However, in contrast to the findings of these observers, patients with neurotic depressions were not benefited. There was an impression that in certain cases the drug was superior to barbiturates, and a further trial is in progress to determine whether this can be substantiated.

The subjective effects noted following injection of the drug during the E.E.G. investigation are of some interest. Jacobsen (1955) interprets the feeling of heaviness of the legs as being due to muscle relaxation. We believe that it is more likely to be due to a change in perception, since some of the subjects reported other perceptive changes; objects felt heavier, patterns for flicker were more coloured or intricate, and distances seemed altered.

Therefore it seems likely that the electroencephalographic change observed in five of our subjects is comparable to that following mescaline in which the subject's attention to altered perceptions is thought to be an important factor.

Summary and Conclusions

Benactyzine ("suavitil") is a new drug at present under trial for the treatment of certain psychiatric disorders. A brief review is given of its properties; on the basis of animal and human experiment it has been claimed to alter reactions to stress.

A pilot study on 43 out-patients with various psychiatric disorders suggests that patients with a symptomatology in which anxiety and tension predominate respond favourably (of 18 cases, 8 were much improved and 4 improved); those with depressive, hysterical, and obsessive symptoms do not. About half the patients receiving 2 mg. three times a day experienced side-effects, the commonest being heaviness of the limbs. On a dosage of 1 mg. three times a day side-effects did not occur, and the higher dosage could be tolerated provided its increase was gradual.

Ten healthy volunteers were given the drug subcutaneously. Subjective effects and E.E.G. changes were noted. Changes in perception were predominant, and in half the subjects there was a marked diminution in the amount of alpha rhythm. This change is thought to be non-specific and comparable to that seen following the administration of mescaline.

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ADDENDUM.—Since this paper was submitted two other reports have appeared. Beresford Davies (1956) claims improvement in 67 of 110 patients, with particularly encouraging results in patients with anxiety symptoms and psychosomatic disorder. Coady and Jewesbury (1956) found no effect on muscle tone in a group of 80 neurological patients. Flexor spasms, however, appeared to be relieved in some cases. They also note a striking suppression of the normal rhythm of the E.E.G. in two cases.

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OCULAR SARCOIDOSIS

BY

D. AINSLIE, M.D., F.R.C.S.

Assistant Ophthalmic Surgeon, Middlesex Hospital

AND

D. GERAINT JAMES, M.D., M.R.C.P.

Leverhulme Scholar, Institute of Clinical Research, Middlesex Hospital Medical School, London

The cause of sarcoidosis is unknown. It is probably an indolent infection, but, since no causal organism has been isolated, early recognition of the disease depends upon an awareness of the various clinical manifestations. Diagnosis may often be confirmed by histological examination of affected tissue. The systemic nature of sarcoidosis is indicated by the widespread distribution of the lesions, which may be found in the lungs, skin, lymph nodes, spleen, liver, kidneys, nervous system, bone, and eyes. In all these sites the histological picture is the same, the lesions consisting of aggregates of large pale epithelioid cells and occasional giant cells grouped into nests compressing or displacing normal tissue. There is little or no necrosis or caseation, which distinguishes the appearance from that of tuberculosis.

In the course of time these active granulomatous lesions resolve and are replaced by acellular hyaline material. This in turn is followed by dense fibrosis. At an intermediate stage in this evolution, granulomatous foci, hyaline tissue, and fibrosis may be seen together. Although these pathological changes are common to all involved tissues, their effects vary with the sites of the deposits, the most serious symptoms occurring when the eyes and the lungs are involved. Iridocyclitis is the commonest ocular manifestation of sarcoidosis, and, while in most cases this is self-limiting, the fibrosis associated with healing may lead to disorganization of the globe and loss of sight. Often the eyes are involved, and the importance of early diagnosis cannot be overstressed, since the prognosis is greatly improved by early treatment.

Present Series

Eye Changes

In a series of 100 patients with histologically confirmed sarcoidosis, eye changes were observed in 28 (see Table).

Ophthalmic Manifestations Seen in 28 Cases

Subacute iridocyclitis	8
Chronic iridocyclitis	12
Keratoconjunctivitis sicca with enlarged lacrimal glands	2
Keratoconjunctivitis sicca alone	1
Enlarged lacrimal glands alone	1
Infiltration of eyelids	1
Eales's disease (periphlebitis retinae)	1
Macular oedema	1
Phlyctenular conjunctivitis	1

Subacute Iridocyclitis.—This was unilateral in two and bilateral in six cases. The clinical picture was similar in all these cases. The patients complained of sudden onset of pain in the affected eye or eyes, usually accompanied by lacrimation and mistiness of vision. The eyes showed ciliary congestion, and, in addition to this, turbidity of the aqueous humour, due to excess protein and circulating cells, could be observed by using the biomicroscope. In each instance the iridocyclitis was associated with active sarcoidosis elsewhere. In four patients there was associated erythema nodosum and bilateral hilar lymphadenopathy, one had sarcoid meningitis, and two developed transient enlarged cervical and supraclavicular glands at the same time as the

onset of the iridocyclitis. The remaining patient showed bilateral hilar lymphadenopathy and diffuse mottling in both lung fields. In all of these cases the iridocyclitis appears to have been a transient episode. The inflammation subsided within three months, and there have been no recurrences during the follow-up periods, the shortest of which is one year. In this group the Mantoux reaction at a dilution of 1:100 was positive in four cases. The Kweim test was positive in seven of the eight patients.

Chronic Iridocyclitis.—In all 12 cases this was bilateral. The severity varied greatly, but the appearances were essentially the same in all. In no case was there any ciliary congestion to suggest ocular inflammation. All, however, showed numerous grey precipitates on the back of the cornea. In addition, innumerable fine keratic precipitates and cellular particles circulating in the anterior chamber were made visible by using the biomicroscope. In two cases choroiditis was present in addition to the iridocyclitis. Although nodules in the iris have often been described as typical of iridocyclitis due to sarcoidosis, such nodules were seen in only two cases in this series. Just as the eye lesions were chronic, so were the other manifestations of the sarcoidosis. Extensive diffuse pulmonary fibrosis was present in six patients and persistent diffuse mottling lasting three years in one. Of the remaining five, three had bilateral hilar lymphadenopathy for up to nine months, one had transient diffuse mottling of the lung fields shown in a single radiograph, and in one no pulmonary changes were observed. One of the patients with chronic fibrotic pulmonary and ocular sarcoidosis also had nephrocalcinosis, suggesting long-standing disease. The Mantoux reaction at a dilution of 1:100 was positive in two cases and negative in ten. The Kweim test was performed in seven cases and was positive in six of these.

Other Ocular Signs.—There remains a group of eight patients suffering from generalized sarcoidosis who showed ocular signs other than iridocyclitis. It is possible that the macular oedema seen in one case was purely coincidental, since there was no evidence of any choroiditis. In the remaining seven cases it seems probable that the eye changes were associated with the sarcoidosis. Two of the three patients with keratoconjunctivitis sicca also had enlarged lacrimal glands, and in one of these a lacrimal-gland biopsy revealed sarcoid tissue. The patient with thickening of the eyelids had a specimen taken from the subcutaneous lid tissue, and the biopsy indicated sarcoidosis. Phlyctenular conjunctivitis and Eales's disease are often associated with tuberculosis, though they are not generally described as manifestations of sarcoidosis.

Other Findings

In the 28 cases with eye involvement the following other manifestations of sarcoidosis were found :

Skin Changes.—These were present in 14 patients, and comprised the following : erythema nodosum, 4 ; lupus pernio, 2 ; dusky-red papules, 4 ; herpetiform lesions, 1 ; scars of old injuries in which biopsy revealed sarcoid tissue, 3. It is common to find sarcoid tissue involving old cutaneous scars, and such scars may become red and livid during exacerbations of the disease. This phenomenon was noted by three patients in this series during exacerbations of their iridocyclitis.

Pulmonary Changes.—These occurred in 23 patients, as follows : bilateral hilar lymphadenopathy, 9 cases ; diffuse mottling of lung fields, 7 ; bilateral hilar lymphadenopathy and diffuse mottling of lung fields, 7.

Superficial Glandular Involvement.—Of the 12 cases, peripheral lymph-node involvement was present in 8 (in addition, three of these patients had enlarged spleens) and parotid gland enlargement in 4.

Diagnosis

The appearances of the eye changes may be suggestive of sarcoidosis, but no eye signs are characteristic enough to be diagnostic in themselves. Other clinical and radiological features found elsewhere in the body may provide strong support for the diagnosis. In the present state of our knowledge, however, histological proof of the presence of sarcoid tissue provides the most satisfactory confirmatory evidence. When skin lesions or enlarged superficial lymph nodes are present biopsy may be easily performed. In this series eight skin biopsies and seven lymph-node biopsies revealed sarcoid tissue. Other sites from which material containing sarcoid tissue was obtained were tonsil (1), soft palate (1), excised eye (1), and hilar glands at necropsy (1). Alternatively, tissue for histological examination may be obtained by aspiration liver biopsy, but the process is not entirely without danger, and, furthermore, it is not always possible by this method to distinguish between sarcoidosis and tuberculosis. A positive liver biopsy was observed in four instances in this series.

Kweim Test.—This consists of intradermal injections of a saline emulsion prepared from sarcoid tissue. In patients with active sarcoidosis a dusky-red nodule develops at the site of injection during the ensuing three to four weeks. Histological examination of the nodule reveals characteristic sarcoid tissue when the test is positive. In the absence of easily accessible lesions for biopsy, the Kweim test is a simple, safe, and specific out-patient technique for providing histological evidence of active sarcoidosis (James and Thomson, 1955). It was performed in 19 of our patients with ocular sarcoidosis and was positive in 15. This rate of 79% is similar to that found in all types of sarcoidosis. In 10 of the 15 positive cases, corroborative histological evidence of sarcoidosis was obtained by other biopsies—skin (5), lymph node (3), and liver (2). Crick *et al.* (1955) have suggested that conjunctival biopsy may reveal sarcoid tissue in patients with sarcoidosis. Conjunctival biopsy was performed in five cases, but in no instance was sarcoid tissue found. In none of these cases, however, was there any macroscopic evidence of conjunctival sarcoidosis, the biopsies being taken from the apparently normal conjunctiva of the lower fornix. Healing after the biopsy was rapid and complete in all cases.

Treatment

The natural course of sarcoidosis is towards spontaneous healing by fibrosis. In many sites this causes little trouble and patients remain without symptoms throughout the disease. In the eye, however, the process is apt to lead to serious complications. Of all the manifestations of sarcoidosis, iridocyclitis is the prime indication for treatment, for, if untreated, vision may be lost before the disease becomes quiescent. The only treatment which materially influences the course of sarcoidosis is the administration of one of the cortisone group of drugs. In the case of generalized sarcoidosis systemic cortisone or corticotrophin must be given, and, while improvement usually occurs almost at once, the side-effects of such treatment may necessitate its being stopped while the disease is still active. In treating lesions involving the eye, however, cortisone or hydrocortisone, applied locally, is usually effective, and such treatment may be continued indefinitely. Only in cases where the posterior part of the globe is involved, as in choroiditis, will systemic therapy be required.

Local cortisone treatment is usually administered as drops (0.25–1%) or ointment (1%) applied to the conjunctival sac at intervals of from 2 to 12 hours, depending upon the severity of the disease. In very severe cases an initial dose of cortisone or hydrocortisone (5–10 mg.) may be given by subconjunctival injection to ensure a high concentration within the eye. The dose may be repeated three to four days later, after which topical application alone is usually all that is required. In all cases of iridocyclitis a mydriatic should be used in addition to the cortisone therapy.

Of the eight cases with subacute iridocyclitis the only treatment needed in six instances was the instillation of atropine drops and the application of heat to the eyes. The two remaining cases were rather more severe, and required treatment with cortisone drops in addition.

All 12 patients with chronic iridocyclitis received cortisone therapy. Eight cases of moderate severity treated early with local cortisone responded readily, and specific mention is not made of each case. However, the four severe cases described below illustrate well the importance of early treatment. In both Cases 1 and 2 treatment was started late and the disease was not sufficiently controlled to prevent serious damage to the eyes. In Cases 3 and 4 treatment was started while the iridocyclitis, although severe, was still in the early stages. Control of the inflammation was rapid and complete. In Case 3 the quiescent phase has been reached, and at the time of writing no further treatment was required. In Case 4 the disease was still active, but harmful effects have been prevented by continued cortisone therapy.

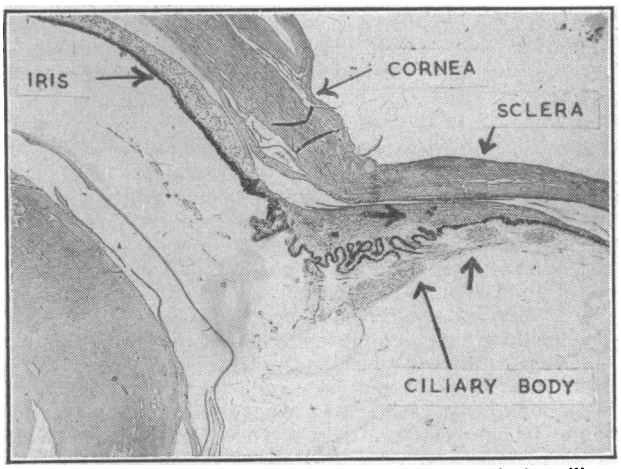

FIG. 1.—Histological photograph of the region of the ciliary of the excised right eye in Case 2.

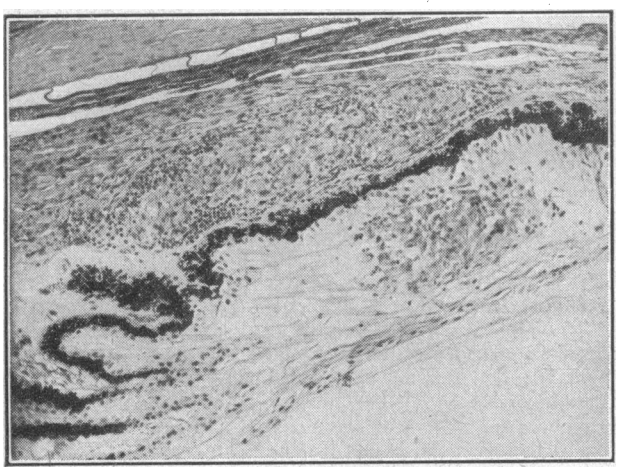

FIG. 2.—Low-power photomicrograph of the region indicated by arrows in Fig. 1. A sarcoid lesion is visible just outside (above) the pigmented ciliary epithelium. (×105.)

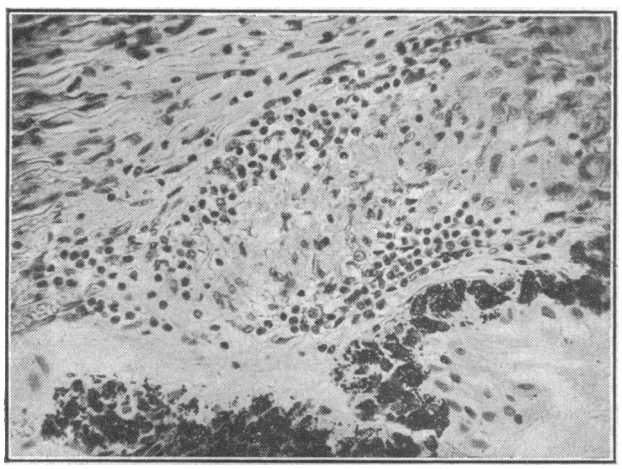

FIG. 3.—High-power view of the lesion shown in Fig. 2. (×240.)

Case 1

A woman aged 49 had had "trouble with the eyes for twenty years" and chronic iridocyclitis had been diagnosed ten years previously. Sight had become gradually worse over this period, and when cortisone treatment was started in 1951 she still had active iridocyclitis and many posterior synechiae were present. Her vision was limited to counting fingers at one metre.. Local cortisone (subconjunctival injections and drops) was given initially, and applications of cortisone drops have been continued. Despite this both eyes have become disorganized and only one has retained even perception of light.

Case 2

A woman aged 47 had had bilateral iridocyclitis for five years before treatment with cortisone was started in 1950. At this time the right eye showed signs of advanced iridocyclitis with numerous keratic precipitates, thick exudate in the anterior chamber, and an occluded pupil. The vision was reduced to perception of light. The left eye showed many keratic precipitates, posterior synechiae, and vitreous opacities, but the vision was 6/12.

A course of systemic cortisone was given in addition to subconjunctival injections and cortisone drops applied to both eyes. Despite treatment secondary glaucoma developed in the right eye, which had to be removed because of persistent pain. On section typical sarcoid lesions were demonstrated in the region of the ciliary body (Figs. 1–3). The iridocyclitis persisted in the left eye, though cortisone reduced the intensity of the activity. As patches of choroiditis were noted, two further courses of systemic cortisone were given, but with little benefit. In late 1953 a complicated cataract developed and progressed rapidly to maturity. In March, 1955, the eye had become quiet and a successful intracapsular cataract extraction was performed. The eye remained quiet with a vision of 6/60, there being considerable macular scarring as a result of old choroiditis.

Case 3

A woman aged 48 had noticed spots before both eyes for three months and very marked deterioration of vision in the right eye for a month. When first seen in 1952, she was found to have massive keratic precipitates covering almost the whole of the posterior surface of the cornea of the right eye, and numerous fine keratic precipitates and a few large ones were seen in the left eye. Numerous cells were visible in the anterior chambers of both eyes. There were no posterior synechiae. Right vision was reduced to hand movements and left vision was 6/9. Local cortisone treatment was given in the form of drops to both eyes, and in addition two subconjunctival injections were given to the right eye initially. Two weeks after starting treatment the right vision had improved to 6/12 and the left to 6/6. Two weeks later vision was 6/6 in both eyes. Local treatment with drops was continued for eight months. No treatment has been given for over two years and there has been no recurrence of activity.

Case 4

A woman aged 54 was first seen in April, 1954, complaining that during the last month her vision had become dim in both eyes and that her right eye was now almost useless. She said that she suffered from "Hodgkin's disease," for which she had had radiotherapy. The right vision was reduced to counting fingers at a distance of one metre, and there were so many massive precipitates on the posterior corneal surface that it was difficult even to examine the anterior chamber. The left vision was 6/18 and there were numerous keratic precipitates and many

cells in the anterior chamber. There were no posterior synechiae. The patient had generalized glandular enlargement and numerous skin lesions. A skin biopsy confirmed the diagnosis of sarcoidosis.

Local cortisone treatment was given in the form of drops to both eyes, with in addition three subconjunctival injections of 6.25 mg. each to the right eye. There was rapid improvement in the vision with the disappearance of the precipitates. Three weeks after the start of treatment vision was 6/6 in both eyes. At the time of writing the patient's vision was still 6/6, but it had not yet been possible to stop applying drops, for cessation of treatment was at once followed by recurrence of inflammatory signs. Until three months previously, she was using cortisone drops, 0.5%, which she had to apply five times a day to keep the condition under control. For the last three months she had been using hydrocortisone drops, 1%, and twice-daily application of this had kept the iridocyclitis controlled. She has also had two courses of systemic cortisone therapy to control her generalized sarcoidosis during periods of exacerbation.

Treatment of Other Ocular Signs

With regard to the conditions other than iridocyclitis, no ocular treatment was given to the patient with Eales's disease or to the patient with macular oedema. The former's condition has remained stationary for two years, while that of the latter subsided spontaneously over a period of three months. The case of phlyctenular conjunctivitis was treated with atropine and sulphacetamide drops, clearing up after three weeks. Of the cases of keratoconjunctivitis sicca two were mild, though there was definite reduction in the quantity of tear secretion, as indicated by Shirmer's test, and early filiform keratitis was present in each case. Symptomatic treatment, using Ringer–Locke solution, sulphacetamide, and methyl cellulose drops, brought considerable relief. One of these patients had moderately enlarged lacrimal glands, which returned to normal size over a period of eight weeks.

The third case had much-enlarged lacrimal glands, severe filiform keratitis, and much-reduced lacrimation. The enlarged glands subsided to normal size spontaneously after three months. The only beneficial treatment in this case was hydrocortisone drops applied to the conjunctival sac. These brought great symptomatic relief.

No treatment was effective in reducing the swelling in the case with infiltration of the eyelids, though systemic cortisone, local radiotherapy, and excision of the subcutaneous tissue were tried.

Summary

Of 100 patients with histological evidence of sarcoidosis 28 had ocular abnormalities. Iridocyclitis, the most serious manifestation, was present in 20 cases.

If untreated, sarcoid iridocyclitis may lead to blindness.

Early treatment of the iridocyclitis with cortisone or hydrocortisone offers the best chance of controlling the disease.

Treatment is unlikely to be beneficial when started at a late stage. Early diagnosis is therefore essential.

Methods which assist in arriving at the diagnosis of sarcoidosis are discussed and a brief description of the Kweim antigen test is given.

[Figs. 1-3 are reproduced by permission of the *Archives of the Middlesex Hospital*, in which they first appeared (Ainslie and James, 1953).]

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PHAEOCHROMOCYTOMA WITH SUSTAINED HYPERTENSION

BY

K. N. V. PALMER, M.D., M.R.C.P.
Senior Lecturer

AND

G. A. McDONALD, M.B., Ch.B.
Senior Research Fellow

From the Department of Medicine, University of Aberdeen

Phaeochromocytomas are functioning tumours of chromaffin tissue, the clinical syndromes which may occur being due to the presence of excess amounts of noradrenaline and adrenaline in the circulation (Goldenberg *et al.*, 1949). Patients may show either paroxysmal hypertension or persistent hypertension mimicking benign or malignant hypertension, with or without increased metabolism or glycosuria (Goldenberg, 1954). Only a quarter to a third of the cases have the classic picture of paroxysmal hypertension (Green, 1946), and a sustained hypertension is the commoner presentation. Usually, however, other manifestations that are uncommon in essential hypertension are associated with sustained hypertension due to a phaeochromocytoma: the most frequent of these are generalized sweating, pallor and coldness of the skin, goose-flesh, unexplained fever, postural hypotension and tachycardia, a normal cold pressor test, a raised basal metabolism, and glycosuria (Smithwick *et al.*, 1950).

Diagnostic Procedures

Adrenolytic agents cause a prompt fall in blood pressure, usually to normotensive levels, in cases of sustained hypertension due to phaeochromocytoma, but only during a hypertensive phase in the paroxysmal type of case. Phentolamine ("rogitine") has rapidly established itself as the adrenolytic agent of choice, for it is almost free of side-reactions, is easy to administer, and, unlike piperoxan, it does not produce a rise in blood pressure in cases of essential hypertension (Helps *et al.*, 1955). False-positive tests may occur if the drug is given intramuscularly (Gifford *et al.*, 1952) and when it is given during barbiturate sedation and in uraemia.

Provocative tests are mainly of value in the diagnosis of patients with the paroxysmal type of hypertension during a normotensive phase. In these cases intravenous injection of histamine causes an abrupt rise in blood pressure (Roth and Kvale, 1945). If a positive result is obtained with the phentolamine or histamine tests, the urinary excretion of the catechol amines (adrenaline and noradrenaline) should be estimated, and this is the most reliable diagnostic test for the presence of a phaeochromocytoma.

Treatment is surgical and consists in the removal of all tumours secreting adrenaline and noradrenaline. During operation two dangers have to be dealt with—namely, severe exacerbations of hypertension during the induction of anaesthesia, positioning of the patient, and handling the tumour; and a severe hypotensive phase when the adrenal veins are clamped before removal of the tumour. The first of these contingencies is met by the use of phentolamine, the second by the use of noradrenaline.

Case Report

A housewife aged 26 was admitted to hospital on April 24, 1955. She complained of frontal headache associated with attacks of sweating for one year. The headache was described as a dull ache, which usually came on in the morning and was made worse by stooping. The attacks