OCULAR LESIONS OF BOECK'S SARCOID*

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About seven decades have elapsed since Jonathan Hutchinson, in 1869, first recognized a disorder of the skin now known as Boeck's sarcoid. During this time its various manifestations have been described as a disease of the skin, a disease of the bone, and a disorder of the lymph nodes. More commonly it has been regarded as a skin disease, and most of the articles concerning it have been written by dermatologists, mainly Scandinavians. According to Hunter,[1] it was Caesar Boeck,[2] of Christiania, who first reported the disease, although Hutchinson,[3] twenty-four years earlier, had regarded it as an entity, but did not give it a name or report it until 1875.

Although various names have been applied to this disease, Besnier-Boeck's disease and Hutchinson-Boeck's disease (generalized sarcoidosis) are perhaps those most to be preferred. The term Boeck's sarcoid is sufficiently accurate, however, and for the sake of simplicity this term will be employed throughout this paper. Due to the varied manifestations of the disease, its multiple terminology, and the high degree of medical specialization, much of the literature on the subject has been repetitious. Many writers have paid little or no attention to previous reports, or have limited their search of the literature to their special field of medicine.

In 1936 Hunter[1] published an account of the history of the disease, and concluded with the following definition: "Hutchinson-Boeck's disease (generalized 'sarcoidosis') is a generalized systemic disease and may involve, in addition to

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the skin, the lymph glands, spleen, lungs, bones, mucous membranes, conjunctiva, and parotid gland."

SYMPTOMATOLOGY

A study of the literature shows that Boeck's sarcoid begins in late adolescence or early adult life. The incidence is highest above the age of thirty. Males and females are about equally affected. The progress is, as a rule, symptomless, and the disease may cause no changes that are clinically evident.[4, 5] The lesions are most frequently found in the lymph nodes, in the skin, in the bones of the hands and feet, and in the lungs.

Its most characteristic feature is the involvement of the lymph nodes, a fact that is only recently being recognized. Schaumann[4] declares that he has never seen a patient in whom the skin was affected without accompanying lymph-node involvement, and that in every case of active sarcoid in which the lymph nodes or tonsils have been subjected to biopsy, they have been found to be involved, even though the nodes were not palpable. In most cases the mediastinal nodes are enlarged. The enlargements of the other lymph nodes may be generalized, or more pronounced in certain regions, but show no regional relationship to lesions of the skin.[6]

Kissmeyer,[7] who has written a monograph on data gathered from 250 cases in the literature and from 28 cases of his own, emphasizes the frequency with which bronchial lymph nodes, lungs, and bones are involved. Lesions in the lungs are apt to give slight or no symptoms and there may be no physical signs, even though the process is extensive. There may be a slight rise in temperature, some loss of weight, and occasionally a non-productive cough.

In most cases *x*-rays of the chest show greatly enlarged hilar glands, and bilateral, fairly dense, diffuse linear infiltration, chiefly in the middle or lower half of the lungs, extending out toward the periphery from the hilum. In addition to

these changes, there may be discrete opaque areas varying in size from miliary nodules to some 1 cm. in size. An especially noteworthy fact is that the apices are rarely involved. In some cases *x*-rays of the chest may show only enlargement of the hilar glands, and Hunter[1] believes that sarcoid may be the true diagnosis when apparently healthy patients, with no lesions of the skin, give evidence of increased hilar shadows, sometimes with a slight diffuse infiltration of the lungs, which is sometimes mistaken for tuberculosis, but should be distinguished from it by the lack of apical involvement. Furthermore, in sarcoid there are frequently no physical signs or symptoms such as occur in extensive tuberculous disease of the lung. In pneumoconiosis, a diagnosis that may be considered, the nodules are more definite and numerous, and there is no linear background.

If *x*-ray examinations are repeated in a month or two, the process may be found to have cleared up completely, but, on the other hand, it may continue for months or years. Necropsies have proved that the lungs may be riddled with microscopic sarcoid lesions that gave no macroscopic evidence of their existence.

The lesions revealed by *x*-rays of the bones are quite characteristic. They are most commonly seen in the phalanges of the hands, but are also frequently found in the phalanges of the feet. Occasionally they involve the metacarpal bones, and in a few instances changes have been found in the lower ends of the radius and ulna, about the elbow-joint, and in the lower lumbar spine. Sarcoid tissue has been found, on microscopic examination, in these sites,[4, 5] and also in the femoral marrow.[5]

Fairly often the fingers are deformed by subcutaneous nodules that are arranged symmetrically around the interphalangeal joints. The *x*-rays may disclose two types of lesions: in the first type the trabeculae become coarse, and areas of distention appear that are central or cortical or both; in the second type there is a punched-out area. There is no

atrophy of the remainder of the bone, nor any sequestrum or periostitis. Schaumann[4] states that the disease, which is primary in the marrow, may fill the marrow without the *x*-ray revealing its presence. Since the periosteum and joints are spared, patients may have striking deformities and still be able to use their hands with slight or no discomfort.

Lesions have also been reported in the mucous membrane of the nose, larynx, nasopharynx, stomach, and intestine. When they have been situated in the ileum, they have been diagnosed clinically as "regional ileitis." However, except for regional ileitis, gastro-intestinal involvement in Boeck's sarcoid is probably exceedingly rare. Nickerson[5] has reported finding lesions in the liver in five of his six necropsies. Lesions have also been found in the pituitary, pancreas, kidney, prostate, and epididymis. Reis and Rothfeld[8] have found involvement of the optic nerve and brain in a patient who had sarcoid of the bone and skin.

In the literature, iritis is frequently referred to as a manifestation of Boeck's sarcoid—it is said to occur in about 10 per cent. of such cases.[9] In appearance this type of iritis resembles tuberculous iritis, but often runs a milder course and has a better prognosis. Small nodules may be seen on the iris, and the media of the eye may become cloudy. There are frequently precipitates on the cornea, and synechias, secondary glaucoma and cataract formation may occur. These ocular lesions may appear as the first symptoms of Boeck's sarcoid, and, according to Blegvad,[10] this form of iritis shows a tendency to heal without any great impairment of vision. This observer believes that, in spite of the fact that Boeck's nodular iritis strongly resembles tuberculous iritis, the former presents so characteristic an ocular picture that it can easily be differentiated from the latter. Osterberg[11] published a treatise on iritis in Boeck's sarcoid, and he and Blegvad now apply the term "Boeck's iritis" to this disease. In reviewing the literature, Osterberg found, among about 400 cases of Boeck's sarcoid, 26 cases of iritis; however, he calls attention

to the fact that, from the history of the disease in question, it is not always possible to conclude with certainty whether a report is dealing with Boeck's iritis or with an iritis having some other origin. Osterberg believes further that Boeck's iritis is a rare disease, and that it is impossible to differentiate it from tuberculous iritis by its ocular morphology. Apparently iridocyclitis occurs less frequently than does iritis, but this may be only a matter of the terminology employed.

Conjunctival lesions occur apparently much less often than do lesions of the iris. Blegvad,[9] in 1931, reported three cases of his own and could find only five others in the literature. He described the conjunctival lesions as small to large, chalazion-like tubercles, varying in number from one to many, and studding the conjunctiva. These tubercles appear as clear yellowish, speck-like follicles. There is no scarring, as in trachoma, but one of Blegvad's cases showed a symblepharon. The conjunctival disease displays no tendency to affect the cornea. The only symptoms are the presence of slight lacrimation and mucous secretion. The histologic picture of conjunctival sarcoid is similar to that of sarcoid elsewhere. Strandberg[12] reported a case of conjunctival lesions in sarcoid. In 1917 Derby and Verhoeff,[13] in our hospital, reported a case of sarcoid of the eyelid, but in this case the conjunctiva was not involved. There have been no cases of conjunctival sarcoid reported from the Pathological Laboratory of the Massachusetts Eye and Ear Infirmary nor from the Howe Laboratory.

PATHOLOGY

In all the lesions the histologic picture is essentially the same. The typical "hard miliary tubercles" appear to be the same whether they occur in the skin, the lymph nodes, or the internal organs. These lesions are well defined, single or confluent, inflammatory foci consisting essentially of large, pale-staining epithelioid cells and occasional giant cells. At

the periphery of the lesions there are a few lymphocytes. A characteristic feature of these lesions is the relatively slight or complete absence of inflammatory reaction in the surrounding tissue. There is usually a lack of caseation, but in some instances there are a few necrotic cells in the center of the "tubercle." Nickerson[5] asserts that the giant cells, although much less numerous than in tuberculosis, are, as a rule, much larger and contain more nuclei—often as many as 25 or 30. The nuclei are said to be evenly distributed throughout the cell, and are rarely arranged in the elliptic manner typical of tuberculous giant cells. In the liver the lesions are most numerous in the portal triads, only a few occurring in the mid-zones of the lobules. This is the opposite of the picture seen in tuberculosis. Healing of the lesions may occur through fibrosis. In agreement with clinical evidence, Schaumann,[4] who reported necropsies in four cases, emphasizes the fact that the disease is always more or less generalized, and that it has a predilection for lymphoid tissue. Goeckerman[14] states that in early lesions the histologic picture is nonspecific and cannot be differentiated from erythema nodosum.

Blood studies on patients with Boeck's sarcoid have failed to reveal any characteristic significant changes. Longcope and Pierson[6] were unable to substantiate the findings of Salvesen,[15] who reported increased serum proteins due to a rise in the globulin fraction. Hunter,* who alone determined the sedimentation rate in several cases of sarcoid, has found it to be high. Many have reported the presence of an eosinophilia and a monocytosis, but these findings are inconstant. Leukocytosis does not occur, but a relative monocytosis may be present. Leukopenia has been found in some cases.

ETIOLOGY

The etiology of Boeck's sarcoid is still obscure. Although many investigators regard it as a peculiarly benign form of tuberculosis, this contention has never been proved satisfac-

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torily. Kyrle[16] believed sarcoid to be a distinct type of foreign-body reaction to tubercle bacilli and their disintegration products. In experimental tuberculous lesions of the skin this investigator found that bacilli that were abundant during the first ten days after injection into the skin had practically disappeared after five weeks, and at this time the typical histologic picture of sarcoid was present. It has been stated repeatedly in the literature that acid-fast bacilli are not usually found in the lesions. Schaumann,[4] after observing many cases of sarcoid, concluded that sarcoid is probably caused by a variant of the tubercle bacillus, possibly one of a non-acid-fast nature. It has even been contended that in some instances sarcoid was caused by a "filtrable" form of the tubercle bacillus. The literature contains a few reports of cases in which both sarcoid and tuberculosis have been present, although the relation of the two diseases has never been determined. Cases that have been proved to be tuberculous have not been proved to be actual cases of sarcoid, and in cases proved to be sarcoid, the possibility has not been eliminated that the presence of tuberculosis was not merely coincidental.

In the majority of cases of sarcoid the skin tuberculin reaction is negative. Schaumann[4] states that he has never seen a positive skin reaction in an uncomplicated case of "lymphogranulomatosis benigna"—that is, Boeck's sarcoid. Kissmeyer,[7] however, in 1932, found a nearly 40 per cent. incidence in the reported cases, but he also discovered that the reaction, when positive, was mild. He believed that the incidence of positive tuberculin reactions was the same as that which is to be expected in any group of patients of the same age without clinical tuberculosis. He was unable to produce a focal tuberculin reaction in his own patients, and cited the work of other investigators who were also unable to produce a focal reaction in 15 out of 18 patients. Lomholt,[17] in his 49 cases of sarcoid, found that 72 per cent. gave negative, 8 per cent. questionable, 18 per cent. mildly positive, and

only 2 per cent. strongly positive, tuberculin reactions. Those who believe in the etiologic agency of tuberculosis generally explain their concept on the basis of Jadassohn's theory of anergy, *i. e.*, almost complete desensitization to the tubercle bacillus and its products. Sulzberger[18] contends that although certain tuberculoderms (especially scrofuloderms, lichen scrofulosorum, and rosacea-like tuberculids) are hypergic the allergy in others has progressed almost to a stage of desensitization, and these form a relatively or completely anergic group. He places sarcoid in this group, and contends further that both hyposensitization and hypersensitization are aberrations from the normal and must be regarded as related immunologic phenomena, stating that "both evidence a change from the *normergic* reaction and that both speak, to a certain degree, in favor of a tuberculous etiology" of Boeck's sarcoid. He explains the occasional occurrence of active tuberculosis of the lungs, which some claim to have found along with typical skin sarcoid, by postulating that certain parts of the body may be in varying immunologic states at the same time.

Acid-fast bacilli have rarely been found in suspected sarcoid lesions, and in most of the cases in which acid-fast bacilli have been discovered on section the investigators have not proved that they were tubercle bacilli, since animal inoculations were universally negative. Jordon and Osborne,[19] in 1937, collected 114 cases of sarcoid that had been reported in the American literature of the previous ten years. Acid-fast bacilli were not found in any of the lesions in these cases, and in only 7 of the cases were there typical tuberculous in addition to the sarcoidal lesions.

Longcope and Pierson[6] state: "As one reviews the published data, it must be concluded that there is little proof that the lesions of 'sarcoid' are caused by the tubercle bacillus, or, indeed, as has been suggested by several investigators, by the action of the products of its growth. The view prevails

at the present time, however, that the disease is a peculiar form of benign tuberculosis."

Kissmeyer and Nielsen[20] contend that the lesions of the bone bear a greater resemblance to those of leprosy than to those of tuberculosis or syphilis. Filho[21] believes that the whole syndrome of Boeck's sarcoid can be produced by leprosy, and Murdock and Hutter[22] have described, in leprous patients, cystic changes of the bones that resemble closely those seen in sarcoid.

Certain investigators do not regard Boeck's sarcoid as an entity, but contend that the condition may be caused by a variety of agents, notably tuberculosis, syphilis, and leprosy. Kissmeyer,[7] Nickerson,[5] and Williams and Nickerson[23] suggest that sarcoid may be a virus disease, and the last named observers have furnished some evidence for this contention.

It is extremely unlikely that such strikingly characteristic lesions as occur in the lymph nodes, skin, lungs, spleen, and bones in cases of Boeck's sarcoid can be produced by multiple factors. It seems certain, therefore, that sarcoid is a definite entity, and that it must be due to a single cause. A review of the literature affords no conclusive evidence as to the exact nature of this cause.

DIAGNOSIS

The diagnosis of sarcoid of the skin is usually made with ease, but when the condition occurs without accompanying skin lesions, it is often difficult to detect, even when it has become generalized. The changes in the lung must be differentiated from those produced by tuberculosis and pneumoconiosis. The involvement of the lymph nodes must be differentiated, by biopsy if possible, from that caused by lymphoblastoma and tuberculosis. Lesions of the bones may be differentiated from those of tuberculosis by the absence of joint and periosteal involvement and the absence of sequestra and sinus formation. Sarcoid lesions, in contradistinction to those of syphilis, do not involve the diaphysis.

Carcinoma produces a multiplicity of lesions and destroys the cortex of the bone. Lesions in the eye must be differentiated from those of tuberculosis. The tuberculin test in these cases is usually negative, and in the presence of a strongly positive test the diagnosis of uncomplicated sarcoid should be questioned.

When characteristic changes are revealed by biopsy of the skin, lymph node, or bone, and by *x*-ray; when the Wassermann and tuberculin tests are negative and the constitutional symptoms are relatively slight, a diagnosis of sarcoid becomes as nearly positive as it can be with our present knowledge.

Treatment is unsatisfactory. Some dermatologists and older clinicians regard the use of arsenic as beneficial. Ultraviolet ray therapy is also being employed for the lesions of the skin. Fulguration and *x*-ray treatment have not been accepted as valuable therapeutic agents. Lomholt[17] has recently reported good results following intramuscular injections of "Antileprol," a preparation extracted in part from chaulmoogra oil. The consensus of opinion, however, is that the most satisfactory treatment is that prescribed in tuberculosis, *i. e.*, rest, fresh air, and a high vitamin-high caloric diet.

CASE REPORTS

For many years oculists have been familiar with various forms of ocular tuberculosis, but they have rarely associated Boeck's sarcoid with ocular disease. The tuberculin test has long been accepted as a valuable aid in confirming or disproving a diagnosis of ocular tuberculosis. In a patient whose tuberculin reaction is negative it is rare to find an infection that can be proved to be tuberculous.

In the Howe Laboratory, during the past six and one-half years, we have tuberculin-tested over 1,700 patients with various forms of chronic ocular inflammations. In about two-thirds of these patients positive skin tests have helped to confirm a clinical diagnosis of ocular tuberculosis. A considerable number of the patients tested were found to give a

negative reaction, or were practically insensitive to tuberculin. Of this non-allergic group the following seven cases were finally found to be affected with Boeck's sarcoid:

CASE I.—M. J. C., a white female, aged twenty-three years, was first seen in the Eye Clinic of the Massachusetts Eye and Ear Infirmary on November 18, 1933, at which time she gave a history of having had poor vision in the right eye for at least twenty years. One year before her first visit to the Infirmary the right eye had become very red and was slightly painful for a few days. Shortly after this the vision in the left eye became blurred. The redness had continued, and since then the vision in both eyes had failed progressively. During the past year the patient had been under the care of a physician in Canada, who had given her "eye-drops."

At the time of her admission to our Out-patient Department there was ciliary injection of the right eye, with diffuse old corneal nebulae and masses of old precipitates on the back of the cornea.

The vision of the right eye consisted of good light projection, and that of the left eye was 2/200. The pupil of the right eye could indistinctly be seen to be irregularly dilated, the anterior chamber was deep, and the iris, which was seen with difficulty, was muddy and contained numerous elevated nodules resembling tubercles. There was ciliary injection in the left eye, and in the central and lower portions of the left cornea there were deep infiltrations suggesting fat deposits. Many medium-sized and large precipitates could be seen on the upper posterior corneal surface. The iris details were almost completely obscured. Marked enlargement of the preauricular and posterior auricular lymph nodes was observed. The condition suggested tuberculous kerato-uveitis.

The patient was examined in the Medical Clinic of the Massachusetts General Hospital on November 25, 1933, at which time the axillary and inguinal nodes, as well as the cervical and auricular nodes, were found to be markedly enlarged but not tender. There were no mediastinal signs, and examinations of the heart and lungs were essentially negative. There were sarcoid lesions of the skin of the arms and legs. Laboratory reports were: Urine negative; red blood cells, 5,110,000; hemoglobin, 85 per cent.; white blood cells, 5,500; polymorphonuclear cells, 72; lymphocytes, 24; monocytes, 3; and basophiles, 1 per cent. The Wassermann test was negative. Intradermal tuberculin tests were negative in dilutions of Old Tuberculin ranging from 0.001 mg. up to 0.5 mg.

On November 27, 1933, the *x*-ray report was: "The hilus shad-

ows are increased in width and density—both sides and the larger lung markings are thickened in the medial portion of the chest. The increase in shadows is consistent with any acute respiratory infection. Hilum tuberculosis cannot be ruled out. Impression, probably lymphosarcomatous pathology of Hodgkin's type." The patient was now admitted to the Massachusetts General Hospital for study and biopsy. On December 18, 1933, she was referred to the Howe Laboratory, where the tension of the right eye was found to be 56 mm. Hg (old Schiötz) and that of the left eye, 48 mm. Hg (old Schiötz). The vision still consisted of good light projection in the right eye and counting fingers at one to two feet in the left eye. At this time the corneal opacities were unchanged and there were numerous bullae on the right cornea. The patient was transferred to the Massachusetts Eye and Ear Infirmary for operation, and the next day an iridectomy was performed on each eye. The report of the biopsy from the irides was: "Under low power several small focal lesions are seen in the iris. Under high power these lesions are found to contain many plasma cells and small epithelioid cells. The epithelioid cells are distinguished by having a considerable amount of protoplasm and not having the shape or characteristic nuclei of plasma cells; they are not round. There is no necrosis and no giant cells are present. It is noteworthy that the iris in general shows almost no infiltration with chronic inflammatory cells."

On January 2, 1934, the patient was returned to the Massachusetts General Hospital, where, two weeks later, a biopsy of a cervical node disclosed typical Boeck's sarcoid. Another *x*-ray of the chest was taken in January, and the changes were then interpreted as sarcoid.

On March 3, 1934, the tenson was normal and the eyes were practically white. The vision in each eye was 1/200. The patient had gained 15 pounds in weight. Sarcoid lesions of the skin, which had appeared on December 2, 1933, were still present on the arms and legs, but the lymph nodes had decreased in size.

One month later the eyes were white and the lymph nodes were considerably smaller. Faint sarcoid lesions still persisted on the skin of the arms. At the time of our last examination, on May 5, 1934, the eyes were practically white, and the corneas were much clearer. The vision was 1/200 in the right eye and 12/200 in the left. A moderate number of keratitic precipitates were seen above the corneal nebula in the right eye. It was still impossible to see the fundi. The tension was 10 mm. Hg (old Schiötz) in each eye. In May, 1934, the patient returned to Canada. Four years later she

wrote that she felt well, that her eyes were white and had not been painful, that with her left eye she could see to write and read with some difficulty, and that she was able to assist with the housework. She had not been examined since she returned home.

This case is one of severe kerato-uveitis with secondary glaucoma. The glaucoma was controlled by iridectomy operations, and in spite of the corneal scarring the patient had at least partially useful vision four years after our last examination.

The history of the case and the presence of old corneal scars indicate that the patient had previously had similar trouble with her right eye, and had apparently recovered from other manifestations of sarcoid. The condition was first diagnosed definitely by biopsy of a cervical node, although sarcoid lesions had appeared on the skin of her legs and arms four weeks before the node was excised for biopsy purposes. *X*-ray changes, which at first were believed to be due to tuberculosis or Hodgkin's disease, were later interpreted as those of Boeck's sarcoid.

CASE II.—A white, married, Italian housewife, aged forty-six years, was first seen in the Medical Out-patient Department in April, 1935. She complained that she had recently begun to notice gradual, painless, bilateral swellings behind the angles of the jaws, "pushing the ears out." These cervical node swellings increased in size over a period of two weeks, remained unchanged for two months, and then rapidly disappeared. There were no systemic symptoms except frontal headaches, with malaise, for two or three days at the onset, and a "sore tightness" when the swellings had reached their maximum size. In October, 1935, examination disclosed that the anterior cervical nodes were now only slightly enlarged. No other abnormalities were found at this time, but six months later she complained of a progressive dimness of vision in the right eye, which had been increasing over a period of about one year.

She was first seen in the Eye Clinic of the Massachusetts Eye and Ear Infirmary in May, 1936, one year after the onset of the blurred vision, and at this time her vision consisted of counting fingers at three and one-half feet with the right eye, and 20/30+ in the left

eye, which was normal. The right eye was deeply injected. There were numerous deep infiltrations in the lower half of the cornea, which here was invaded by deep blood vessels. There was marked iritis. The pupil was bound down by posterior synechias, and several ovoid raised nodules could be seen in the iris, with fine blood vessels extending into them. A diagnosis of tuberculous iridocyclitis of the right eye was made. Tuberculin tests were negative in amounts ranging from 0.001 mg. up to 0.5 mg., but they were slightly positive with 1 mg. The patient was given local treatment and, even though she was relatively insensitive to tuberculin, she received a series of tuberculin injections from July 2, 1936, through February, 1937.

On January 7, 1937, there was still a deep infiltration of the right cornea, especially in the lower half. The anterior chamber, the tension, and the optic disc were normal. The pupil was partly dilated. The iris nodules were extremely small and hardly visible. The vision in this eye consisted of counting figures at three feet; and that of the left eye was 20/70, improved by a lens to 20/30. The reduced vision in the right eye was due to the scarring of the cornea.

On August 18, 1937, an *x*-ray of the chest and abdomen showed: "Generalized thickening of lung markings. Aorta tortuous. Appearance consistent with fibrosis and emphysema. Abdomen negative." At this time the right eye was white and free from inflammation, but the deep corneal infiltrations persisted.

In September, 1937, two years after the onset of her disorder, first the right and then the left nodes at the angles of the jaws just below the mandible began to increase in size. The enlargement was associated with headache and malaise for two or three days, but the patient did not report to the Eye Clinic again until November 18, 1937, when the vision of the right eye had improved to 20/100−, and the cornea was clearer than on her last visit. There was still some cloudiness below and above the center of the cornea. The pupil was slightly irregular. There was now a membrane on the anterior lens capsule, and a moderate number of cells were present in the aqueous. At this time there was a marked bilateral enlargement of the submaxillary nodes, as well as of the parotid glands.

On November 29, 1937, the report of the *x*-ray of the chest was: "Tuberculosis of both upper lobes." She was referred to the Medical Out-patient Department, where another *x*-ray was taken on December 4, 1937. At this time the hilar shadows were increased in width on both sides, without definite visible glands. Miliary

areas of consolidation were scattered throughout both lung fields, particularly in the medial two-thirds of the lung. The apices were not involved. The roentgenologist listed the diagnoses in the order of their possibilities as: 1, Sarcoid; 2, tuberculosis, and 3, carcinomatosis. The latter two he considered improbable.

On December 11, 1937, the patient returned to the Medical Outpatient Department and was found to be free from symptoms and to have a normal temperature. She returned home, where morning and evening temperatures were taken daily for one week by a nurse, and no rise recorded.

On January 6, 1938, she was admitted to the Massachusetts General Hospital for further study. During the past two years, throughout her mild illness, no cardiorespiratory symptoms had manifested themselves, except once, in April, 1936, when there was severe, knife-like pain in the left lower chest, with a hacking, nonproductive cough, the patient remaining in bed for twelve days. Since then she had noticed a painless "rattle" in the left chest, with a non-productive cough accompanying rare and brief upper respiratory infections. There has been no change in weight.

Physical examination on January 6, 1938, showed that the patient was a well-developed and well-nourished female. Her right eye was white; the pupil was bound down by posterior synechias, and the corneal infiltration persisted. The cervical, submaxillary, and posterior auricular nodes were enlarged bilaterally, firm, discrete, movable, and non-tender. The parotid swellings had subsided. The blood-pressure was 132/80. On auscultation and palpation the heart was found to be normal. The chest was barrel shaped, and there were râles at the right base posteriorly, close to the spine. In the axillae there were discrete, firm, non-tender nodes, about 2 mm. in diameter.

Laboratory examination: The urine was normal. The blood count was as follows: Red blood cells, 4,100,000; hemoglobin, 70 per cent. (Tallqvist); white blood cells, 8,300; polymorphonuclears, 64; lymphocytes, 36; eosinophiles, 1; basophiles, 0; platelets, normal. Blood phosphorus, 4.00 mg.; phosphotase, 2.96 Bodansky units. The Wassermann test was negative. Intradermal tuberculin tests were repeated and were found to be negative with 1 mg. of Old Tuberculin.

The *x*-ray report on January 7, 1938, was as follows: "Chest shows diffuse changes in both lungs as before (November 29, 1937). They radiate from the hili, but are also present in the periphery and are definitely consistent with sarcoid. Enlarged glands in right

trachea and bronchus. Questionable enlargement of glands in hili."

On January 11, 1938, biopsy of an axillary lymph node showed an enlarged, smooth, pink-red node, 2 x 1.6 x 1 cm., with a smooth, homogeneous, lavender cut surface. Examined microscopically, it showed collections of epithelioid cells without necrosis, and with occasional giant cells, a condition typical of Boeck's sarcoid. An *x*-ray of the toes taken on January 12, 1938, was negative, but an *x*-ray of the fingers showed foci of rarefaction in the phalanges, such as are sometimes found in sarcoid.

On January 17, 1938, three small, reddish, slightly elevated lesions of the skin, about 3 mm. in diameter, were observed on the forehead above the left eye. They were diagnosed by the dermatologists as sarcoid.

The patient was discharged on January 17, 1938, with a diagnosis of sarcoid. The following treatment was recommended: Rest, a high vitamin and high caloric diet, haliver oil capsules (2 capsules thrice daily), and 4-grain ferrous sulphate tablets three times a day. Since leaving the hospital she has been examined, at two-month intervals, in the Tumor Clinic. On February 10, 1938, the right eye was seen to be the seat of deep corneal infiltrations with fine, deep blood vessels invading the lower cornea. No cells were found in the aqueous, and no nodules were observed. There was an organized pupillary membrane. The left eye, except for the sarcoid lesions of the skin of the lid, was normal. On July 11, 1938, the right cornea was clearer. The *x*-ray of the chest disclosed no new changes. The lymph nodes were hard and smaller. On November 14, 1938, there was no apparent change in the condition of the nodes, eye, or chest.

Case II illustrates many of the most important manifestations of Boeck's sarcoid. The cervical, submaxillary, and axillary lymph nodes and the parotid glands were involved, and typical sarcoid lesions appeared in the skin of the forehead and eyelids. There was a severe form of uveitis with keratitis, and at one time a condition arose that simulated uveoparotitis. Typical sarcoid changes were found by *x*-rays in the lungs and in the phalanges of the hands. The eye condition was considered to be tuberculous, and the pulmonary changes were also regarded as due to tuberculosis or to

Hodgkin's disease, when, after a period of two years, a biopsy of a lymph node showed the presence of Boeck's sarcoid.

CASE III.—J. S., a white female, aged thirty-nine years, a private patient, referred to me on July 12, 1935, for tuberculin tests. Her chief complaint was that vision had begun to blur in the right eye about four months previously, whereas the vision in the left eye had been failing for from four to six weeks. The patient was a school teacher, and stated that for about six months she had been very tired, had lost 24 pounds in weight, and felt "all dragged out" by the end of a school day. A general physical examination had been negative. When I first saw her, her vision was 8/200 in the left eye, and 20/40− in the right. There was marked ciliary and corneal injection in both eyes. The tension of the right eye was 22 mm. Hg (old Schiötz), and that of the left eye was 20 mm. Hg (old Schiötz).

The left cornea was covered with medium-sized and large posterior corneal precipitates of the "mutton-fat" variety, and deep and superficial blood vessels were seen coursing into the cornea from the limbus. The iris and pupil were made out with difficulty through the edematous, nearly opaque cornea, but the pupil was moderately although irregularly dilated.

The right eye, which was said to be "very sore," was not so greatly involved. The back of the cornea was studded with fine and medium-sized precipitates. Many cells were present in the aqueous, and four definite nodules could be seen in the iris, which was muddy and showed dilated blood vessels. It was difficult to perceive any details in the fundus, but no localized patch of posterior uveal involvement could be made out.

Repeated Wassermann tests were negative, and the intracutaneous tuberculin tests were also negative in amounts ranging from 0.001 mg. up to 0.1 mg., but the reaction was slightly positive with 1 mg.

The *x*-ray report of May 2, 1935, was as follows: "There is a marked enlargement of the glands at the lung roots, this condition being more marked on the right side than on the left. There is peribronchial thickening in the lower parts of both lungs, which may be due to pulmonary congestion. The apices are clear, and there is nothing to suggest the presence of a tuberculous process in the chest. With the enlarged glands here the possibility of Hodgkin's disease is to be thought of." As is often the case, the roentgenologist did not recognize the *x*-ray changes that are produced by Boeck's sarcoid.

A second physical examination and further studies of the blood were made, and no evidence of a tuberculous infection or of Hodgkin's disease could be found.

Because the eye picture was so typical of tuberculous iridocyclitis with involvement of the cornea of the left eye, and since the patient's condition was so desperate and was gradually growing worse, a series of tuberculin treatments were begun on August 6, in spite of the fact that she was practically tuberculin-negative. These injections were given twice a week, and at the end of four weeks, to our amazement, both eyes were practically white, and there was a marked decrease in the number of posterior corneal precipitates, clearing of the left cornea, and improvement of vision from 20/200 to 20/40 in the left eye, and from 20/100 to 20/20 in the right eye.

The patient had gained weight and felt very much better, and one month after the first tuberculin treatment she was permitted to resume her work. The tuberculin treatments were continued until April 24, 1937. Eight weeks after the first tuberculin injection vision in each eye was normal, and seven months after these treatments were begun all corneal precipitates and iris nodules had disappeared. There has never been a recurrence of the ocular symptoms, and at no time since her recovery has the slit-lamp revealed any activity.

In this case, as in Cases I and II, the diagnosis of sarcoid was not made at the time of her first *x*-ray examination, although the condition should have been suspected. On July 31, 1937, two years after the first roentgenograms had been taken, and two years after the onset of the uveal inflammation, the *x*-ray report by another roentgenologist was: "Miliary areas scattered equally throughout both lungs. Diagnosis of sarcoid." The first *x*-ray films were then studied again and this time were interpreted as sarcoid.

The patient has since had physical examinations at intervals over a period of three years. At no time has she shown any evidence of a tuberculous infection, and her eyes have remained uninvolved.

In this case of Boeck's sarcoid the essential feature was the severe form of bilateral iridocyclitis, which cleared very rapidly without recurrence. Although the first roentgenograms presented a picture typical of sarcoid, the condition was not diagnosed as such, probably because of the relative rarity of the condition. No enlargements of the lymph nodes or lesions of the skin were found in this patient. It is interesting

to note that the ocular inflammation subsided rapidly after tuberculin therapy was instituted, in spite of the fact that the patient was practically anergic. However, this may have been only a coincidence.

CASE IV.—M. C., a white female, aged forty-two years, was referred to me in October, 1938, with a diagnosis of sarcoid of the lungs, which had been made in March, 1938, after she had been admitted to the Massachusetts General Hospital complaining of weakness and a sensation of tightness and distress in the chest. These symptoms had been present for about one and one-half years, and during this time she had also been treated with "eye-drops" for mild, chronic iritis of unknown etiology in both eyes. Unlike the three cases previously described, the eye symptoms in this case had been of secondary importance—the eyes had been only moderately red and almost painless, but the vision had been somewhat blurred. On examination, both eyes were found to be white, the pupils were dilated from the use of a mydriatic, there were fine precipitates on the backs of the corneas, and a moderate number of cells were present in the aqueous. The fundi were normal except for a mild degree of arteriosclerosis of the retinal vessels. The tension was normal in both eyes, and the vision was 20/20 in each eye.

On March 2, 1938, the *x*-ray report was as follows: "Hilus shadows on both sides are wider than normal, with slight lobulation of the hilus shadows on the left side. There are disseminated areas of increased density, measuring 2 to 3 mm., scattered over both lung fields, one area being fairly discrete. Also slight increase in the linear lung markings. Findings are those of miliary processes scattered through both lung fields in addition to hilar glands. Suggest check of eye grounds and tuberculin test. Knowing that the patient is well clinically, I would place sarcoid as first choice."

The patient had been re-examined on May 16, 1938, at which time roentgenograms showed the presence of the same changes in the lungs that were found two months previously, but there had been improvement in her physical and ocular condition. Several sarcoid lesions were now present on the skin of the arms.

By October 24, 1938, the patient had gained 14 pounds in weight and was practically asymptomatic. The *x*-ray report revealed that the hilar glands had decreased definitely in size, and that the miliary processes had also decreased considerably. The patient

had received no treatment other than rest, sunshine, and cod liver oil.

On October 31, 1938, when I first examined her, intradermal tuberculin tests were negative in amounts of Old Tuberculin ranging from 0.001 mg. up to 0.5 mg., but were slightly positive with 1 mg.

The patient's last visit was in February, 1939, at which time the vision was still normal in both eyes and the low-grade serous iritis of about two years' duration was continuing to improve.

Case IV is of particular interest because, unlike the other three cases reported here, the ocular symptoms were mild. It also emphasizes the fact that in a patient with low-grade serous iritis of unknown etiology the possibility of Boeck's sarcoid should be considered.

CASE V.—This was a case of Dr. T. L. Terry's, who kindly gave me permission to include it in this report. The patient is a white male, aged thirty-five years, who was seen by Dr. Terry on June 25, 1937, at which time there was slight blurring of vision in the right eye. There was mild circumcorneal injection in this eye, and about 12 small posterior corneal precipitates were observed in the lower portion. No cells could be seen in the aqueous.

A tuberculin test was negative with 0.01 mg. The Wassermann test was also negative. On July 7, posterior corneal precipitates were found for the first time in the left eye, but there was only slight ciliary injection. Within a few days the precipitates in both eyes became larger and somewhat lardaceous, and the clinical picture resembled that of tuberculous uveitis.

On July 12 the patient was believed to have pulmonary lesions, which at first were regarded as tuberculosis, but roentgenograms of the chest were interpreted as sarcoid. Repeated tests of sputum for tubercle bacilli were negative. Exhaustive general physical examinations revealed no other findings of diagnostic significance.

A low-grade inflammatory condition persisted in both eyes for several months, but by February, 1938, the posterior corneal precipitates were much smaller and more translucent. The vision in both eyes was normal and the general condition of the patient was good.

This case and Case IV are similar in that they present a low-grade inflammatory involvement of the anterior uveal

tract, as contrasted with the first three cases, all of which had severe involvement of the uvea with masses of posterior corneal precipitates and readily discernible iris nodules.

CASE VI.—A white female, aged twenty-five years, was first seen in March, 1932. At that time she complained of blurred vision and redness of three days' duration in the left eye. She stated that she had had a fever, that both of her "mumps glands" had been swollen for about four weeks, and that her family physician had told her that she had mumps. When first examined in the Eye Clinic there was slight conjunctival and ciliary injection in the left eye; there were many cells in the aqueous, and only very small precipitates could be seen on the back of the cornea. The vision was 20/20−2 in each eye. Both parotid glands were about the size of English walnuts. The right eye was normal. Two days later the left eye was practically unchanged, except for the presence of a yellowish nodule, about 2 mm. in diameter, near the sphincter of the iris at 6 o'clock. On this day a medical consultant confirmed the diagnosis of uveoparotid fever, and found no other evidence of disease in the patient. The Wassermann test was negative, as were also the sinus tests and dental *x*-rays. Because of a fever and illness, the patient did not return to the Eye Clinic for six weeks, at which time the left eye was still slightly injected, the aqueous was loaded with cells, there were many fine precipitates on the back of the cornea, and two nodules were now present in the iris. The right eye had also become involved, with folds on Descemet's membrane, many cells in the aqueous, and fine precipitates on the back of the cornea.

By May 3, two months after the onset of the disorder, the patient had lost 15 pounds, and the right eye was still slightly injected. There were fewer cells in the aqueous, and many fine vitreous opacities were present. The left eye showed numerous dense opacities on the posterior surface of the cornea, wrinkles in Descemet's membrane, and several nodules were present on the iris. There were also many vitreous opacities which blurred the fundus details in the left eye. *X*-ray studies showed the presence of miliary tubercles in the lower lung lobes, and the condition was diagnosed as tuberculous uveitis. The patient refused sanatorium care, but returned for observation at bi-weekly intervals for another two months, at the end of which time her condition was excellent and both eyes were white. No cells could be found in the aqueous of either eye. The corneas were free from precipitates, but fine

vitreous opacities were still present in the left eye, and in the lower nasal fundus there was a patch of active chorioretinitis about the size of the nerve head. The parotid glands had now returned to normal size, but the posterior cervical lymph nodes were enlarged. However, the patient considered herself well, and failed to return to the Eye Clinic again for three years. At this time she was apparently perfectly well—her vision was 20/20 in each eye. There were a few fine fibrinous strands in the vitreous of the right eye, and one disc-sized patch and two small patches of healed chorioretinitis were seen in the left eye in the lower nasal quadrant.

Seven years after the onset of the uveoparotitis the patient returned for examination at my request. At this time she stated that she had gained about 25 pounds, had borne two children, and was perfectly well. Her vision was 20/20 in each eye. Both eyes were normal except for one deeply pigmented focus of healed chorioretinitis, about the size of the nerve head, in the left eye, and just beneath this two smaller foci, each deeply pigmented except for small whitish centers. The report on the roentgenograms of the chest was: "There is a thickening in the hilus region on both sides, with miliary thickenings in both lung fields that are distinctly abnormal and are entirely consistent with Boeck's sarcoid." Intradermal tuberculin tests were negative with 1 mg. of Old Tuberculin.

This case is interesting because the patient's first manifestations of disease were those of uveoparotitis, regarded as tuberculous because *x*-ray studies of her chest at that time showed changes that were interpreted as those of tuberculosis. Seven years later, however, when *x*-rays were taken again and her case was restudied, the lung changes were interpreted as those of Boeck's sarcoid.

CASE VII.—A white, married housewife, aged sixty-four years, first came to the Eye Clinic on June 7, 1932, because of a "little lump under the lower lid of the left eye," which had been present about a week. The eye had been slightly red and painful for about the same length of time. Examination revealed the presence of a firm, nodular mass, about 1 cm. in diameter, beneath the conjunctiva, projecting upward from behind the globe into the lower fornix. The ocular excursions were not impaired. Both eyes were normal and each eye had normal vision. An *x*-ray of the orbit on this date showed: "Increase in density in region of the growth. No bony involvement noted. Transillumination good."

One week later the patient was admitted to the Infirmary. At this time the vision in the left eye was still 20/20, and there was no apparent change in the hard tumor mass which projected under the conjunctiva into the fornix. The conjunctiva over the nodule had a peculiar slaty color and was freely movable. General examinations at this time revealed nothing of significance—the urine was normal and the blood Wassermann test was negative.

On June 15, 1932, under local anesthesia, the smooth, fleshy tumor mass, about 2 cm. in length and 1 cm. in diameter, was excised from its bed in the orbital fat beneath the eyeball. The wound healed promptly, and the patient was discharged from the Infirmary about one week later.

Dr. Verhoeff's pathologic diagnosis of the orbital mass was as follows: "The tumor consists of a number of large giant cells, epithelioid cells, and lymphocytes. These are arranged in nodules, the giant cell frequently being at the periphery. There is slight fibrosis. There is absolutely no necrosis. The blood supply is very poor. This apparently is typical of Boeck's sarcoid. However, one must consider tuberculosis, and numerous unseen foreign bodies, such as caterpillar hairs. Diagnosis: Boeck's sarcoid." I have made exhaustive search in sections of the tumor for acid-fast bacilli, but have been unable to find any.

On August 4, 1932, about six weeks after the biopsy, there was a small depression at the site of the conjunctival scar. There was moderate impairment in motion when the eye was turned down and in. Otherwise both eyes were normal. However, the patient complained of numbness of the left leg, and of weakness and dizziness. Neurologic and other physical examinations at this time were negative, the Wassermann test was again negative, and the spinal fluid was normal.

By October 22 the patient had developed a slight cough and dyspnea, and the weakness, dizziness, and paresthesias were more pronounced. On October 27 the patient was admitted to the Massachusetts General Hospital for further observation. She was discharged on November 9, 1932, with a diagnosis of a malignant growth of the mediastinum. The left lung was found to be partially collapsed, and bronchoscopic examination revealed a narrowing of the left main bronchus, evidently by pressure from without. *X*-ray examinations showed the presence in the mediastinum and lung of changes that were suspected of being produced by a neoplasm. The temperature was not elevated at any time during the period of hospitalization. In addition to the collapse of the lung, the only

other abnormalities found were enlargement of the posterior auricular lymph nodes and enlargement of the liver. The cause of the dizziness, numbness, and paresthesia of the left leg was unexplainable.

The patient was observed at regular intervals, and after about one year's time the changes in the lung had practically disappeared, she had gained in weight, and said she felt much better.

Two years after the appearance of the orbital tumor there had been no recurrence in the orbit. The patient had gained 24 pounds in weight, the lung had re-expanded, and the mediastinal nodes had decreased in size. At this time the case was reviewed and the old and new roentgenograms were interpreted as being typical of sarcoid.

Six and one-half years after the onset of her disorder there had been no demonstrable recurrence of the sarcoid either in the orbit or elsewhere in the body.

This patient was last seen by me in February, 1939, about seven years after the onset, and at that time was free from symptoms except for those ascribable to hypertensive disease and senility. In spite of incipient lenticular opacities which had developed in both eyes, the vision was 20/20 in each eye. An intradermal tuberculin test at this time showed no reaction with 0.005 mg. of Old Tuberculin, but was faintly positive with 0.01 mg.

This case presents three interesting features: first, the presence of an orbital mass which was excised and diagnosed as sarcoid; second, the occurrence of unexplained neurologic symptoms, and third, mediastinal sarcoidal involvement with nearly complete collapse of the left lung. In spite of the fact that the orbital tumor was found, on histologic examination, to be sarcoid, the intrathoracic condition was not regarded as sarcoid until two years later, when the *x*-ray films were reviewed by a roentgenologist who was familiar with the changes produced by sarcoid.

DISCUSSION

The seven cases reported here, all with ocular lesions, illustrate most of the important manifestations of Boeck's sarcoid except for those occurring in the conjunctiva. In six cases there was uveitis, which in three was associated with

keratitis and in two with parotitis. In these cases a clinical diagnosis of ocular tuberculosis had been made. In the seventh case the globe was unaffected, but there was sarcoidal involvement of the orbit. Six of the patients were females, and their ages ranged from twenty-three to sixty-four years. The onset of the ocular disease was insidious, and constitutional symptoms were relatively slight, even when there was extensive involvement of the lungs, lymph nodes, and bones of the hands. Lesions of the skin were found in only three cases, which corroborates the findings of Longcope and others that the disease occurs often without attendant abnormalities of the skin. In all cases definite typical changes in the mediastinum or lungs were demonstrated by the *x*-ray. Changes in the bone, as shown by the *x*-ray, were found in one of my patients whose hands and feet had been radiographed. In only one case (Case II) were constitutional symptoms observed by the patient before the ocular symptoms were noted.

The occurrence, in two of my cases, of parotitis with iridocyclitis, accords with the view that uveoparotitis may be one of the symptoms of Boeck's sarcoid. Uveoparotitis was first described as an entity by Heerfordt,[24] in 1909, when but little was known regarding sarcoid. The condition has been considered rare, but Savin,[25] in 1934, collected 66 cases "with ease and without exhausting the literature." Uveoparotitis affects either sex, and the age incidence is the same as that of Boeck's disease. There is a bilateral uveitis, preceded by, simultaneous with, or followed by an enlargement of the parotid gland which is nearly always bilateral. The glands are usually firm, painless, and nodular, and never suppurate. The enlargement generally subsides within a few weeks or months. The uveitis, as a rule, presents the picture of a chronic iridocyclitis resembling tuberculous involvement of the iris and ciliary body. The degree of severity varies, and there is usually only moderate to slight ciliary injection, with little or no pain unless glaucoma intervenes. As a rule, the aqueous is turbid, posterior corneal precipitates are generally

present, posterior synechias and vitreous opacities may form, and there is a protracted course, varying from several months to several years. The pathologic picture, in the few cases in which the iris or parotid gland has been biopsied, is entirely consistent with that of Boeck's sarcoid.

More recent observers have adduced convincing evidence that uveoparotitis is a manifestation of Boeck's sarcoid, and my two cases provide additional evidence. Longcope and Pierson[6] reported a case of typical Boeck's sarcoid beginning with bilateral uveitis, but which later involved the parotid glands, as well as the submental and submaxillary lymph nodes. Strandberg[12] describes a case of Boeck's sarcoid with bilateral parotid gland involvement, as well as sarcoid lesions in the breasts, conjunctivas, and skin. Blegvad[9] published the report of a case of Boeck's sarcoid with involvement of both parotid glands and with skin lesions. Hamburger[26] differentiates uveoparotitis from sarcoid on the basis of the absence, in the former, of skin lesions and of *x*-ray changes in the bones. However, no one has reported having taken such *x*-rays, and, furthermore, even in Boeck's sarcoid, these lesions may not be found by *x*-ray examination. Savin[25] found skin lesions resembling erythema nodosum to be present in 16 of 66 cases of uveoparotitis. Many of these lesions were not clearly described nor were they studied by biopsy, so that they may well have been sarcoids. Souter[27] performed a necropsy in which he found sarcoid skin lesions and parotid enlargement. In 1935 Kruskal and Levitt[28] reported two cases of tuberculous uveoparotitis. Since one of these cases exhibited reddish-purple blotches on the legs, increased hilar shadows, palpable spleen, enlarged supraclavicular nodes, and a biopsy of a gland disclosed a picture consistent with sarcoid, it is probable that this was really a case of Boeck's sarcoid, especially since the patient had negative Mantoux tests (0.1, 0.5, and 1.0 mg. Old Tuberculin). Bruins Slot[29] described two cases of uveoparotitis occurring in patients with Boeck's sarcoid, and he believes that uveoparotitis is a

special form of Boeck's sarcoid. Tillgren,[30] in a case of uveoparotitis, found skin lesions that were of "the 'forme érythrodermique' of lymphogranulomatosis benigna described by Schaumann," *i. e.*, Boeck's sarcoid.

It has been suggested by several observers that Mikulicz's disease may also be a manifestation of sarcoid. Having made a histologic examination of enlarged glands removed from three patients with Mikulicz's syndrome, I am in accord with this view. In 1892 Mikulicz described a case of chronic, bilateral, painless enlargement of the salivary glands of unknown origin. Since then many cases believed to be Mikulicz's disease have been reported. Leukemia, tuberculosis, syphilis, and lymphosarcoma have been described as etiologic factors, so that the disease has been considered as a syndrome of unknown causation rather than as a disease entity. Hamburger and Schaffer[31] place uveoparotitis under the heading of Mikulicz's syndrome, a classification that is not justifiable, since uveitis is not present in Mikulicz's syndrome, and the lacrimal glands are generally not involved in uveoparotitis.

I have never seen a sarcoid patient with lacrimal gland enlargement, but Longcope and Pierson[6] found swelling of this gland in two of their eight reported cases of sarcoid. Since it is impossible to determine what the etiology in the case originally described by Mikulicz was, Mikulicz's disease is best regarded simply as a clinical syndrome that may be due to various causes, of which Boeck's sarcoid is certainly an important one.

Case VII is of special interest because, judging from the literature, this is the only case in which a sarcoid tumor mass has been found in the orbit, and, so far as I can ascertain, it is only the second case that presented neurologic symptoms. In spite of the fact that the orbital mass was originally found, by biopsy, to be typical of sarcoid, the *x*-ray changes in the patient's mediastinum and lungs were for two years regarded as due either to neoplasm or to tuberculosis. At the end of this time the patient's roentgenograms were re-examined and

the condition was diagnosed as sarcoid by an interpreter who was familiar with the roentgenologic changes produced by sarcoids. The patient had also displayed peculiar neurologic symptoms that indicated intracranial disease. In the case reported in the literature by Reis and Rothfeld,[8] in which neurologic symptoms similar to those in my case were present, the patient came to necropsy. There was no involvement of the orbit, but papilledema and retinal lesions were found, and sarcoid lesions were present on the cheeks and extremities. Almost coincidentally with the appearance of the skin sarcoids there were headaches accompanied by vomiting. The left eye became totally blind, and the vision of the right eye was reduced to counting fingers at 40 cm. There was bilateral exophthalmos. Ophthalmoscopic examination showed the entire retina of the left eye to be "transformed by a white tumor" which had an uneven surface and was covered with retinal vessels. The elevation of the retinal separation was 20 D. Optic atrophy with choked disc was present in the right fundus. Before death, which occurred during an epileptic seizure one and one-half years after the onset, this patient developed a slight weakness of the right leg. At autopsy there was found, at the base of the brain, a fleshy, somewhat translucent, golden, hard infiltrate that involved the whole region of the infundibulum, the optic chiasm, as well as both optic nerves, and extended on the right side to the olfactory bulb. Histologic changes typical of sarcoid were found in the brain, the optic nerve, the retina of the left eye, and in the skin. The tubercle-like infiltrations in the brain were composed chiefly of epithelioid cells, contained giant cells of the Langhans type, and showed "keratinized caseation." In the retina and in the septa of the left optic nerve, lymphoid cell foci containing epithelioid cells were present, but there was no caseation. A noteworthy fact is that this is the only case of sarcoid reported in which papilledema was observed ophthalmoscopically, and it is also the

only case in which lesions have been found microscopically in the retina and optic nerve.

In the Howe Laboratory Dr. Verhoeff and I have recently examined sections of an enucleated eye in which typical sarcoid nodules were present in the retina and in the distal portion of the optic nerve. The patient from whom the eye was removed lives at too great a distance to afford us the opportunity of examining her, but her oculist reports that no evidence of a tuberculous infection has been found either by clinical or by *x*-ray examinations, and that the tuberculin test is negative. Since the lesions in the retina and optic nerve in this patient are almost identical with those described by Reis and Rothfeld,[8] this may be a case of Boeck's sarcoid. It is possible that, as in Case VII, neurologic symptoms will develop later.

In only one of my cases, Case VI, was there chorioretinitis associated with Boeck's sarcoid. This patient had uveoparotitis, lymph-node involvement, and pulmonary sarcoid. Except for the case reported by Reis and Rothfeld,[8] I have been unable to find in the literature any case of involvement of the choroid or retina in association with sarcoid. Verhoeff* found that in all cases of localized chorioretinitis in an active stage in which he examined the eyes histologically the lesions were characteristic of tuberculosis. Necrosis of the retina over the choroidal focus was always present. Whether or not this could occur in sarcoid remains to be determined. It is evident that sarcoid is an extremely rare cause of localized chorioretinitis, but it should be regarded as a possible cause in cases in which tuberculin tests are negative and syphilis has been ruled out. In these cases careful *x*-ray studies of the chest should be made before the diagnosis of sarcoid is dismissed.

It is difficult to distinguish clinically between the ocular lesions produced by Boeck's sarcoid and tuberculosis. Since tissue from the eye is not readily available for biopsy, and

* Personal communication.

since ocular lesions are secondary manifestations, the differential diagnosis is usually dependent upon the identification of the primary disease process elsewhere in the body. This identification can often be made through biopsy of the affected skin or lymph nodes, together with *x*-ray examinations, serologic studies, and tests for allergy.

Involvement of the iris is the most common ocular manifestation of Boeck's sarcoid. This iritis may be of a relatively benign serous form, or of a more extensive nodular type, with corneal involvement. In the serous variety the only significant findings are the presence of slight ciliary injection, fine posterior corneal precipitates, and a moderate number of cells in the aqueous. In the nodular type, however, ciliary injection is more marked, the cornea is usually edematous and cloudy, the posterior corneal precipitates are larger and more numerous, and there are many cells in the aqueous. The iris, which can be seen only with difficulty through the hazy cornea and cloudy aqueous, contains a few fairly discrete nodules invaded by blood vessels. These nodules, as a rule, are smaller and apparently situated more superficially than are the nodules of tuberculous iritis. The clinical course of Boeck's iritis is usually not so severe, but may be complicated by corneal opacification and the development of synechias and secondary glaucoma. In ocular lesions healing occurs with complete resolution of the nodules, often with little scarring and slight impairment of vision.

As to the tuberculous etiology of Boeck's sarcoid, the evidence may be summarized as follows:

A. That in support of this theory:

1. In Boeck's sarcoid the distribution of the lesions in the hilum and mediastinal nodes, with miliary dissemination in the lungs in some cases, resembles that of tuberculosis, and the general distribution of the lesions in the spleen, liver, and other internal organs also resembles that of tuberculosis. Skin lesions occur both in sarcoid and in tuberculosis.

2. Bone changes, especially in the fingers and toes, occur both in Boeck's sarcoid and in tuberculosis.

3. There is a great similarity in the histologic picture of Boeck's sarcoid and that of tuberculosis.

4. In a few cases of Boeck's sarcoid the presence of undoubted tuberculous lesions has been proved by demonstration of the tubercle bacillus in the tissues or by animal inoculation.

5. It is true that in the vast majority of cases of Boeck's sarcoid tuberculin tests are negative or only slightly positive. This, and also the character of the lesions, could, however, be explained on the basis of tuberculous etiology by the fact that the patients are anergic to tuberculoprotein. This anergy may be due to some peculiarity in the resistance of the patient to the usual tubercle bacilli, or to atypical bacilli.

6. In certain cases of sarcoid, fever and other clinical symptoms generally associated with tuberculosis are present.

7. In some cases of Boeck's sarcoid the rate of sedimentation of the red blood corpuscles has been found to be increased, a condition that generally occurs in tuberculosis.

B. The following facts, however, constitute evidence, which I believe to be more conclusive, that Boeck's sarcoid is not of tuberculous etiology:

1. Although there is a similarity in the distribution in the hilum and mediastinum in both sarcoid and tuberculosis, in Boeck's sarcoid the apical portions of the lungs are characteristically free from involvement, whereas in tuberculosis the apices of the lungs are the portions most frequently involved. Skin involvement occurs much more often in sarcoid than in tuberculosis. Reports in the literature indicate that involvement of the liver, spleen, and other internal organs is much more frequent in tuberculosis than it is in sarcoid. When sarcoid lesions do occur in the liver, they are most numerous in the portal triads, whereas true tubercles are found most often in the mid-zones. Unlike tuberculosis, gastro-intestinal lesions are apparently exceedingly rare in sarcoid. However,

in the recent literature several cases of regional ileitis have been attributed to Boeck's sarcoid.

2. In Boeck's sarcoid, bone lesions of the phalanges are characteristic and, unlike those of tuberculosis, do not involve joints and periosteum, nor do they form sequestra and sinuses. Other skeletal structures are less commonly involved in Boeck's sarcoid than in tuberculosis.

3. Histologically, typical sarcoids can usually be distinguished from true tubercles by the fact that in sarcoids necrosis, caseation, and calcification are absent or extremely rare. Furthermore, in Boeck's sarcoid there is a characteristic absence of inflammatory reaction in the tissue surrounding the nodules, *i. e.*, the nodules are surrounded by almost normal tissue.

4. Although tubercle bacilli have in rare instances been demonstrated in suspected cases of Boeck's sarcoid, tuberculosis is so common a disease that co-existence of the two diseases would be expected in a certain proportion of cases. If such co-existence were much more infrequent than would be expected on the theory of separate etiology, this fact would be in favor of a tuberculous nature of Boeck's sarcoid, but at present there are insufficient data bearing on this question.

5. The skin tuberculin reaction is negative in the majority of cases of Boeck's sarcoid, or only slightly positive.

6. Clinical symptoms may be present in sarcoid, but they are, as a rule, very mild or even negligible.

7. Although Hunter has found increased sedimentation rates in a few cases of sarcoid, there have been no reports from other investigators regarding such tests.

8. It is characteristic of sarcoid that the lesions almost invariably heal, with practically complete resolution.

9. Eosinophilia is often found in Boeck's sarcoid.

SUMMARY AND CONCLUSIONS

Seven cases of Boeck's sarcoid with ocular manifestations are described. Boeck's sarcoid is a generalized granuloma-

tous disease involving primarily the lymph nodes, the lungs, the bone marrow, and the spleen. When the skin, the eye, and other organs are involved, the condition may be regarded as secondary. Contrary to general opinion, typical sarcoid skin lesions are frequently absent—skin lesions were found in only three of the seven cases. Involvement of the mediastinum and the lung roots is common, and was present in all seven cases. In one of my cases enlargement of the hilar nodes caused massive atelectasis of a lung. Miliary involvement, which radiographically resembles miliary tuberculosis, is often seen in Boeck's sarcoid and was demonstrated in four of the cases. Enlargement of various lymph-node groups, an extremely common finding, occurred in five of my cases, and in four of these the posterior auricular chains of nodes were enlarged. Specific changes in the bone, primarily in the phalanges of the hands and feet, may be demonstrated by means of x-rays. Such changes were found in the hands of one of three of my cases whose hands and feet were radiographed.

Involvement of the anterior uveal tract is of fairly common occurrence in Boeck's sarcoid. Iritis of a severe nodular type was present in four of my cases, whereas in two a milder serous type of iritis existed. Complications that may arise in cases of iritis are involvement of the cornea; formation of posterior synechias and cataract; and development of secondary glaucoma. Permanent corneal opacities resulted in two of my cases, and posterior synechias in three patients. Glaucoma, which developed in two cases, was successfully controlled. In no instance did cataracts form as a result of the iritis.

The posterior uveal tract is rarely involved. In one of my cases localized patches of chorioretinitis were observed in one eye, in addition to involvement of the irides and parotid glands.

Sarcoidal invasion of the base of the brain, optic nerve, and choroid, with neurologic symptoms, has been found at

autopsy in one case and was reported in the literature. Such symptoms occurred in one of my cases, and it is suggested that they were due to intracranial lesions of sarcoid.

Parotid gland enlargement, which occasionally occurs in Boeck's sarcoid, was found in conjunction with uveal involvement in two of my cases. Uveoparotitis and Mikulicz's syndrome may both be manifestations of Boeck's sarcoid.

Orbital involvement in Boeck's sarcoid occurred in one of my cases. Subsequent to the development of the orbital mass the patient exhibited mediastinal changes, with atelectasis of a lung, as well as enlargement of the posterior auricular nodes and of the liver. No case of orbital involvement in sarcoid has been found in the literature.

During the active stage of the disease constitutional symptoms are variable, but relatively mild considering the extent of the involvement. In four of my cases with extensive miliary involvement the constitutional symptoms were very mild.

Recovery with subsidence of the lesions is the rule in Boeck's sarcoid, but the prognosis is necessarily dependent upon the localization of the disease. In my cases the patients have been observed over periods of from one and one-half to seven years, and all have shown great improvement, whereas some have apparently been cured. In rare cases, extensive fibrous tissue formation in the lung during the healing process has caused death by interference with the right ventricle, but in all my cases the pulmonary lesions have cleared without the development of such a complication.

Although Boeck's sarcoid sometimes causes blindness, in five of my six cases of iritis very good vision resulted and in the sixth case corneal opacities prevented the return of useful vision. In the case in which there was an orbital mass the vision was never impaired.

No specific therapy for Boeck's sarcoid is known.

Histologically, there is a marked resemblance between true tubercles and sarcoid "tubercles." However, necrosis, caseation, and calcification occur extremely rarely in sarcoid, and,

furthermore, in contradistinction to tubercles, such foci are usually surrounded by a relatively non-inflammatory zone. In only two of my cases lymph nodes were excised for biopsy, but in each case the classic picture of sarcoid was present. The orbital mass was also found on biopsy to be typical of Boeck's sarcoid, and histologic examination of bits of iris that were removed in one case also showed epithelioid foci that strongly suggested sarcoid.

The tuberculin test in Boeck's sarcoid is often negative. The Mantoux test was negative with 1 mg. of Old Tuberculin in one of my cases, negative with 0.5 mg. in three cases, negative with 0.1 mg. in one case, negative with 0.01 mg. in one case, but the test was slightly positive with 0.01 mg. in one case.

At present we are obliged to admit that Boeck's sarcoid has not been proved to be due to tuberculosis, to an unknown virus, or to the lepra bacillus, and that its etiology is still unknown. However, whatever its etiology may be, it is a clinical entity of great importance to medical science in general and to ophthalmology in particular.

Since the completion of this manuscript I have had access to a monograph on Besnier-Boeck's disease, by Professor I. Snapper, published in Haarlem, Holland, in 1938. Professor Snapper reports 13 cases of Besnier-Boeck's disease. In each case localizations of sarcoids were observed in the hilum and mediastinal glands, in the liver in four cases, in the bones of the hands and feet, or in either alone, in five cases, in the peripheral lymph nodes in eight cases, in the skin and in the spleen in seven cases. There was miliary dissemination in the lungs in eight cases. "Eye symptoms were often found—iridocyclitis five times, sarcoids of the conjunctivae twice. Once diabetes insipidus developed—a rare complication, as was dryness of the mouth caused by localization of sarcoids in the salivary glands." Tuberculin tests were made in 11 of the 13 cases—the von Pirquet test was negative in nine cases

and positive in two. The Mantoux test was negative in three cases and slightly positive (1: 10,000) in one case. In one of these cases enlargement of the glands at the roots of the lungs caused extensive atelectasis. An increased sedimentation rate was found, thus corroborating the findings of Hunter. Professor Snapper is of the opinion that the etiology of Besnier-Boeck's disease is still unknown. He was unable to confirm the conception of Schaumann that patients with Besnier-Boeck's disease often die of tuberculosis, nor does he agree with Schaumann's contention that the disease is a benign anergic phase of tuberculosis of the lymphatic apparatus which is usually followed by true active tuberculosis. None of Snapper's cases exhibited symptoms of active tuberculosis.

Another article by Horton, Lincoln and Pinner (Am. Rev. Tuberc. **39:** 186, 1939) has just come to my attention. These authors report four cases of non-caseating tuberculosis (type: Boeck's sarcoid). Active uveitis was present in two of these cases, and in one patient chorioretinitis was present in addition to iridocyclitis. These authors suggest that Boeck's sarcoid is a non-caseating phase of tuberculosis, and they present necropsy findings in one case which, after years of undergoing a non-caseating phase, finally developed caseating lesions. "This case shows the close association of tuberculin anergy with the non-caseating phase and tuberculin allergy with the terminal caseating destructive phase." They refer to two previous papers on non-caseating tuberculosis (Pinner, M.: Am. Rev. Tuberc. **36:** 706, 1937, and Pinner, M.: *Ibid.* **37:** 690, 1938).

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COLOBOMA OF THE OPTIC NERVE IN THE HUMAN EMBRYO*

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Colobomas of the optic nerve are so rare in the human embryo that an exhaustive study of the literature failed to show a single case as typical as the one obtained in 1934, which forms the basis of this report. Several colobomas in the embryonic eyes of animals and chicks have been described. The few cases that occurred in man were reported after enucleation had taken place, and were either adult eyes or eyes that had been removed some time after birth.

The coloboma to be described occurred in a human embryo measuring 61 mm. in length, corresponding to an approxi-

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