BRITISH MEDICAL JOURNAL
LONDON
SATURDAY DECEMBER 3 1960

## AETIOLOGY OF SARCOIDOSIS

The suggested causes of sarcoidosis are exceedingly diverse. They include infection by an at present unidentified agent, or with *Mycobacterium tuberculosis*, leprosy, syphilis, fungi, protozoa, and helminths, or tissue reaction to beryllium, silica, and pine pollen, or an inflammatory response of the type occurring in the collagen diseases. No definite proof has been provided for any of these hypotheses and the aetiology of sarcoidosis remains baffling. Particularly timely and important therefore is evidence of the causal role of *M. tuberculosis* in sarcoidosis, which Dr. J. G. Scadding has described in his Mitchell Lecture, published in the opening pages of the *Journal* this week.

Discussion of the aetiology of sarcoidosis has been confused by difficulties imposed by the definition of the disease. Dr. Scadding adopts the helpful concept that sarcoidosis is a syndrome whose principal defining feature is essentially histological and has suggested the following definition: "Sarcoidosis is a disease characterized by the presence in all the affected organs of epithelioid cell tubercles without caseation, the older lesions tending to become converted into hyalinized fibrous tissue." This makes no mention of aetiology and so allows the addition of a term indicative of aetiology to the word "sarcoidosis" if in a case which conforms to the descriptive definition of sarcoidosis there is sufficient evidence of this aetiology—for instance, "tuberculous sarcoidosis" or "beryllium sarcoidosis."

Among Dr. Scadding's series of 230 cases of sarcoidosis tubercle bacilli were isolated from 29, or 13%. In 18 cases (8%) tubercle bacilli were found without the clinical course, tuberculin sensitivity, response to treatment, or prognosis deviating in any way from that observed in the rest of the series in which tubercle bacilli had not been found, and without the appearance of any other evidence of caseating tuberculosis. The tubercle bacilli were found at all stages of the disease and at various periods from the apparent onset. In all of five cases in which the tubercle bacilli were appropriately examined they were found to be of human strain and of normal virulence for guinea-pigs. In another five cases tubercle bacilli were first found at a time of change from the clinical picture of sarcoidosis to one of caseating tuberculosis. All these cases were tuberculin-negative in the "sarcoid phase" and became tuberculin-positive when tubercle bacilli were found, and in three cases some of the clinical features of sarcoidosis resolved at this time. In another six cases tubercle bacilli were isolated at varying periods before the appearance of manifestations of sarcoidosis at a stage when the clinical picture was that of overt caseating tuberculosis.

Dr. Scadding contends that the entire illness was attributable to the tubercle bacilli both in the patients in whom tubercle bacilli were found in the "sarcoid phase" and in those in whom there was evidence of caseating tuberculosis before or after the "sarcoid phase." He suggests that the reason for the development of sarcoidosis rather than caseating tuberculosis rests on a peculiarity of the tissue reactivity of the patient. In those patients in whom a change from a caseating to a sarcoid phase or vice versa was observed, this peculiar tissue reactivity must be supposed to have developed or disappeared during the observed course of the disease.

There is good evidence for the peculiar tissue reactivity invoked by Dr. Scadding. Study of immunological reactions in sarcoidosis has revealed an abnormality characterized by poverty of reactions of the delayed hypersensitivity (tuberculin) type, while responses of the immediate hypersensitivity type remain normal or are increased.[1-3] Using the tuberculin tests as an indication of the changed immunological reactivity, Dr. Scadding and his colleagues have produced evidence suggesting that the immunological abnormality is not produced by sarcoidosis but is likely to have preceded the occurrence of sarcoidosis.[4] This immunological abnormality may have been the reason why sarcoidosis rather than caseating tuberculosis was associated with tuberculous infection. Thus the cause of sarcoidosis may have to be sought as much in the altered reactivity of the host as in external causative agents.

Attempts to grow *M. tuberculosis* from sarcoidosis tissue have generally been a notable failure.[5]

[1] Sones, M., and Israel, H. L., *Ann. intern. Med.*, 1954, **40**, 260.
[2] Citron, K. M., *Tubercle (Lond.)*, 1957, **38**, 33.
[3] Sands, J. H., Palmer, P. P., Mayock, R. L., and Creger, W. P., *Amer. J. Med.*, 1955, **19**, 401.
[4] Citron, K. M., and Scadding, J. G., *Quart. J. Med.*, 1957, **26**, 277.
[5] Longcope, W. T., and Freiman, D. G., *Medicine (Baltimore)*, 1952, **31**, 1.
[6] Nethercott, S. E. and Strawbridge, W. G., *Lancet*, 1956, **2**, 1132.
[7] Warfvinge, L. E., *Acta med. scand.*, 1943, **114**, 259.
[8] Rostenberg, A., Jr., Szymanski, F. J., Brebis, G. J., Haeberlin, J. B., Jr., and Senear, F. E., *Arch. Derm. Syph.*, 1953, **67**, 306.
[9] Michael, M., Jr., Cole, R. M., Beeson, P. B., and Olson, B. J., *Amer. Rev. Tuberc.*, 1950, **62**, 403.
[10] Gentry, J. T., Nitowsky, H. M., and Michael, M., Jr., *J. clin. Invest.*, 1955, **34**, 1839.
[11] Cummings, M. M., Dunner, E., Schmidt, R. H., Jr., and Barnwell, J. B., *Postgrad. Med.*, 1956, **19**, 437.
[12] —— and Hudgins, P. C., *Amer. J. med. Sci.*, 1958, **236**, 311.
[13] Hardy, H. L., *Amer. Rev. Tuberc.*, 1956, **74**, 885.

However, S. E. Nethercott and W. G. Strawbridge[6] claim to have found in sarcoidosis lesions diaminopimelic acid and mycolic acid, which occur in myocobacteria but not in other micro-organisms or in normal human tissue. Moreover, tubercle bacilli alive or dead, B.C.G., and lipopolysaccharide of mycobacteria may produce sarcoidosis lesions when injected into patients with sarcoidosis.[7 8]

A new approach to the problem of aetiology has been made in the U.S.A., where extensive epidemiological studies have revealed an apparent correlation between the birth-places of sarcoidosis patients and the distribution of forests.[9-11] This led M. M. Cummings and P. C. Hudgins[12] to investigate various forest products. They found that pine pollen (of two species) takes up acid-fast Ziehl–Neelsen stain like tubercle bacilli. The pollen contains diaminopimelic acid, which as already mentioned occurs in mycobacteria and also in sarcoidosis tissue. Pine pollen and phospholipid derived from it when injected into guinea-pigs produced localized sarcoid-like lesions. This is proof that substances other than mycobacteria can stimulate sarcoid-like lesions. Similar naturally occurring substances may await discovery. Epidemiological and tissue assay studies have confirmed that a disease closely resembling sarcoidosis clinically and identical with it histologically occurs in some people after the inhalation of certain compounds of beryllium.[13]

Many investigators deny that sarcoidosis is a syndrome with many causes and hold that it is a single disease due to a single unknown cause. In support of this view they point out that sarcoidosis as described round the world presents a pattern which is remarkably uniform clinically, radiologically, and histologically. However, the same might be said of erythema nodosum, a condition known to have several causes. It is probable that the causes of sarcoidosis are multiple, and vary from one part of the world to another. In Great Britain *M. tuberculosis* is likely to be one of the most frequent causes.

## CONTROL OF URINARY INFECTION IN UROLOGY AND GYNAECOLOGY

The introduction of infection by catheterization is a well-known risk and constantly warned against in the textbooks. Nevertheless, the procedure is so commonly employed, and so often delegated to the inexperienced, that the appropriate precautions are occasionally apt to be overlooked. Laboratory studies in fact show a high incidence of bacteriuria after instrumentation, and, whereas clinical evidence of infection may be less evident, there can be no doubt that in some instances permanent harm has resulted. Complications are particularly likely when renal function is already impaired or when catheterization is associated with local surgical procedures, especially if it has to be repeated at intervals or the instrument is left indwelling. There seem to be two schools of thought on these problems. On the one hand the "idealists" seek to eliminate infection altogether by scrupulous attention to all aspects of catheterization and drainage, using special apparatus and a highly trained and intelligent team of assistants and nursing staff. On the other hand are those who appear resigned to the possibility of infection following in some cases, regarding the consequences as insignificant provided free drainage is maintained. This somewhat complacent attitude may be to some extent fostered by a reliance on antibiotic therapy if infection does occur. The rational attitude no doubt lies somewhere between these two extremes, but there is little question that some improvement in the general standard of pre- and post-operative catheterization in urological and gynaecological surgery is badly needed.

Recent studies of this subject have been made by W. A. Gillespie and colleagues[1] at Bristol, and as a result a number of modifications have been suggested in the management of catheter drainage which, when adopted in combination, have been shown to reduce post-operative urinary infection. In brief, an infection rate of 83% after prostatectomy and 73% after simple emergency bladder drainage for acute retention of urine before the introduction of such measures was reduced subsequently to 6% and 10% respectively. Bacteriological investigations showed that infection of the urinary tract after instrumentation might come from a number of sources, predominantly from other patients or from the patient's own body. The main route of infection was undoubtedly urethral, organisms either being carried up by the passage of the instrument or being conveyed by air bubbles from an open drainage bottle. As a result, a series of technical modifications were individually adopted in different order in two hospitals and the effect on the reduction of the infection rate duly noted. First, these included an attempt to sterilize the urethra by the instillation of chlorhexidine, and later a combination of chlorhexidine and mercury oxycyanide, before the passage of instruments. Secondly, attention was directed to the disinfection of catheters and cystoscopes (a procedure often inadequately and casually attended to). Drainage of catheters into an open-mouthed bottle

[1] Gillespie, W. A., Linton, K. B., Miller, A., and Slade, N., *J. clin. Path.*, 1960, 13, 187.
[2] Clarke, S. H. C., *Brit. med J.*, 1960, 2, 1491.