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 SARCOIDOSIS

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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

was studied in the same way. The term "reticulosis" is used throughout this paper to refer collectively to Hodgkin's disease, lymphosarcoma, and multiple myeloma.

Tetanus Antitoxin Investigation

Clinical Material

Three groups of volunteers were studied.

Group I comprised 22 patients with sarcoidosis, of whom 12 had not been immunized against tetanus and 10 had been immunized at least four years before the disease was diagnosed. In 17 patients the diagnosis was confirmed histologically; in the remaining 5 it was made on clinical grounds. At the time of diagnosis 21 patients had radiographic evidence of intrathoracic sarcoidosis; this took the form of pulmonary infiltration with associated hilar-node enlargement in 16, of bilateral hilar-node enlargement alone in four, and of pulmonary infiltration alone in one. In the remaining patient skin lesions were the only evidence of the disease. Cultures were made from the sputum and urine of each patient; all were negative for *Mycobacterium tuberculosis*. Sensitivity to tuberculin was usually absent or low. The state of the sarcoid process at the time of the investigation was arbitrarily assessed as active or inactive. In seven patients who had lost all clinical and radiological evidence of sarcoidosis and in one who had pulmonary fibrosis following sarcoidosis seven years previously the disease was classed as inactive; in the remaining 14 it was regarded as active, lesions being still readily demonstrable.

Group II consisted of 24 control subjects, of whom 10 had and 14 had not been immunized previously against tetanus. All had recently been fully investigated and treated in hospital for various conditions and were known to be free from tuberculosis, sarcoidosis, and reticulosis.

Groups I and II were comparable for age, but of the 22 patients with sarcoidosis 14 were females, whereas only 6 of the 24 controls were females. This difference, however, we did not regard as important, because what evidence there is suggests that women respond better than men to tetanus toxoid (Marvell and Parish, 1940). Thus the advantage, if any, would lie with the group suffering from sarcoidosis.

Group III consisted of 13 patients with histologically confirmed reticulosis, either Hodgkin's disease or lymphosarcoma. Five of them had and eight of them had not been immunized previously against tetanus. All the patients were reasonably well and ambulant during the investigation.

Method.—Each patient received two intramuscular injections of 1 ml. (about 9 Lf) of the same batch of tetanus toxoid, at six weeks' interval. Blood was taken for estimation of antitoxin at the time of each injection and exactly two weeks after the second. Tetanus antitoxin titrations were performed in mice, at approximately twofold differences, by the method described by Glenny and Stevens (1938.)

Response to Primary Immunization

Twelve patients with sarcoidosis, eight patients with reticulosis, and 14 controls received primary immunization with tetanus toxoid. No detectable antitoxin was present in the sera taken from these patients at the time of the first and second inoculations. This served as some confirmatory evidence of the accuracy of each patient's history—namely, that he had not received previous immunization against tetanus.

Table I records the tetanus antitoxin titres found two weeks after the second of the two primary inoculations. Consideration of the results from all patients with sarcoidosis shows that the levels attained were below those of the control group in many cases. Though the number of patients in these groups is admittedly small, the compact distribution of titres and the absence of poor responders in the control group contrast markedly with the wide distribution in the sarcoidosis group. The difference between the two groups is significant at the 2% level of probability.

Table I also shows a striking difference of response within the sarcoidosis group when it is subdivided according to the state of the disease process; the poorest responders were four of the six whose disease remained active throughout the investigation. By contrast antitoxin titres within the range of those of the control group were found in the sera of all six patients in whom sarcoidosis was classed as "inactive."

Mantoux-testing was carried out on the 12 patients with sarcoidosis; there was no obvious correlation between tuberculin sensitivity and antitoxin response.

Of eight patients with reticulosis, four made no detectable antitoxin response to primary immunization; three of these non-responders were given radiotherapy during the investigation. This treatment was unlikely to have had any effect on the antibody response, since deep *x* rays were seldom given to more than a single group of glands and never to the whole body. Moreover, two of the five untreated patients produced less antitoxin than any of the controls.

TABLE I.—*Tetanus Antitoxin Responses of Previously Unimmunized Patients Two Weeks After the Second of Two Injections of Tetanus Toxoid*

Clinical Group	No. of Persons with Tetanus Antitoxin Titres (units/ml.)									Total
	<0·01	0·01–	0·02–	0·05–	0·1–	0·2–	0·5–	1–	2–5	
Controls ..						5	2	5	2	14
Reticulosis ..	4				1		2		1	8
Sarcoidosis:										
(a) Active ..	2			2		2				6
(b) Inactive ..						3	1	2		6
Sarcoidosis a+b	2			2		5	1	2		12

Applying Fisher's exact method for difference between results of controls and all sarcoidosis patients, P=0.016.

Response to Reimmunization

Table II shows the tetanus antitoxin response of 10 patients with sarcoidosis, of 5 with reticulosis, and of 10 controls, all of whom had a history of earlier immunization against tetanus.

TABLE II.—*Tetanus Antitoxin Responses of Previously Immunized Persons*

		No. of Persons with Tetanus Antitoxin Titres (units/ml.)												Total
		<0·01	0·01–	0·02–	0·05–	0·1–	0·2–	0·5–	1–	2–	5–	10–	20–	50	
A	Controls ..	4			2		2	1	1						10
	Sarcoidosis	4		1	2	1	1		1						10
	Reticulosis	1		1	1	1	1								5
B	Controls ..	1				1		2			2	4			10
	Sarcoidosis	1				1	1	2	1			1	3		10
	Reticulosis							1	1		1	1		1	5
C	Controls ..						1	2	1		3	3			10
	Sarcoidosis					1	2	1	2		1	2	1		10
	Reticulosis							1	1		1	1		1	5

A=Before injection. B=Six weeks after first injection, at the time of the second injection. C=Two weeks after second injection.

The pre-injection titres of these persons reflect differences in immunization history, inevitable in any random sample. Thus 9 out of 25 had no detectable antitoxin when the first dose of tetanus toxoid was injected. Six weeks later, at the time of the second injection, one patient with sarcoidosis and one control had failed to respond. This may be attributable to inaccurate history or to loss of previous immunity owing to the long interval (10 and 20 years) since the last injection of toxoid (Barr and Sachs, 1956).

The results in Table II show that there was little, if any, difference in the capacity of the sarcoidosis and reticulosis patients or of the controls to respond to one, or to two, boosting doses. There was no correlation between antitoxin response and the activity of the sarcoid process.

The greatest response ever encountered in the fairly extensive experience of one of us (M. B.) was given by a patient with Hodgkin's disease; his antitoxin titre rose from 0.02–0.05 to 300–500 units per ml. within six weeks of his first booster injection. This case serves to emphasize the well-known fact that the amount of antibody produced in response to a boosting dose shows much greater variation than that to primary immunization. It is affected not only by the interval since the last inoculation, but also by the number and size of previous doses, the type of antigen previously used, and the size of the boosting dose. We used, as is customary, the same dose both for primary immunization and for reinforcing immunity; this dose, which produces adequate immunity in normal previously non-immune persons, must be more than adequate as a boosting dose to immunized persons. It is therefore possible that with a smaller dose we might have detected a difference in the response of these groups to reimmunization.

Staphylococcal Alpha-antihaemolysin Investigation

Material and Methods

Sera were obtained from three groups of patients.

Group I consisted of 50 patients with sarcoidosis, in 40 of whom the diagnosis had been proved histologically; in the remainder it had been made on clinical grounds alone. At the time of the investigation 24 patients were thought to have active sarcoidosis, 18 were clinically and radiologically clear, and in 8 patients with pulmonary fibrosis following sarcoidosis the activity of the sarcoid process was doubtful.

Group II consisted of 19 patients with histologically proved reticulosis—Hodgkin's disease, lymphosarcoma, multiple myeloma.

Group III comprised 75 control subjects matched as to age and sex distribution with the patients in Groups I and II. All attended hospital for conditions other than sarcoidosis and reticulosis, and none were suffering from either of these diseases.

The staphylococcal alpha-antitoxin content of serum was determined by assay against a serum of known potency, using constant toxin and rabbit erythrocytes as indicator.

Results

The sera of patients with sarcoidosis and reticulosis did not differ significantly in staphylococcal alpha-antitoxin content from those of control patients, though the results (Table III) show that there was, in fact, a slightly higher

TABLE III

Clinical Group	No. of Persons with Staphylococcal Alpha-antitoxin Titres (units/ml.)					Total
	<0·3	0·3–	0·6–	1·2–	2·4	
Controls ..	20	19	24	10	2	75
Sarcoidosis ..	8	12	16	11	3	50
Reticulosis ..	6	2	6	4	1	19

proportion of the sarcoidosis group with titres over 1.2 units/ml. There was no correlation between the activity of the sarcoid process and antitoxin content of the serum.

When the results of these titrations were analysed by age groups a trend was found towards the greater frequency of low titres with age over 25 years. Further investigations are planned to assess the significance of this finding. This trend, which was found within each clinical group, did not materially affect the comparison between groups.

Discussion

It is not surprising that previous assessments of antibody production in sarcoidosis and reticulosis have given conflicting results, because the test antigen has sometimes been given to patients with no previous immunity and has at other times served to reinforce existing immunity. It is certain that many of the observed groups contained unknown proportions of patients receiving primary immunization and boosting inoculations. When the results of these earlier trials are reviewed in the light of the probable state of immunity before immunization more conformity is found. Thus Sones and Israel (1954) found normal antibody production in sarcoidosis to what were obviously reinforcing doses of pertussis and T.A.B. vaccines. All 20 patients immunized against pertussis and all but one of the 14 patients inoculated with T.A.B. vaccine had demonstrable antibody before injection. In reticulosis also the response to a reinforcing stimulus (mumps vaccine) was found by Schier *et al.* (1956) to be similar to that of controls, of whom 90% gave a positive skin reaction to mumps virus before vaccination; the mean pre-injection titres of the reticulosis and control groups were very similar. Thus, so far as reimmunization is concerned, published work is in general accord with ours, in detecting no abnormal response in reticulosis and sarcoidosis. There is one exception, the report of Sands *et al.* (1955), whose patients with sarcoidosis responded to an injection of incompatible red cells with higher agglutinin titres than tuberculous or control patients. The only explanation we have to offer for this discrepant result is the great variation in the pre-injection titres of all their groups. No reference to the initial state of their patients was made by Hoffmann and Rottino (1950), who found the agglutinin response to T.A.B. vaccine to be normal in patients with Hodgkin's disease.

Primary immunization in reticulosis was studied by Geller (1953), but because a few of his patients possessed circulating antibodies before injection and because the pattern of response of some others was not typical of a response to a primary stimulus, we are not in a position to contend that the diminished antibody response of his patients is essentially similar to the poor response to primary immunization of our patients with sarcoidosis and reticulosis.

It is tempting to assume that the impaired primary response is due to the partial replacement of the reticulo-endothelial system by abnormal tissue. An alternative explanation is that the antibody-producing mechanism is "crowded out" by its response to another antigen; Barr and Llewellyn-Jones (1953) found that a diminished primary response may occur when the primary stimulus of one antigen is given simultaneously with the boosting dose of another. It may be that in active sarcoidosis the antibody-forming cells are already responding to a strong and continued stimulus; if so, the antigen responsible has yet to be determined.

The general level of staphylococcal antitoxin rises progressively between the ages of 2 years and early adult life (Bryce and Burnet, 1932), a rise that may be ascribed to the cumulative effect of infection (clinical and subclinical) with *Staphylococcus aureus* (Cunliffe, 1949). The relatively small variations in titre among groups of adults suggest that routine metabolic loss is continuously replaced. Whether the maintenance of antitoxic titre is dependent on repeated natural antigenic stimuli is a matter for conjecture; but, since the chance of recent contact with staphylococci would be at least as great among the sarcoid and reticulosis patients as among controls, this variable should not affect the validity of our findings. The absence of any difference between the staphylococcal antitoxin titres of these patients and of controls, therefore, suggests that there is no impairment of the ability of cells, already in a state of secondary responsiveness, to produce antibody to the antigen concerned.

Depression of the delayed types of allergic skin response is a feature common to both sarcoidosis and reticulosis (Jadassohn, 1914; Dubin, 1947; Hoyle *et al.*, 1954; Schier *et al.*, 1956; and others). The results of the present study point to a second similarity between these widely differing diseases—namely, poor response to primary immunization. The association suggests that both phenomena are due to altered function of the reticulo-endothelial system, but the question of whether depression of delayed skin reactions is related to impaired production of antibody remains unanswered.

Summary

Attention is drawn to the conflicting results reported by investigators on the effect of sarcoidosis and other diseases of the reticulo-endothelial system on circulating antibody production. Since previous studies were concerned chiefly with the response to reimmunization, we decided to test the response to this and to primary inoculation, using tetanus toxoid as the antigen in both instances.

Twelve patients with sarcoidosis produced significantly less circulating antitoxin after primary immunization than did 14 controls. The poorest responders were those in whom the sarcoid process was " active."

A normal response to reimmunization was given by 10 patients with sarcoidosis who had been immunized against tetanus some years earlier.

The serum staphylococcal alpha-antitoxin level of 50 patients with sarcoidosis and 19 patients with reticulosis was of the same order as that of 75 control patients.

The study of a small number of patients with reticulosis suggested that a poor response to primary immunization also occurs in this condition.

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Nearly one million Arab refugees from Palestine are now living in the Gaza Strip, Jordan, Lebanon, and Syria. Now, nearly ten years after their exodus from their homes, they remain mainly dependent upon the United Nations Relief and Works Agency for Palestine Refugees (U.N.R.W.A.) for their basic needs. Besides providing them with food, shelter, welfare services, and education, U.N.R.W.A. operate a large and comprehensive health service, the technical direction of which remains the responsibility of the World Health Organization. The unsatisfactory living conditions of the refugees in an area like the Middle East which is especially open to epidemics have prompted U.N.R.W.A. to give special emphasis to preventive measures in its overall health programme. Under the supervision of a sanitary engineer seconded by W.H.O., strict sanitation measures are applied in all camps. These include the provision of a clean water supply, an efficient garbage disposal system, and proper sewage arrangements. Flies and other insects which help in spreading disease are combated through regular spraying with insecticides. Health education workers are now employed in camps teaching refugees the elements of hygiene and how to combat the spread of disease through proper health habits. Malaria is now on the way to being eradicated. Last year 254,000 refugees were inoculated against typhoid, 497,000 against smallpox, 51,000 against diphtheria, and 32,000 against whooping-cough.

METABOLISM OF ^{131}I-LABELLED ALBUMIN IN AFRICAN SUBJECTS

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Reports from Africa (Arens and Brock, 1954; Holmes *et al.*, 1955), Jamaica (Garrow, 1954), and the United States of America (Milam, 1946; Rawnsley *et al.*, 1956) have consistently shown that Negroids have lower serum albumin levels than Caucasoids living in the same regions. In this investigation an attempt has been made to establish whether the two racial groups also differ in regard to albumin distribution and turnover. ^{131}I-labelled albumin was injected into five healthy African male subjects, and rates of albumin katabolism were calculated from plasma specific activity curves as well as from urinary ^{131}I-excretion data. Results are compared with those obtained by McFarlane and co-workers (personal communication), who have studied the turnover of the same labelled albumin in a group of young English adult males.

Validity of the ^{131}I-albumin Label

The validity of metabolic data obtained through the use of ^{131}I-labelled plasma proteins has been seriously questioned in recent years (Goldsworthy and Volwiler, 1957). Published reports indicate that the metabolic fate of ^{131}I-labelled molecules is greatly influenced by such factors as the method of preliminary protein fractionation (McFarlane, 1956), pasteurization of the protein solution (Merchant *et al.*, 1957), the degree and evenness of iodination (McFarlane, 1956), and the occurrence of radiation damage to the protein prior to injection (Yalow and Berson, 1957). The studies of McFarlane and his co-workers have shown, however, that the *in vivo* behaviour of their ^{131}I-labelled albumin and globulin in both the rabbit (Cohen *et al.*, 1956) and the rat (Campbell *et al.*, 1956) is almost identical with that of the corresponding proteins labelled with ^{14}C by the biosynthetic procedure. Moreover, the fate of ^{14}C and ^{131}I-labelled antibody globulins is identical in either the presence or absence of an immune response (McFarlane, 1957).

Since it is generally accepted that protein molecules are not significantly altered by substitution of ^{14}C for natural carbon, these experiments show that under certain conditions of fractionation and iodination ^{131}I can serve as a reliable protein label in biological investigations. In addition to its simplicity, the method has the advantage that the ^{131}I released during protein breakdown is quantitatively excreted, and this provides a valuable independent measure of the rate of katabolism.

Methods

Preparation of Albumin for Iodination.—Albumin was prepared from the serum of healthy European subjects by two different methods. The first preparation was made according to the ether fractionation procedure of Kekwick and Mackay (1954) and was incubated at 60° C. for 12 hours prior to iodination. Albumin was also prepared by zone electrophoresis on a column of acetylated cellulose (Porath, 1954).

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