortality data (8.3 times higher) and is compatible with the trends in national mortality statistics (Vessey and Weatherall, 1968; Markush and Seigel, 1969).

The estimate of the risk of admission for cerebral thrombosis is less certain, because it is based on smaller numbers; but the best estimate of the relative risk, derived from our data and from the mortality data of Inman and Vessey (1968), appears to be about the same as that for venous thromboembolism. Moreover, this is compatible with the hospital experience of Bergeron and Wood (1969). Clinical, angiographic, and post-mortem evidence from these and other series (see Salmon *et al.*, 1968) leaves little doubt that the thrombosis affects the cerebral arteries rather than the veins.

The best quantitative estimate of the annual risk of hospital admission for any of the three conditions ("idiopathic" deep vein thrombosis, pulmonary embolism, or cerebral thrombosis) is about 0.5 per 1,000 for married women who are using oral contraceptives and 0.06 per 1,000 for married women who are not.

The data for duration of use provide no evidence that the risk is concentrated during the early months or that it increases with increasing duration of use. Jick *et al.* (1969), however, have obtained strong evidence to suggest that the absolute risk of venous thromboembolism in association with the use of oral contraceptives is only about one-third as great among women who belong to blood group O as among those who belong to the other three groups. No comparable data have been obtained for cerebral thrombosis, and it cannot be assumed that the same genetic factors necessarily affect the risk of this condition, which is due to arterial rather than venous occlusion.

We should like to express our thanks to Miss Keena Jones for tracing and interviewing the patients; to Miss Rosemary Emerson for technical assistance; to Dr. P. Fraser and Dr. G. M. Stern for assessing many of the case histories; and to Intercontinental Medical Statistics Ltd. for providing market research figures concerning sales of oral contraceptives.

This investigation would not have been possible without the co-operation of many consultants, general practitioners, and hospital record officers, and we are most grateful for their help.

REFERENCES

- Bergeron, R. T., and Wood, E. H. (1969). *Radiology*, **92**, 231.
British Medical Journal, 1967, **2**, 68.

- British Medical Journal*, 1968a, 1, 690.
British Medical Journal, 1968b, 2, 187.
Cabot, D. A. (1965). *British Medical Journal*, 2, 1180.
Doll, R., and Hill, A. B. (1964). *British Medical Journal*, 1, 1399.
Drill, V. A., and Calhoun, D. W. (1968). *Journal of the American Medical Association*, 206, 77.
Frederiksen, H., and Ravenholt, R. T. (1968). *British Medical Journal*, 4, 770.
Inman, W. H. W., and Vessey, M. P. (1968). *British Medical Journal*, 2, 193.
Jeffcoate, T. N. A., Miller, J., Roos, R. F., and Tindall, V. R. (1968). *British Medical Journal*, 4, 19.
Jick, H., et al. (1969). *Lancet*, 1, 539.

- Kemsley, W. F. F., Billewicz, W. Z., and Thomson, A. M. (1962). *British Journal of Preventive and Social Medicine*, 16, 189.
Markush, R. E., and Seigel, D. G. (1969). *American Journal of Public Health*, 59, 418.
Medical Research Council (1967). *British Medical Journal*, 2, 355.
Millar, D. G., and Robertson, E. G. (1968). *British Medical Journal*, 4, 452.
Pike, M. C. (1969). To be published.
Registrar General (1966). *Census 1961, England and Wales, Fertility Tables*. London, H.M.S.O.
Salmon, M. L., Winkelman, J. Z., and Gay, A. J. (1968). *Journal of the American Medical Association*, 206, 85.
Vessey, M. P., and Doll, R. (1968). *British Medical Journal*, 2, 199.
Vessey, M. P., and Weatherall, J. A. C. (1968). *Lancet*, 2, 94.

Thermal, Metabolic, Blood, and Circulatory Adjustments in Prolonged Outdoor Exercise

L. G. C. E. PUGH,* M.A., B.M., B.CH.

British Medical Journal, 1969, 2, 657-662

Summary: Thermal, metabolic, and circulatory responses were studied in six hill-walkers taking part in a 28-mile (45-km.) walk in rough country in autumn and winter, air temperatures being 6 to 12° C. and -2 to 2° C., respectively.

Though they were an apparently well-matched party, the walkers had to split into three pairs to avoid exhaustion. They adjusted their clothing so that mean skin temperatures were similar in both warm and cold conditions, the average value being 30.5° C. compared with the resting comfort range of 33 to 34.5° C. When, on the winter trial, skin temperatures were lowered by reduction of clothing, mean skin temperatures fell to 26.5 to 27.8° C., one subject showing a value of 21.3° C. These temperatures were associated with moderate discomfort from cold.

Gut temperatures during exercise, measured with a radio pill, averaged 38.7 to 37.9° C. on the autumn exercise. Slightly lower values were observed in winter, but this was associated with slower walking rather than cold stress. A fat and a thin subject walking together with minimal clothing showed widely different temperature responses, the fatter subject having a lower skin temperature and higher gut temperature than his companion. These results were compared with other results on extreme cold stress and discussed in relation to hypothermia. Heart rate and blood pressure findings were unremarkable, except for increased post-exercise heart rates and standing/lying heart rate differences, and a tendency to postural hypotension associated with exhaustion. Blood volume was not reduced in exhaustion and there were no significant changes in blood electrolytes or other constituents apart from a small rise in potassium. Ketonuria developed in all subjects.

Introduction

The investigations described in this article were part of an extended inquiry into the causes of accidental hypothermia in hill-walkers and climbers in Britain. The intention was to follow body temperature changes during long-continued outdoor exercise in warm and cold conditions, and to look for circulatory and biochemical changes that might account for the severity of hypothermia in these cases.

Methods

The investigation took place in the Derbyshire Peak District and involved a 28-mile (45-km.) trek over the moors. Two

trials were carried out, one in fine autumn weather (Edale I), the other in dry cold winter conditions (Edale II). Meteorological details are given in Table I. Six experienced hill-walkers acted as subjects (Table II). They supplied their own clothing, which consisted of a string vest, shirt, woollen sweater, anorak, long trousers, cotton drawers, thick woollen socks, and heavy boots. On the second exercise they were given special jeans, in which small slits had been cut for insertion of probe thermocouples. These slits were situated over each of Hardy's (1949) surface regions for the lower limb.

TABLE I.—Details of the Route and Weather Conditions During 28-mile (45-km.) Trek. Total Ascent, 3,780 ft. (1,166 m.). Total Descent, 3,840 ft. (1,184 m.)

	Edale I. October	Edale II. January
Air temperature (°C)	+6 to +12	-2 to +2.5
Wind velocity { m.p.h. k.p.h.	Calm to 7 Calm to 11	10 to 18 16 to 29
Cloud	Nil	Nil
Condition of terrain	Dry	0-5 cm. Snow
Time spent walking:	hr. min.	hr. min.
Group 1	8 9	8 14
Group 2	8 35	8 52
Group 3	8 58	9 10
Time spent at check-points:		
Group 1	1 31	2 31
Group 2	1 53	2 53
Group 3	1 55	2 55

TABLE II.—Physical Characteristics of Subjects. Skinfold Results are Means of Readings Taken Over 11 Regions of the Body Surface

Group	Subject	Age in Years	Weight (kg.)	Height (cm.)	Surface (sq.m.)	Mean Skinfold (mm.)	Blood Volume (ml./kg.)	Total Hb (g./kg.)
1	R.M.	19	67.0	180	1.85	4.4	75.7	11.7
	B.H.	18	69.7	177	1.86	7.2	72.7	11.3
2	B.N.	25	75.7	193	2.05	3.4	80.1	11.6
	S.H.	19	60.6	178	1.76	4.9	76.2	12.0
3	M.C.	24	61.2	172	1.72	3.6	84.7	12.3
	R.R.	21	61.6	178	1.77	4.1	80.1	11.1

There are six check-points along the route at which food and fluid were available. The subjects spent 10 to 20 minutes at each check-point in order to allow time for physiological observations. These consisted of heart rate, blood pressure, regional skin temperatures, and gut temperature. Urine samples were also collected.

On the first exercise (Edale I) the party set off in a single group at 08.45 hours, about one and a half hours after a normal breakfast. They were asked to walk as fast as they

* Laboratory for Field Physiology, National Institute for Medical Research, London N.W.3.