A similar reduction in incidence was shown among those children who were known to be in contact with measles in their own homes and presumably exposed to heavy infection. The attack rates in a representative sample of children exposed at home were 9% in the killed/live-vaccine group, 6% in the live-vaccine group, and 83% in the unvaccinated group.

Those children who defaulted from vaccination and those who were ineligible were also followed up in the same way as the children who took part in the trial. It was shown that the excluded children were in general as susceptible to measles as the unvaccinated control group, and it was thus most unlikely that their exclusion had materially affected the results of the analysis of the main trial.

Although vaccination was highly effective it was unable to protect all children from measles. It is true that a few of the cases occurred soon after vaccination, perhaps before immunity had had time to develop, but most of them occurred later and were probably due to the inability of some children to produce an adequate antibody response. This view is supported by the results of the serological study in which a small proportion of children vaccinated by each method showed no antibody response. It is possible that a less attenuated live vaccine would produce protection in a greater proportion of children, but there is the probability that it would also produce more pronounced reactions and in consequence be less suitable for large-scale routine use.

In considering which of the two procedures studied is the more suitable to use in vaccinating against measles, the follow-

ing points should be taken into account. Both live vaccine alone and killed vaccine followed by live give a substantial and similar degree of protection in normal children aged 1 to 2 years, but it is not yet known how long the immunity will last. Killed vaccine given before live vaccine has the advantage of reducing the frequency of reactions including convulsions. On the other hand, vaccination with live vaccine alone requires only one injection.

But no matter which procedure is chosen it is clear from the results of this trial that vaccination, if done on a large scale, could produce a substantial reduction in the incidence of measles in this country. Such a reduction would undoubtedly lighten the burden placed on family doctors and parents, especially in an epidemic year, when approximately half a million cases occur.

The Measles Vaccines Committee of the Medical Research Council thanks Mrs. A. Allchin and her staff of the Medical Research Council Laboratories, Hampstead, London, for co-ordinating the clerical work of the trial; Miss C. Bramley, of the Medical Research Council Computer Services Centre, for the computer programme; and Mr. H. Ward, Mrs. J. Hall, and Miss R. Porter, of the Division of Immunological Products Control, Medical Research Council Laboratories, Hampstead, London, for the distribution of vaccines.

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Risk of Serious Infection Following Splenectomy

A. G. R. LOWDON,* F.R.C.S., F.R.C.S.ED.; R. H. M. STEWART,† M.D.; W. WALKER,‡ M.D., M.C.PATH.

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The possibility that splenectomy might predispose to infection was first reported by King and Schumacker (1952), and since then there have been several communications on this subject. Even so, there is no accepted opinion regarding the numerical risk of this complication nor whether it is restricted to certain age groups or specific conditions for which splenectomy is performed. It is generally conceded that any risk is greatest if splenectomy is performed in infancy (Huntley, 1958), especially if the underlying disease itself carries a high risk of infection (Robinson and Sturgeon, 1960), but infections have followed splenectomy for traumatic rupture in adults.

Characteristically such infections have been acute septicaemic illnesses often leading to death of the patient from adrenal haemorrhage within a few hours of onset, and the organisms most frequently concerned have been the pneumococcus and *Haemophilus influenzae*. Infections have not always been septicaemias; Gofstein and Gellis (1956) reported a fatal case of tracheobronchitis, and the activation of tuberculosis (Edwards, 1951; MacPherson, 1959) and the dissemination of lupus erythematosus (Carpenter *et al.*, 1959) have been attributed to splenectomy. A third feature has been a recurrent pattern of infections in some patients (Lowdon *et al.*, 1962; Horan and Colebatch, 1962).

It is estimated that 80% of serious infections occur within two years of operation (Smith *et al.*, 1957; Horan and Cole-

batch, 1962), and Gordon (1960) believes that the shorter the interval the worse the prognosis. Doan *et al.* (1960), however, reported serious infections in three adults between five and eight years after operation.

Present Study

Because we had recognized four cases of severe infection in 75 children subjected to splenectomy (Lowdon *et al.*, 1962), and because there was no accepted opinion concerning the existence, frequency, or nature of increased susceptibility we felt that a review of a large group of cases was indicated.

We therefore made a direct approach to all regional senior administrative medical officers and professors of surgery in England and Wales asking for their co-operation by supplying us with a list of all patients who had undergone splenectomy during 1961, whatever the reason. The year 1961 was chosen because this, at the start of the study, was the latest year for which results of the Hospital In-patient Enquiry had been published by the Central Registry Office of the Ministry of Health. In the Hospital In-patient Enquiry there were 89 cases of splenectomy; therefore we expected 890 for the whole year, but in fact 1,167 were notified.

Comparison of the 10% sample with the total group showed two significant differences. The age distribution of the "sample" was low, while the number of cases in the "total" group where splenectomy had been performed as part of some other major operation was high. These we attributed to the

* Department of Surgery, University of Newcastle upon Tyne. (Professor Lowdon died on 2 September 1965.)

† Newcastle Regional Hospital Board.

‡ Department of Child Health, University of Newcastle upon Tyne.

methods adopted in recording the diagnosis for the Hospital In-patient Enquiry, which gives emphasis to main diagnosis at discharge. We cannot be sure that all cases of splenectomy were identified, but it seems unlikely that many relevant cases have been missed.

Technique of Follow-up.—We argued that any serious infection attributable to splenectomy would probably occur within two years of operation and would necessitate admission to hospital unless the patient died before this could be achieved. We therefore wrote to all patients' general practitioners explaining the purpose of the inquiry and asking two questions: (1) Had the patient required hospital admission since operation? and (2) Had the patient died since operation? If the answer to either question was yes, we asked for the name of the hospital and date of admission or the certified cause and date of death. If the patient was still alive we asked for comment on his present state of health. If indicated we wrote to the family doctor or hospital consultant for any further information required.

Results

In response to our initial inquiry satisfactory information was obtained for 820 (70%) cases. Many of the other patients had died or transferred from their doctors' panels since operation, but for most of these the local executive council was able to supply the name of the new doctor or that of the doctor signing the death certificate. Further inquiry brought the number of replies to 991 (85% of the total). There thus remained 176 cases for which adequate data were not available. We therefore wrote to the surgeons under whose care the patients had been at the time of operation, and they were able to give us follow-up data for a further 127 patients.

There thus remained 49 (4%) cases that could not be traced, and these are summarized in Table I. Only 6 of the 49 untraced patients were children, but unfortunately two had had splenectomy performed during the first year of life. Twenty-one of the adults had had splenectomy performed because of traumatic rupture, while in 18 others it was part of another operation.

TABLE I.—Summary of 49 Untraced Cases

Age at Splenectomy	No. of Cases	Reason for Splenectomy	Reason not Traced
< 1 year	2	Acquired haemolytic anaemia (1) Hereditary spherocytosis (1)	No fixed abode (1) Gone abroad (1)
1–14 years	4	Accidental rupture (3) Hereditary spherocytosis (1)	Gone abroad (1) Not traced (3)
> 14 years	43	Portal hypertension (1) Accidental rupture (21) Malignant disease (7) Non-malignant disease (11) Idiopathic thrombocytopenic purpura (1) Miscellaneous (2)	Gone abroad (7) Not traced (34) No fixed abode (1) Left area (1)

Though it is disappointing that 100% follow-up had not been achieved the majority of the missing cases are those in which the risk of infection would not be expected to be high.

Indication for Splenectomy

The reason for splenectomy in relation to the age of the patient is summarized in Table II. Splenectomy was performed in 195 (17.5%) cases during childhood, five in the first year of life, and 25 at age 1–4 years. All indications were represented in this group, but half were due to accidental injury, while congenital haemolytic anaemia and idiopathic thrombocytopenic purpura accounted for almost 40%.

All told, 71% of the splenectomies were carried out because of accidental injury or as part of some other operation, especially operations for malignancy or peptic ulcer, usually in

patients over 45 years of age. Spontaneous rupture of the spleen occurred in 10 patients. One occurred during labour, one was due to adherence to a diverticulum, and one was in a patient with acute leukaemia. There was no evidence of trauma or underlying disease in the remaining seven, who were all aged 10–17 years.

TABLE II.—Indication for Splenectomy in Children and Adults

Reason for Splenectomy	Age in Years			All Cases
	< 15	≥ 15	Not Known	
Accidental rupture of spleen ..	97	197	17	311 (27%)
Operation for malignant disease ..	2	321	2	325 (28%)
Operation for non-malignant disease ..	3	188	1	192 (16%)
Operation for portal hypertension ..	3	23	1	27 (2%)
Hypersplenism ..	1	23	4	28 (2.5%)
Congenital haemolytic anaemia ..	44	28	4	76 (6.5%)
Acquired haemolytic anaemia ..	5	11	3	19 (2%)
Other anaemias ..	3	13	2	18 (2%)
I.T.P. ..	31	54	1	86 (7%)
Miscellaneous ..	6	74	5	85 (7%)
Total ..	195	932	40	1,167

The male/female ratio for all cases was 1.5:1, mainly due to an excess of males in the trauma (3:1) and other operation groupings (1.5:1). Females were in excess only in idiopathic thrombocytopenic purpura, portal hypertension, hypersplenism, and the miscellaneous disease groups.

Cause of Death

Death within three years of operation occurred in 417 (35%) patients. The reason for splenectomy and the time of death are shown in Table III. The cause of death in relation to the reason for splenectomy is shown in Table IV.

TABLE III.—Time of Death of Patients Undergoing Splenectomy 1961

Reason for Splenectomy	Post-operation (Months)						Total	3-Year Mortality
	< 1	1–6	6–12	12–24	24–36	N.R.		
Accidental rupture	18	2	—	—	—	—	20	6%
Malignant disease	110	27	45	70	13	—	265	82%
Non-malignant condition ..	34	3	7	7	2	1	54	28%
Portal hypertension	7	4	2	1	—	—	14	52%
Hypersplenism ..	3	—	—	4	1	—	8	28%
Congenital haemolytic anaemia ..	—	—	—	3	1	—	4	5%
Acquired haemolytic anaemia ..	1	—	3	1	—	—	5	26%
Other anaemia ..	4	1	2	1	—	—	8	44%
Idiopathic thrombocytopenic purpura ..	5	—	—	2	1	—	8	9%
Miscellaneous ..	15	6	4	5	1	—	31	37%
All cases ..	197	43	63	94	19	1	417	35%

Of the 417 deaths 319 were due to the primary disease for which splenectomy was performed or some complication of operation; three patients died with mesenteric thrombosis, respectively 10, 17, and 23 days after operation. Some died from unrelated cause—for example, a patient killed in a car accident two years to the day after a similar accident which led to splenectomy. In 23 instances, however, death was associated with infection.

Infection Following Splenectomy

A total of 93 patients (8%) developed serious infection within two to three years of splenectomy, but in 71 this was thought to be coincidental rather than a sequel of operation. Twenty-three patients died from infection, but in nine of these the infection was thought to be coincidental. There thus remain 22 patients—of whom 14 died—in whom infection was

TABLE IV.—Cause of Death in Patients Undergoing Splenectomy 1961

Reason for Operation	Primary Disease*	Un-related Cause	Infections			Not Known	All Deaths		All Cases
			Coincidental	Uncertain Relationship	Probable Relationship		No.	%	
Accidental rupture	12	6	1	1 Fulminating broncho-pneumonia	—	—	20	6	311
Operation (malignant disease) ..	243	17	4	1 (Subphrenic abscess)	—	—	265	82	325
Operation (non-malignant condition) ..	20	27	2	1 Severe bronchopneumonia and hepatitis	—	4	54	28	192
Portal hypertension	12	1	—	1 (Peritonitis empyema)	—	—	14	52	27
Hypersplenism	3	4	—	—	1 (Miliary T.B.)	—	8	28	28
Congenital haemolytic anaemia ..	—	1	—	—	3 Pneumococcal septicaemia	—	4	5	76
Acquired haemolytic anaemia ..	1	—	—	2 Lobar pneumonia 2 mths	—	2	5	26	19
Other anaemia	2	5	1	5 mths	—	—	8	44	18
I.T.P.	2	3	—	2	1 Wound infection, subphrenic abscess	—	8	9	86
Miscellaneous	24	5	1	Generalized sepsis 2 mths Bronchopneumonia and gangrene	—	—	31	36	85
				1 Wound infection and bronchopneumonia 6 mths	—	—			
Total	319	69	9	9	5	6	417	35	1,167

* Including deaths due to operation.

possibly related to splenectomy. The clinical histories of these cases are summarized below.

In only seven cases (five fatal) did we feel certain that infection was a consequence of splenectomy. Six of these had pneumococcal illnesses, three of which were septicaemias with terminal adrenal haemorrhage. The other was a patient who developed acute miliary tuberculosis and died within 24 hours of the initial symptom. In the group where the causal relationship was uncertain, pyogenic infections predominated.

The occurrence of infection in relation to the reason for splenectomy is shown in Table V. "Coincidental" infections occurred in all groups, but were highest where infection could be a feature of the primary disease—for example, portal hyper-

tension, anaemias being treated with corticosteroids, idiopathic thrombocytopenic purpura, and the miscellaneous group, which contains many examples of reticuloses. Infections with a "doubtful" relationship were also widely distributed, but this was not so for the "probable" group.

The age distribution and reason for splenectomy for the patients developing infections (other than coincidental ones) are shown in Table VI.

Three of the seven serious infections occurred in children aged 1–4 years, while four occurred in adults.

Infections Thought to be a Sequel of Splenectomy

Male aged 7 months. Congenital spherocytosis. Splenectomy, April 1961. Familial haemolytic anaemia operated on at age of 7 months. Good response. Eight months after splenectomy the child had been well the previous evening but a little fretful during the night and vomited on two occasions. Doctor was called urgently in the morning because the baby had collapsed, and when he arrived the child was apparently dead in his mother's arms. Mouth-to-mouth respiration and external cardiac massage was carried out en route to hospital, but without effect. Necropsy confirmed pneumococcal septicaemia with bilateral adrenal haemorrhage.

Female aged 2 years. Acquired haemolytic anaemia. Splenectomy, August 1961. Severe haemolytic anaemia, ecchymoses, haematemeses, gross splenomegaly developing during the neonatal period. Coombs test negative. Hb 5.5 g./100 ml., platelets 75,000/c.mm. Splenectomy (weight 340 g.) at 2 years 3 months; good haematological response. Three months after splenectomy, pyrexia of unknown origin; at eight months, influenzal meningitis; at 22 months, pneumococcal meningitis. No further illness.

Male aged 3 years. Congenital spherocytosis. Splenectomy, September 1961. Ten weeks after splenectomy, unwell and

TABLE V.—Infections Following Splenectomy in England and Wales, 1961

Reason for Operation	All Cases	Infections			Percentage 1-Year Survivors
		Coincidental	Doubtful Relationship	Probable Relationship	
Accidental rupture	311	18 (6%)	2 (0.6%)	—	—
Operation (malignant disease) ..	325	7 (2%)	—	—	—
Operation (non-malignant condition) ..	192	8 (4%)	1 (0.5%)	—	—
Portal hypertension ..	27	3 (11%)	2 (7%)	—	—
Hypersplenism ..	28	2 (7%)	1 (3.5%)	2 (7%)	8
Congenital haemolytic anaemia ..	76	5 (7%)	—	2 (2.5%)	2.5
Acquired haemolytic anaemia ..	19	4 (21%)	2 (11%)	1 (5%)	7
Other anaemia ..	18	2 (11%)	1 (5.5%)	—	—
I.T.P. ..	86	10 (12%)	3 (3.5%)	1 (1%)	1
Miscellaneous ..	85	12 (14%)	3 (3.5%)	1 (1%)	1.7
Total ..	1,167	71 (6%)	15 (1.3%)	7 (0.6%)	2.0

TABLE VI.—Infections* in Relation to Age and Reason for Splenectomy

Age:	<1	1–4	5–9	10–14	15–24	25–34	35–44	45–64	65+	Adult	N.R.
Accidental rupture of spleen					(1)	(1)		(1)			
Operation for non-malignant disease ..					(1)		(1)	(1)			
Operation for portal hypertension ..							(1)	1 (1)		1	
Hypersplenism								(2)			
Congenital haemolytic anaemia ..	1	1									
Acquired haemolytic anaemia ..		(1)									
Other anaemias				(1)	(1)				1 (1)		
I.T.P.									(2)		
Miscellaneous											
Total	1	2 (1)		(1)	(3)	(1)	(1)	2 (5)	1 (3)	1	
All cases	5	25	86	79	127	65	101	348	168	123	40

* Severe infection. Figures in parentheses = Doubtful infection.

increasing drowsiness for three days. Died shortly after admission. Necropsy, pneumococcal meningitis.

Male adult. Hypersplenism. Splenectomy, June 1961. Good response. Sixteen months after splenectomy, sudden onset of pyrexial illness. Admitted to hospital and died next day. Necropsy, miliary tuberculosis.

Female, aged 55. Hypersplenism. Splenectomy, December 1961. Twenty-seven months after splenectomy, unwell and low-grade pyrexia. Two days later suddenly collapsed and died. Condition was thought to be coronary thrombosis. At necropsy an unexpected finding was that of bilateral adrenal haemorrhage, and a heavy growth of pneumococci was found on blood culture.

Female, aged 59. Brill-Symmers disease. Splenectomy. Three months after splenectomy, pneumococcal meningitis; 14 months, virus encephalitis; 16 months, septic arthritis in both knee-joints. Nine, 15, and 24 months after splenectomy, pyelitis. Recovered.

Female aged 70. Idiopathic thrombocytopenic purpura. Splenectomy, August 1961. Post-operatively, wound infection and left pleural effusion. Two and 10 months after splenectomy, left subphrenic abscess—drained repeatedly during next five months until she died with what was thought to be a cerebral haemorrhage. Necropsy, purulent pneumococcal meningitis. Left subphrenic abscess (*Staphylococcus pyogenes*).

Infections where Relationship of Infection to Splenectomy was in Doubt

Male aged 2 years. Thalassaemia major. At six months after splenectomy, lobar pneumonia; at eight months, urinary infection; at 26 months, chicken-pox. Survived.

Female aged 11. Idiopathic thrombocytopenic purpura. Three years and three months after splenectomy she developed a very severe attack of chicken-pox. Recovered and remained well.

Male aged 17. Motor-cycle accident. Twenty months after splenectomy developed severe influenzal pneumonia. Recovered.

Female aged 19. Portal hypertension. Six attacks of severe tonsillitis in two years after splenectomy.

Male aged 33. Ruptured spleen after enema. One day after splenectomy he suddenly collapsed, and, despite active resuscitation, died. At necropsy found to have fulminating bronchopneumonia of right lung. Organism not identified; adrenals not examined. Mentally defective patient.

Female aged 38. Aplastic anaemia. Died four days after splenectomy. Pneumonia.

Male aged 50. Hypertrophy of pylorus. One year after splenectomy died from staphylococcal pneumonia.

Male aged 52. Pyrexia, pleural effusion, and splenomegaly. Two weeks after splenectomy he developed non-haemolytic streptococcal septicaemia. Responded to penicillin; remained well.

Female aged 54. Felty's syndrome. Nine months after splenectomy was admitted to hospital with ulcerative colitis, urinary infection, and thrombophlebitis. Progress was satisfactory.

Female aged 56. Acquired haemolytic anaemia. Ten weeks after splenectomy developed lobar pneumonia and died.

Male aged 69. Splenomegaly. Ruptured abdomen two weeks and four weeks after splenectomy. Severe wound infection (*Staph. aureus*). Died five months after splenectomy, bronchopneumonia.

Male aged 73. Idiopathic thrombocytopenic purpura. Five days after splenectomy developed bronchopneumonia and died. Necropsy, bilateral lower-lobe bronchopneumonia with gangrene of lung in some areas.

Female aged 75. Tuberculosis of spleen. Six weeks after splenectomy developed bronchopneumonia and hepatitis. Good recovery.

Male adult. Carcinoma of colon. Died from staphylococcal pneumonia 22 days after splenectomy.

Female aged 47. Acquired haemolytic anaemia on corticosteroid therapy. Three months after splenectomy she had an attack of sickness and oedema. Six months after splenectomy developed an upper respiratory infection which progressed; she died on 14 January 1962. Necropsy showed right lower-lobe confluent bronchopneumonia. The adrenals were found to be thin and atrophic.

Discussion

Perhaps the most interesting feature about this study is that it has been possible at all. We have been able to assemble data concerning 1,167 patients who had splenectomy performed in England and Wales during 1961, and though we do not know that this is complete it must be substantially so. Moreover, we have been able to achieve a two-year partial follow-up for 96% of these patients. These facts speak highly for the co-operation of colleagues, whether specialists, administrators, or family doctors, and it is doubtful whether elsewhere in the world such a study would be possible.

That so few patients have developed serious infections is reassuring. In 8% of all patients infection developed during the two to three years after operation, but in less than 2% was this thought to be possibly due to splenectomy. Indeed, in only 0.6% did we think that this was certain, but 303 patients died from the primary illness within one year of operation, so this figure is an underestimate, and, calculating only for patients who survived operation by at least one year, the incidence of "certain" serious infections is 2%. The risk was highest in hypersplenism and acquired haemolytic anaemia, both conditions with an increased susceptibility to infection and where corticosteroid therapy might have been employed. Of 311 patients operated on because of traumatic rupture of spleen only 20 subsequently developed infection. Any relationship was considered coincidental in 18 and "doubtful" in two.

It seems clear that in about 2% of cases splenectomy does predispose to serious infection. The risk is probably high in patients where the primary disease is associated with increased susceptibility to infection—for example, portal hypertension, hypersplenism, idiopathic thrombocytopenic purpura, and "reticuloses"—but an important precipitating factor may be the prolonged use of corticosteroids in conditions such as idiopathic thrombocytopenic purpura and acquired haemolytic anaemia. The danger of infection is also high when splenectomy is performed in the first four years of life, and fatal pneumococcal septicaemia did occur when splenectomy for hereditary spherocytosis had been performed in childhood and where corticosteroids had not been employed.

Only two of the 22 related infections occurred more than two years after operation and in only one of these did we regard the relationship as certain. This patient was a woman aged 55 who had had splenectomy performed because of hypersplenism. Two years and three months after operation she developed pneumococcal septicaemia and died two days later with Waterhouse-Friderichsen syndrome.

In another study (R. H. Jackson and W. Walker—unpublished observation) we achieved an 86% two-year follow-up of 310 children operated on for appendicitis. Ten had subsequent infections, but none were acute septicaemic illnesses. All were regarded as normal childhood infections, and we believe that splenectomy rather than operation *per se* is the precipitating factor.

Before a precise estimate of the risk of infection following splenectomy can be achieved it will be necessary to study a larger group of patients than those presented here. It would not seem worth while to study patients in whom splenectomy is part of a major operation, especially one for malignant disease, because a large proportion die within one to two years of operation, and in any event any risk of infection is irrelevant to management. This group comprises nearly half of the cases, and, excluding these, there would remain about 650 cases of splenectomy a year in England and Wales, of which 200 would be in children. The extension of this study to cover the five years 1959–63 should provide data for an authoritative statement regarding any risk of infection following splenectomy.

In the meanwhile we would make two recommendations: (1) That splenectomy be deferred whenever possible until the age of 4 years. (2) That penicillin be administered prophylactically for two years after splenectomy in all children, but also

in adults where the primary illness predisposes to infection. This is also indicated in patients in whom the spleen has been removed whenever the patient is receiving corticosteroids.

Summary

During 1961 1,167 patients had splenectomy performed in England and Wales.

A postal follow-up of these patients was carried out, information being sought from the family doctor or hospital consultant in whose care the patient had been. Altogether, details were achieved from 1,118 (96%).

The reason for splenectomy, cause of death, and occurrence of infection in the subsequent two to three years is reported.

It was confirmed that pneumococcal septicaemia and other fulminating infections sometimes follow splenectomy. Such infections are more common in childhood, in patients where the underlying disease predisposes to infection, and in patients on continued treatment with corticosteroids.

Further study is needed before an authoritative estimate of the risk in relation to age and underlying condition can be achieved. In the meanwhile it is suggested that splenectomy be avoided whenever possible during the first four years of life, and that post-operative antibiotic cover for two years might well be provided in young children, in patients where the primary illness may predispose to infection, and in any patient while receiving corticosteroid therapy.

This study has been made possible by the co-operation of hundreds of doctors throughout the country. We acknowledge with thanks the trouble that family doctors have taken to supply data about their patients, and to hospital staff for abstracting relevant data from hospital records.

This could not have been carried out without the good will of senior administrative medical officers in all regions and the generosity of the many surgeons and physicians who have allowed access to their records. When patients had "disappeared" the surgeon has often gone to considerable effort to trace them and provide the information requested.

Executive council staffs have played a large part in tracing patients who had changed their doctor.

All the secretarial work has been done by Mrs. M. Malaghan.

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Calcium Phosphate and Oxalate Ion-products in Normal and Stone-forming Urines

B. E. C. NORDIN,* M.D., PH.D., M.R.C.P.; W. G. ROBERTSON,* B.SC.

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The common assumption that urine is supersaturated with respect to calcium phosphate and calcium oxalate has not until recently been tested by actual determination of the relevant ion-products, mainly because of the difficulty of measuring ionic calcium in urine. Several workers have attempted to overcome this problem (Vermeulen *et al.*, 1956; Thomas and Howard, 1959; Nordin, 1959; Nordin and Tribedi, 1962), but while their results are of interest none of the methods can be described as satisfactory. The introduction of the dye tetramethylmurexide by Raafaub (1962) made accurate measurement of urinary ionic calcium practicable for the first time, and, using this technique, he has recently reported calcium phosphate and calcium oxalate ion-products in eight normal urines which he found to be more or less at the saturation level for these salts (Raafaub, 1963). We have now applied a slightly modified version of Raafaub's method to the measurement of calcium phosphate and oxalate ion-products in 50 male cases of renal-stone disease and 50 male age-matched controls, and the results are presented in this paper.

Methods

Twenty-four-hour samples of urine were collected with preservative from 50 men attending a renal-stone clinic. Twenty-three of them had a calculus at the time of observation, 14 had passed one in the previous year, and 13 had had no stones

for more than one year. The 50 controls were age-matched male patients and members of staff who had never suffered from calculi or any other kidney disease.

When the fresh urines were received the pH and volume were measured and the following analyses performed: total calcium by the modified AutoAnalyzer technique described by MacFadyen *et al.* (1965); oxalic acid by the method of Zarembski and Hodgkinson (1965a, 1965b); and ionic calcium by a slight modification of Raafaub's (1962) method. The latter modification consisted essentially in reading the absorbance of the calcium tetramethylmurexide complex at two wavelengths (480 and 530 millimicrons) as recommended by Etori and Scoggan (1962) for plasma, instead of at one wavelength only. The reproducibility of the estimation in 20 duplicate determinations was $\pm 6.1\%$. Phosphate was estimated by the standard AutoAnalyzer method.

Calculations

The calcium phosphate salt thought to govern the solubility of kidney stones is octocalcium phosphate (MacGregor *et al.*, 1965a, 1965b), and the approximate product $[\text{Ca}^{++}]^4 [\text{H}^+] [\text{PO}_4^{=}]^3$ may be calculated with the help of Table I as follows.

* Medical Research Council, Mineral Metabolism Research Unit, Leeds General Infirmary.