The difficulty of feeding the patients and the frequency of respiratory complications when tube feeding was employed led to the practice of withholding food by mouth and maintaining hydration and electrolyte balance by parenteral fluid administration without regard to calorie or protein requirements.

Respiratory complications accounted for a number of deaths. Recent writers stress the importance of maintaining a good airway, if necessary by tracheotomy. It is likely that some of the deaths could have been avoided if this operation had been carried out.

My thanks are due to Professor A. W. Woodruff for his advice on the preparation of this paper, to Mr. D. L. N. Sly for help with the statistics, and to the medical and nursing staff of the children's department, University College Hospital, Ibadan.

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CALCIUM AND PHOSPHATE METABOLIC STUDIES IN PATIENTS WITH URINARY CALCULI*

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As approximately 60% of urinary calculi contain calcium and 30% phosphate, it is tempting to think that abnormalities of calcium and phosphate metabolism play an important part in their development. The influence of the parathyroid glands on the metabolism of these ions, established by MacCallum and Voegtlin in 1908 and Greenwald in 1911, has been extensively investigated (Albright *et al.*, 1929, 1934) by balance studies and calcium infusion tests (Howard *et al.*, 1953; Nordin and Fraser, 1956), and the incidence of urinary calculi in cases of hyperparathyroidism has been stated to be 5% (Albright and Reifstein, 1948) and 8% (Beard and Goodyear, 1950): the high urinary output of calcium and phosphate which occurs in such circumstances predisposes to this.

The present investigation was undertaken to determine the incidence of calcium and phosphate metabolic disorders in a series of patients with urinary calculi. It was thought that such studies might reveal previously overlooked cases of parathyroid dysplasia and perhaps also demonstrate the incidence of "idiopathic" hypercalciuria (Flocks, 1940) and/or hyperphosphaturia. Eighty-five patients were studied after their urological treatment had been completed.

* Details of this paper were read at the Annual Meeting of the Surgical Research Society, held on July 19, 1957, at the Hammersmith Hospital and Postgraduate Medical School of London.

Methods

The patients were first screened by a simple out-patient test which was applied without preliminary dietetic or fluid restriction. A urethral catheter was passed and the bladder was emptied and washed with distilled water: the specimen was kept for analysis. The catheter was then clamped and left in position for one hour, at the end of which time the bladder was emptied again and the urine kept separately. A venous blood specimen was taken at the mid-point between the two urine collections.

Blood and urine specimens were quantitatively analysed for calcium, phosphate, and creatinine, and the urine calcium concentration/urine creatinine concentration (mg./100 ml.) and the urine phosphate concentration/urine creatinine concentration (mg./100 ml.) ratios were calculated.† Calcium in the blood and urine was determined by the method of Clark and Collip (1925), phosphate by the method of King and Wootton (1956), and creatinine by the method of Brod and Sirota (1948).

When abnormal values were found in the blood calcium and blood phosphate, or when abnormal urine calcium/creatinine or phosphate/creatinine ratios were detected, the particular patients were asked to come into hospital so that 24-hour urine calcium and phosphate excretions could be determined and in some cases calcium infusion tests carried out: 29 patients were found with one or more of these abnormalities, but only 15 agreed to come in. A low calcium diet (100 mg. daily) containing 500–700 mg. of phosphate preceded for four successive days the 24-hour urine collections, which were separately analysed for calcium, phosphate, and creatinine content; daily blood samples were obtained for creatinine estimations so that 24-hour creatinine clearances could be determined.

Intravenous calcium infusion tests were carried out on the fourth day of the low-calcium diet: 15 mg. of calcium per kg. body weight was given and 10% calcium gluconate in 500 ml. of 0.9% sodium chloride was used. The infusion was administered for four hours, from 10 a.m. to 2 p.m. Voided specimens of urine were obtained every four hours throughout the 24 hours which succeeded the commencement of the infusion and were kept separately. Blood specimens were taken at 9 a.m., 2 p.m., and 10 p.m. on the day of the infusion and at 10 a.m. on the following day. The blood and urine specimens were quantitatively analysed for calcium, phosphate, and creatinine.

The amount of calcium excreted in the urine in the 12 hours after the infusion is expressed as a percentage of the intravenous dose after due allowance is made for the 24-hour basal calcium output.

Iliac crest bone biopsy was performed on three patients, but no bone changes were found.

The Sulkowitch test was not done. It is a qualitative test and is positive when the urine contains 7–10 mg./100 ml. of calcium. It has little diagnostic value except when the total urinary output for 24 hours is known.

Results

Blood calcium values were estimated in all 85 patients: in 49 patients these were less than 10.5 mg./100 ml.; in 19 they ranged between 10.5 and 11 mg.; and in 17 they were greater than 11 mg. In 14 of the 17 patients who had

† Calcium clearance = $\frac{\text{urine calcium}}{\text{plasma calcium}}$ (mg.) and creatinine clearance = $\frac{\text{urine creatinine}}{\text{plasma creatinine}}$ (mg.) then $\frac{\text{calcium clearance}}{\text{creatinine clearance}} = \frac{\text{urine calcium} \times \text{plasma creatinine}}{\text{plasma calcium} \times \text{urine creatinine}}$. This ratio is found to be 0.03 in normal subjects when the average daily excretion of creatinine is 1.5 g. in males and 1 g. in females. And since the serum calcium value is approximately 10 mg./100 ml. and the plasma creatinine value 1 mg./100 ml., it is more convenient to use the urine calcium/creatinine ratio, which is found to be 0.3 in normal subjects. The phosphate/creatinine clearance ratio, deduced in a similar way, is found to be 0.12 in normal subjects (B. E. C. Nordin, personal communication).

blood calcium values greater than 11 mg., repeated determinations confirmed the abnormality: the estimations were not repeated in three cases (Fig. 1).

Blood phosphate values were estimated in all 85 patients, and in 27 the values were less than 3 mg./100 ml. Repeated

FIG. 1.—Relation of serum calcium to serum phosphate in 85 patients. The 15 points in the top left-hand quadrant are thought to be significant, for these represent serum calcium values greater than 11 mg./100 ml. and serum phosphate values less than 3.5 mg./100 ml. Serum calcium: >11 mg./100 ml.=17; <11 mg./100 ml.=68. Serum phosphate: >3 mg./100 ml.=58; <3 mg./100 ml.=27.

determinations made in 14 of the 27 cases confirmed the abnormality: the estimations were not repeated in 13 cases. Six of the 27 patients in whom the blood phosphate values were less than 3 mg. had blood calcium values greater than 11 mg. (Fig. 1).

Serum alkaline phosphatase was estimated in all 85 patients and the values were all within normal limits. No patients presented radiologically demonstrable lesions of bone.

Creatinine Clearance.—Twenty-four-hour creatinine clearance, determined in 32 of the 85 patients, showed values which ranged from 34 to 113 ml. a minute: 10 patients (Cases 3, 5, 16, 17, 27, 32, 43, 46, 56, and 69) were thought to have some degree of glomerular damage.

Urine calcium concentration/creatinine concentration ratios greater than 0.3 were found in 11 of the 85 patients: eight of these had blood calcium values greater than 11 mg./100 ml. **Urine phosphate concentration/creatinine concentration ratios greater than 0.12** were found in 18 of the 85 patients: seven of these had blood phosphate values less than 3 mg./100 ml. (Table I). In only 5 of the 85

TABLE I.—Calcium/Creatinine and Phosphate/Creatinine Ratios in Urine Related to Serum Calcium and Serum Phosphate in 85 Patients

		Calcium/Creatinine Ratios	
		<0.3	>0.3
Serum calcium	>11 mg./100 ml. ..	6	8
	<11 „ ..	68	3
Total No. of patients ..		74	11
		Phosphate/Creatinine Ratios	
		<0.12	>0.12
Serum phosphate	≤ 3 mg./100 ml. ..	12	7
	>3 „ ..	55	11
Total No. of patients ..		67	18

patients were the urine calcium/creatinine ratios, urine phosphate/creatinine ratios, and blood calcium and phosphate values all abnormal.

Twenty-four-hour urine calcium excretion, determined in 15 patients after a low-calcium diet for three days,

showed values ranging from 125 to 300 mg. in 10 patients and from 40 to 97 mg. in 5. In 8 of the 10 patients with high calcium excretion values the blood calcium values were elevated, and in 6 the blood phosphate values were low. In 9 of the 10 patients the calcium/creatinine urine ratios were greater than 0.3 and in seven the phosphate/creatinine urine ratios were greater than 0.12 (Table II). Five of the patients submitted to 24-hour calcium excretion

FIG. 2.—Serum phosphate and urinary excretion of PO_4 during and after the infusion of calcium gluconate in five patients with abnormal serum calcium and PO_4 values and Ca/Cr and PO_4 /Cr urine ratios.

studies presented intermittent hypercalciuria. This observation is very important, as it might be explained by the action of a substance on the renal tubules in such a way as to vary, from time to time, the rate of calcium excretion.

Calcium infusion given to four patients with abnormal calcium/creatinine and phosphate/creatinine urine ratios gave normal calcium excretion during the 12-hour periods which succeeded the beginning of the infusions. A single

TABLE II.—Twenty-four Hour Urine Calcium Excretion Values after 3 Days of Low-calcium Diet (100 mg. a day) in 15 Patients and the Related Serum Calcium and Phosphate Values Together with the Urine Calcium/Creatinine (Ca/Cr) and Phosphate/Creatinine (Ph/Cr) Ratios

No.	Age	Blood Ca	Blood Phosph.	Ca/Cr Ratio	Ph./Cr Ratio	Urinary Ca Excretion (on 3rd Day)
1	55	9.6 mg.	3.5 mg.	0.1	0.21	97 mg.
3	35	10.5 „	2.4 „	0.57	0.06	190 „
6	32	11.3 „	3.0 „	0.43	0.12	300 „
11	63	11.0 „	2.2 „	0.54	0.35	270 „
15	71	10.8 „	3.5 „	0.45	0.37	180 „
16	75	15.8 „	1.9 „	0.9	0.17	190 „
23	47	11.4 „	3.3 „	0.3	0.12	155 „
29	42	11.4 „	2.7 „	0.33	0.24	160 „
30	31	11.8 „	3.0 „	0.3	0.78	125 „
47	67	9.8 „	2.8 „	0.02	0.29	80 „
49	60	9.0 „	3.0 „	0.2	0.37	82 „
69	32	10.2 „	2.2 „	0.25	0.3	40 „
82	37	11.4 „	2.6 „	0.35	0.42	180 „
84	52	12.7 „	2.2 „	0.45	0.41	200 „
85	59	11.8 „	3.5 „	0.1	0.25	50 „

patient with normal calcium/creatinine and phosphate/creatinine urine ratios, but with repeatedly high blood calcium values, had a significantly low urine calcium excretion. The total calcium excretion, expressed as a percentage of the administered dose, ranged from 15 to 43.5%. If the normal value for the net 0–12-hour excretion is taken to be 33 to 53% (Nordin and Fraser, 1956), only one patient showed an abnormally low value. Phosphate excretion after calcium infusion was found to be high in two patients, slightly low in one, and significantly low in two (Fig. 2).

A complete list of results of the examinations carried out on all the 85 patients is given in Table III.

Discussion

Of 85 patients with calculi in the upper urinary tract, there was evidence suggestive of a disordered calcium

metabolism in six, a disordered phosphate metabolism in five, and parathyroid dysplasia in four.

The criteria of abnormal calcium metabolism were raised calcium/creatinine urine ratios and hypercalciuria; the criteria of phosphate metabolic abnormalities were raised phosphate/creatinine urine ratios and hyperphosphaturia; and the criteria of parathyroid dysplasia were elevation of the serum calcium, depression of the serum phosphate, raised calcium/creatinine ratios, and hypercalciuria. No single test is satisfactory for parathyroid dysfunction (McGeown and Bull, 1957).

A raised serum calcium value alone is not regarded as significant, and some patients show no other abnormality. The serum calcium may also be raised in cases of metastatic carcinoma of bone, myelomatosis, sarcoidosis, and vitamin-D intoxication, and in patients on a peptic ulcer regime with a high milk and alkali intake. Myelomatosis, and sarcoidosis with hypercalcaemia, may be confused with hyperparathyroidism complicated by secondary impairment of renal function, but a low serum phosphate and persistent hypercalciuria in the presence of a low calcium intake are points in favour of the diagnosis of primary hyperparathyroidism.

TABLE III.—Results of Examinations

Case No.	Age	Blood		Phosph./Cr Clearance Ratio	G.F.R. (Creat.)	Alkal. Phosph. Units	1st Spec. Urine PO ₄ /Cr Ratio	2nd Spec. Urine Ca/Cr Ratio	1st Spec. Urine PO ₄ /Cr Ratio	2nd Spec. Urine Ca/Cr Ratio	Urine 24-Hour Calcium Excretion
		PO ₄ mg./100 ml.	Ca mg./100 ml.								
1	55	3.5	9.6	0.21	54	10.0	0.53	0.73	0.17	0.06	97
2	72	2.2	10.9	0.09		6.2	0.26	0.16	0.10	0.12	
3	35	2.4	10.5	0.06	77	5.9	0.22	0.12	0.51	0.57	190-310
4	65	3.8	10.1	0.16	77	7.3	0.63	0.60	0.29	0.33	
5	46	2.9	10.5	0.14	34	10.5	0.20	0.17	0.18	0.11	
6	32	3.0	11.3	0.12	113	7.2	0.30	0.30	0.46	0.43	309-340
7	47	3.1	10.6	0.13		8.8	0.18	0.35	0.22	0.24	
8	57	4.0	10.4	0.07		6.0	0.13	0.22	0.22	0.30	
9	49	3.2	10.1	0.19		3.8	0.73	0.60	0.12	0.12	
10	65	3.6	10.7	0.15		10.3	0.16	0.37	0.08	0.10	
11	63	2.2	11.0	0.35		6.5	1.0	0.74	0.55	0.54	158-506
12	33	3.4	9.5	0.21	82	10.5	0.70	0.57	0.12	0.23	
13	46	3.4	10.0	0.08		5.8	0.45	0.36	0.31	0.28	
14	34	4.1	10.6	0.21	92	5.2	0.93	0.74	0.10	0.15	
15	71	3.5	10.8	0.37	73	13.0	0.92	0.92	0.39	0.45	173-198
16	75	1.9	15.8	0.17	48	13.0	0.46	0.26	0.71	0.90	189-194
17	48	3.6	11.0	0.24	54	10.0	0.55	0.54	0.14	0.22	
18	30	3.9	10.6	0.41		13.0	0.92	0.95	0.08	0.10	
19	64	3.5	10.4	0.01		6.2	1.1	0.35	0.30	0.23	
20	37	2.9	8.6	0.08		15.6	0.44	0.22	0.32	0.50	
21	42	3.1	10.0	0.07		5.5	0.43	0.17	0.22	0.19	
22	44	3.4	12.2	0.23		8.1	1.0	0.80	0.20	0.10	
23	47	3.3	11.4	0.12		10.3	0.60	0.80	0.26	0.34	153-214
24	38	5.8	12.8	0.21		4.8	0.25	0.27	0.27	0.27	
25	40	3.6	11.0	0.31	104	7.0	0.60	0.77	0.10	0.37	
26	66	3.8	12.8	0.54	75	7.5	1.3	2.1	0.38	0.75	
27	38	3.2	9.6	0.22	55	4.7	0.50	0.37	0.01	0.38	
28	44	2.9	11.2	0.04		9.5	0.27	0.13	0.02	0.03	
29	42	2.7	11.4	0.24	92	11.0	0.74	0.63	0.26	0.33	161
30	31	3.0	11.8	0.78	85	4.7	1.8	1.4	0.32	0.30	125
31	42	4.0	11.6	0.12		5.0	0.62	0.54	0.02	0.04	
32	48	2.3	10.6	0.37	53	8.9	0.87	0.60	0.06	0.03	
33	45	3.1	9.8	0.18		3.1	0.34	0.43	0.01	0.01	
34	37	3.1	9.6	0.12		5.4	0.50	0.29	0.01	0.02	
35	30	3.7	10.8	0.23		8.3	0.92	0.69	0.23	0.44	
36	39	3.7	9.2	0.35	83	5.1	0.93	1.0	0.02	0.03	
37	31	2.3	11.1	0.12		4.1	0.69	0.19	0.07	0.10	
38	53	2.4	10.0	0.2		7.7	0.62	0.37	0.01	0.01	
39	43	2.1	10.0	0.25		7.7	0.64	0.43	0.01	0.26	
40	28	3.1	8.6	0.49	108	6.5	0.21	1.2	0.01	0.01	
41	67	2.9	9.2	0.33	66	6.3	0.62	0.58	0.01	0.01	
42	29	4.1	11.2	0.22	110	7.5	0.74	0.58	0.18	0.17	
43	49	2.0	9.2	0.38	73	5.8	0.57	0.47	0.03	0.10	
44	42	3.9	10.0	0.27	95	6.9	0.70	0.57	0.09	0.04	
45	47	2.4	10.2	0.40	76	7.9	0.58	0.53	0.14	0.11	
46	30	3.3	11.0	0.48	62	6.4	0.88	0.90	0.01	0.02	
47	67	2.8	9.8	0.29	75	20.2	0.37	0.50	0.02	0.02	71-96
48	29	2.0	8.6	0.06		4.5	0.23	0.10	0.16	0.19	
49	60	3.0	9.0	0.37	88	8.5	1.4	0.84	0.29	0.26	
50	43	3.7	9.6	0.2		7.6	0.51	0.54	0.01	0.01	82
51	40	3.2	11.8	0.22		9.5	0.59	0.54	0.02	0.03	
52	71	2.0	11.6	0.12		9.9	0.11	0.18	0.01	0.02	
53	60	2.9	9.2	0.26		11.1	0.61	0.43	0.01	0.02	
54	32	3.5	10.8	0.27		14.6	0.76	0.95	0.01	0.02	
55	39	3.8	9.0	0.21		4.4	0.59	0.65	0.03	0.04	
56	53	3.5	8.2	0.32	64	2.7	0.62	0.9	0.14	0.49	
57	83	3.1	10.0	0.18		8.2	0.42	0.43	0.23	0.36	
58	39	2.5	9.9	0.03		5.4	0.06	0.07	0.01	0.01	
59	47	2.2	9.3	0.11		6.9	0.32	0.21	0.28	0.34	
60	75	3.8	9.4	0.37		7.8	1.1	0.9	0.02	0.03	
61	38	2.2	9.8	0.2		3.5	0.94	0.37	0.02	0.02	
62	44	3.3	10.2	0.15		13.0	0.45	0.38	0.11	0.03	
63	45	3.3	10.4	0.12		5.1	0.52	0.39	0.20	0.29	
64	30	3.3	9.9	0.2		5.0	0.65	0.54	0.16	0.14	
65	29	2.8	11.0	0.18		4.0	0.42	0.50	0.01	0.08	
66	36	3.2	9.9	0.17		6.0	0.27	0.43	0.03	0.13	
67	41	2.4	9.8	0.10		8.0	0.57	0.23	0.06	0.01	
68	59	3.1	10.6	0.25		8.0	0.81	0.75	0.14	0.06	
69	32	2.25	10.2	0.3	190	5.3	0.12	0.18	0.16	0.25	40
70	26	3.6	9.2	0.01		3.9	0.31	0.27	0.10	0.12	
71	69	2.6	9.2	0.23		11.1	0.56	0.45	0.01	0.01	
72	47	2.9	9.0	0.14		7.9	0.50	0.33	0.03	0.02	
73	32	2.7	10.0	0.08		8.2	0.37	0.19	0.15	0.27	
74	75	3.1	10.1	0.27		9.7	0.42	0.53	0.02	0.11	
75	37	3.1	10.7	0.14		8.5	0.46	0.38	0.18	0.35	
76	43	3.2	9.6	0.35	92	6.4	0.56	0.69	0.14	0.18	
77	55	2.3	10.1	0.12		10.9	0.75	0.16	0.25	0.07	
78	46	2.9	10.0	0.15		9.1	0.33	0.25	0.16	0.21	
79	55	3.0	8.7	0.16		10.1	0.27	0.33	0.13	0.15	
80	63	4.4	9.1	0.02		8.6	0.72	0.53	0.25	0.22	
81	36	3.6	9.6	0.15		6.7	0.48	0.43	0.03	0.03	
82	37	2.6	11.4	0.42		5.3	0.61	0.40	0.29	0.35	186-236
83	38	3.1	10.2	0.22	147	6.1	0.37	0.44	0.08	0.16	
84	52	2.2	12.7	0.41	59	10.2	0.64	0.60	0.43	0.45	200
85	59	3.5	11.8	0.25			0.42	0.32	0.1	0.1	50

All patients with calcium/creatinine urine ratios about 0.3 were found to have hypercalciuria when 24-hour calcium excretion studies were carried out. This observation means that the calcium/creatinine urine ratio is an effective screening test. Some of the patients also had high phosphate/creatinine urine ratios; but this alone does not indicate hyperphosphaturia, as some of the creatinine clearances were abnormal.

Calcium infusion tests carried out on five patients with hypercalciuria and raised calcium/creatinine urine ratios were not helpful: no regular pattern of serum phosphate and urine phosphate excretion was noted and the observations reported by Howard *et al.* (1953) could not be confirmed.

Intermittent hypercalciuria was observed in some patients, and it is possible that this phenomenon represents intermittent parathyroid activity: further studies to explore this possibility are in progress.

Summary

The metabolism of calcium and phosphate has been investigated in 85 patients who had urinary calculi: the investigations were made after urological treatment had been completed.

There was evidence to suggest disordered calcium metabolism in six, disordered phosphate metabolism in five, and parathyroid dysplasia in four.

When the calcium/creatinine urine ratios, calculated from values derived from simple out-patient tests, were found to be greater than 0.3, hypercalciuria was invariably found when the patients were studied as in-patients and the 24-hour urine reactions were determined. Abnormal calcium/creatinine ratios were observed in 11 patients.

Intermittent hypercalciuria was found in five cases.

I am indebted to Professor I. Aird for permission to carry out this work and to Mr. R. Shackman for the help and criticism he gave to me. Thanks are also due to Mr. Alex Roche for permission to study some of the patients who had been under his care in the department of urology at the West London Hospital. All the biochemistry was carried out by the technical staff in the department of surgery at the Postgraduate Medical School of London; special thanks are due to Miss E. Bottoms and Miss S. Levy.

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The London County Council has published the second volume of the new series of London Statistics covering the period 1946–55. The tables cover a wide field of subjects, including vital statistics. Each section is preceded by an account of the services concerned and a brief description of recent developments in it. There has been a decline of population in the county over the last six years (3,295,000 in 1955 compared with 3,358,000 in 1951), which reversed the trend immediately following the war. This overall decline, however, conceals a number of other changes within certain age groups—for example, the school population and the population aged 65 and over were higher in 1955 than in 1951. The price of the volume is 40s. from the County Hall, London, S.E.1.

CIRCULATING ANTIBODIES IN SARCROIDOSIS

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Although the mechanism by which circulating antibodies are produced is still obscure, there is much evidence that the reticulo-endothelial system is intimately involved. Disorders of this system are therefore of particular interest because of their possible effect on antibody production and for the opportunity which they give for investigation of the mechanism concerned. In sarcoidosis, where pathological changes may be widely distributed in the reticulo-endothelial system, it has been suggested that a deficiency in the production or transport of antibodies may be responsible for the well-known "depression" of the delayed or tuberculin type of skin reaction (Urbach *et al.*, 1952). Such investigations of antibody production as have been made, however, have given conflicting results. In sarcoidosis a normal antibody response was found by Sones and Israel (1954) to polyvalent enteric (T.A.B.) vaccine and to pertussis vaccine, while an increased agglutinin response to incompatible red cells was reported by Sands *et al.* (1955). In Hodgkin's disease and lymphosarcoma, Geller (1953) found a diminished antibody response to pneumococcal polysaccharide, whereas in later studies of Hodgkin's disease a normal response to T.A.B. vaccine was recorded by Hoffmann and Rottino (1950) and to mumps virus by Schier *et al.* (1956).

This paper describes an investigation of antibody production in patients with sarcoidosis following artificial immunization with tetanus toxoid. In addition, the serum staphylococcal alpha-antitoxin was studied as an index of the capacity to produce natural antibody. Tetanus toxoid was chosen because accurate and well-established techniques are available for assessing the antitoxin response, and because man does not naturally have circulating tetanus antitoxin: thus the effect of primary immunization could be studied in subjects who were, for practical purposes, in an identical immunological state. Further, a number of patients were available who had been immunized in the armed Forces some years earlier. This investigation therefore differed from previous work in that we were able to study separately the effects of primary immunization and of reinoculation.

The results described show that after primary immunization the antibody response of patients with sarcoidosis was poorer than that of control patients. We found no evidence of impairment in sarcoidosis either of the response to reimmunization or of the production of natural staphylococcal alpha-antitoxin.

A poor response to primary immunization was also given by a small group of patients with reticulosis which