# Neuro-ophthalmology

*Symposium of the University of Miami and the Bascom Palmer Eye Institute*

VOLUME II

# Neuro-ophthalmology

## *Symposium of the University of Miami and the Bascom Palmer Eye Institute*

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*Illustrated*




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# Preface

This volume presents the material discussed at the second postgraduate symposium on clinical neuro-ophthalmology sponsored by the Department of Ophthalmology, University of Miami School of Medicine, which was held at the Americana Hotel, Miami Beach, Florida, January 3-8, 1965. At the first meeting, held the previous year, an attempt was made to try to cover the broad field of neuro-ophthalmology or at least to aim in that direction. That goal was so manifestly impossible, however, that a different approach was employed at the second symposium. Rather than being assigned topics on the basis of the sensory and motor pathways of the visual system, each participant was asked to speak on the subject of his most active current interest. The only restriction was to avoid unnecessary overlapping of content. All who attended were in agreement that this proved to be a far more satisfactory and rewarding plan, for each member of the faculty learned a great deal from the other speakers, and hence a much greater flow of new material was also available to the participants.

It should be emphasized at the beginning that there is no overlap between material presented in the first and second neuro-ophthalmology symposiums. The purpose of the meeting is to bring together persons who are active and interested in clinical neuro-ophthalmology in order to discuss the latest topics and present the most recent research findings of clinical interest. Too much glamor has been placed upon the basic research worker in recent years, with the result that clinical research and clinicians in general have at times been relegated to a somewhat secondary position. That is why the most important part of any such symposium has and must consist of having patients actually present not only to illustrate the various neuro-ophthalmologic entities, but also for examination and for discussion as to management. More than one hundred patients were brought back for each of the symposiums held to date, and, as is nearly always the case with such functions, suggestions as to management and comments in differential diagnosis

offered by both the faculty and the physicians attending the course led to clarification of diagnosis and definite aid in management of more than one case on each occasion. This therefore has made the effort worthwhile to both patient and faculty alike. Because the necessity for patient demonstration must limit the number in attendance at such a course, the advantage of having the material in published form is obvious. This also allows the participants to digest at their leisure, and to review at later dates, material that has been presented in an extremely rapid fashion.

As to the future, it is evident that this field is in a state of extremely rapid development and change. A third symposium has now been definitely scheduled for January 3-7, 1966. The major emphasis will be on pediatric neuro-ophthalmology and on neuropathology of the visual pathways. Again, it is emphasized that these published symposiums are not to be construed as complete texts on the vast field of neuro-ophthalmology, but they do have the advantage of being timely and decreasing the very long lag between clinical developments and their availability to the clinician in review form. Indeed, it has been found that these published symposiums are often available to the practitioner many months earlier than the subjects can appear in the majority of medical journals. There will be no overlap with previous material nor with future symposiums or publications.

I cannot thank the participants and faculty enough, for without their cooperation the symposium could not have been initiated, much less carried to completion. I would like particularly to thank my colleagues in neurosurgery and in neurology who by their support and encouragement have helped the growth of all the neurologic spheres of interest at the University of Miami. I would also like to acknowledge the constant and continuing help from all of the full-time and attending staff members in the Ophthalmology Department who also have played a very real role in making this symposium possible. If this volume serves to help in any way that underappreciated American, the *clinician,* it will have been well worth the effort.

J. Lawton Smith
*Miami, Florida*
*May, 1965*

# Contents

Chapter 1

# Seronegative ocular syphilis and neurosyphilis*

J. Lawton Smith

The purposes of this chapter are (1) to prove that a negative blood test does not rule out syphilis, (2) to show that a negative blood test does not rule out clinically progressive or active syphilis, (3) to show that clinically progressive ocular syphilis or neurosyphilis is frequently seen with an absolutely negative cerebrospinal fluid, (4) to emphasize the importance of the *Treponema pallidum* immobilization (TPI) test in practice, and (5) to point out the even greater sensitivity of the fluorescent treponemal antibody absorbed (FTA-ABS) test in clinical detection of late ocular syphilis and neurosyphilis.

At the outset, the terminology to be employed and the desiderata of this study should be defined. All cases of syphilis in the patients here presented are instances of *late* syphilis. By this it is meant that the signs of interest would be those noted on examination of the eyes and nervous system and hence would be of primary interest to the ophthalmologist, neurologist, and neurosurgeon. Primary and secondary syphilis are hereby disposed of and are of no further concern to this discussion. By ocular syphilis and neurosyphilis, it is meant that the lesions to be considered were found on neuro-ophthalmologic examination and consisted of anomalies of the eyes (as abnormalities of pupils, fundi, or visual fields) or of the nervous system (as tabes dorsalis, optic tabes, or paresis). For example, the Argyll Robertson pupil may be an

*Grateful acknowledgment is here given to all those colleagues at the University of Miami and the Venereal Disease Research Laboratory without whose help this work could not have been done.

isolated finding and may be considered as either an ocular or a neurologic sign of syphilis. Since the majority of the signs to be discussed were noted on neuro-ophthalmologic examination, for practical purposes ocular syphilis and neurosyphilis are herewith classified together as a clinical entity.

*Seronegative syphilis* is here defined as representing the patient with clinical signs of syphilis on examination of the eyes or nervous system and yet whose serum is negative or nonreactive when tested with the conventional reagin tests (as VDRL, Kahn, Kline, Eagle, Mazzini, Hinton, and the like). The term *seronegative syphilis* is *not* used with respect to the *specific treponemal tests*. Other tests (such as the Kolmer-Reiter protein or KRP, the Reiter protein complement fixation or RPCF, the fluorescent treponemal antibody 200 or FTA-200) will be mentioned, but whenever the term *specific treponemal test* is used in this chapter, reference is only to either the *TPI* or *FTA-ABS* test.

The material here presented may be considered a progress report on a combined study which has been in progress during the past two years, involving the Department of Ophthalmology of the University of Miami School of Medicine and the Venereal Disease Research Laboratory, Communicable Disease Center, United States Public Health Service, Atlanta, Georgia. This project has been heavily dependent upon the collaboration of Dr. Moore, Dr. Yobs, Dr. Deacon, Dr. Singer, Dr. Taylor, Dr. Reynolds, and Dr. David, and their help is gratefully acknowledged here. The project has consisted of both clinical and laboratory phases. The clinical studies will be briefly discussed here.

All patients seen in the Ophthalmology Out-Patient Clinic of Jackson Memorial Hospital, Miami, Florida, have been evaluated for eye signs suggestive of late syphilis. These have included light-near dissociation of the pupils, any pupillary inequality or irregularity, iris atrophy, dislocation of the lens, uveitis, fundus lesions suggestive of syphilis, optic atrophy, patchy alopecia, loss of the outer third of the eyebrows, and so forth. Whenever such signs have been suspected by our resident ophthalmologic staff, 10 ml. of whole blood has been drawn from the patient. This blood was centrifuged, and the sterile serum was mailed promptly to the Venereal Disease Research Laboratory in Atlanta, where all serologic testing was done. It should be emphasized that a control is run with each TPI test, and that the FTA-ABS tests were done in duplicate at the VDRL Laboratory. Excellent correlation of this serologic data has been found by the Atlanta laboratory. Conventional reagin tests (VDRL, unheated serum reagin or USR, and the like) were also done in the Jackson Memorial Hospital serologic laboratories. Other tests, as FTA-200, RPCF, and KRP, were done in both the Atlanta and the Miami laboratories.

A brief review of serologic nomenclature is indicated for the clinician at this point. *Treponema pallidum* was discovered as the etiologic cause for

syphilis in 1905 by Schaudinn and Hoffman. The following year Wassermann found that a complement fixation reaction could be obtained from the sera of syphilitic patients, using an antigen obtained from tissues of stillborn syphilitic fetuses. In 1941 Pangborn isolated a principal in beef heart antigens which has been used as the antigen since and has been termed the *cardiolipin antigen*. The antibody has been termed *reagin* which is present in the patient's serum to this cardiolipin antigen. The great number of tests which have since been evolved—as Kahn, Kline, Eagle, Mazzini, unheated serum reagin, rapid plasma reagin, Kolmer, Hinton, and the like—attests to the nonspecificity of the reagin tests. It was not until 1949 when Nelson and Mayer reported the TPI test that the first *specific* serologic test for syphilis was available, which was based upon a serum antibody to *Treponema pallidum* itself. The TPI test has certain characteristics which are of interest. It was based upon Nelson's discovery of a method for keeping virulent treponemes living and motile in an in vitro environment for periods of up to 96 hours. Such motile treponemes when placed in contact with a control (uninfected) serum continued to move. However, when placed in contact with a syphilitic patient's serum, the organisms were found to promptly become immobilized. This immobilization was the basis for the test. However, the TPI is expensive and technically difficult. It requires constant maintenance of a rabbit colony with frequent harvesting of virulent *Treponema pallidum* by passage through rabbit testicular granulomas about every six weeks. As a consequence, there has continued to be a search for other specific serologic tests. Space and time considerations do not allow a detailed review of these tests (such as RPCF, KRP, TPIA, and TPCF), but interested persons should consult Garson for an introduction to this subject.

A few words concerning the FTA test, however, are in order. Fluorescein-tagged antibodies has been a widely used immunologic technique. The technique was first applied to serologic testing for syphilis by Dr. W. E. Deacon. The original FTA (fluorescent treponemal antibody) test, however, was found to be reactive in many normal persons. Later study revealed that, although the test was giving reactions specific for treponemes, other treponemes (such as *Treponema microdentium*, normally found in the mouth) were causing the abnormally high incidence of positive or reactive tests. The test, therefore, had great *sensitivity* but low *specificity*. The next modification tried was to dilute one part of serum with 199 parts of saline solution, and the FTA-200 test was born. This dilution method was found effective in increasing the *specificity* of the test so that patients other than syphilitics did not react to the test; however, the *sensitivity* of the test was so decreased that only about 20% of patients with known late syphilis were found to react to the FTA-200 test. As a result, a new modification has recently been developed by Deacon and associates, the *FTA-ABS* test. This is the test which is of primary interest in this report. The FTA-ABS test is based on treatment of

the patient's serum with an ultrasonically disrupted group of nonpathogenic treponemal antigens. Thus the antibodies to other treponemes are absorbed from the serum, and only those remaining to *Treponema pallidum* are finally tested with the fluorescein technique. This test has shown great sensitivity and specificity, as will be shown in some of the cases discussed here.

Although to one interested in syphilology no reason or explanation for this discussion is necessary, it is fair to point out to the ophthalmologist and neurologist the following points. With the advent of penicillin, the era of syphilis was thought by many clinicians to have passed. Indeed, the teaching of clinical syphilis declined to such a point by the end of World War II that in the past 20 years nearly a generation of physicians has entered practice with little knowledge and practically no exposure to the clinical features of late syphilis. All that is generally known is that a "blood test" should be obtained "routinely" on all hospital admissions, and that if the test is reported to be "negative," the diagnosis of syphilis can be dispensed with from a practical point of view. Furthermore, if the test be reported "positive," the patient might then well have a "biologic false positive" reaction. Such reactors often had even more interesting diseases, as disseminated lupus, other collagen vascular states, malaria, and the like. Finally, things went to such a point that many hospitals abandoned routine serologic testing for syphilis. However, the situation is rapidly changing. There has been a sevenfold rise in the incidence of infectious syphilis from 5,000 to 35,000 cases per annum in this country in the past five years. It is obvious that if primary and secondary syphilis are on the increase only the passage of time is necessary before the ophthalmologist and neurologist see a proportionate rise in late syphilis. However, that the problem is of far greater magnitude than can be imagined by investigators following reactive reagin test groups, is the burden of this discussion. In one community hospital, Jackson Memorial in Miami, over 200 cases of late seronegative syphilis have been detected within the past two years. Criteria for diagnosis in these cases have been the following: (1) a history of venereal infection, usually with inadequate treatment, (2) clinical signs of syphilis, and (3) a reactive specific treponemal test (TPI and/or FTA-ABS). If one considers that over 200 cases have been detected in patients with nonreactive reagin tests in one community, the number of cases of late syphilis in the population with nonreactive reagin tests (as VDRL) is staggering. It is obvious that this message must be promptly conveyed to ophthalmologists and neurologists and all practitioners in this country. Finally, even the efficacy of penicillin in the treatment of late syphilis has been questioned. Pierre Collart has reported the recovery of *Treponema pallidum* from human syphilitics who have been treated with 150 million (150 mega units) units of penicillin! The work of this French investigator has not as yet been confirmed but is under active investigation at this time. Clearly, the problem is a major one in medicine today, for as is well known, syphilis involves all

fields, being of equal interest to the ophthalmologist, neurologist, internist, cardiologist, psychiatrist, and neurosurgeon, to mention only a few of the more frequently involved specialists.

## CLINICAL MATERIAL

From the material available in the study to date, only a few cases of late ocular syphilis and neurosyphilis have been selected for presentation. The reason for this is that the cases must be carefully documented to offset any possible criticism from physicians who may think this is a rare problem. The serologic data have been analyzed for a part of the group, however. At the present time, approximately 90 sera a week are submitted from the Department of Ophthalmology of Jackson Memorial Hospital to the VDRL Laboratory in Atlanta for specific treponemal testing.

For this chapter, data obtained on patients between September 1963 and June 1964 has been analyzed. This is considerably less than one half of the series now available. In the nine-month interval stated, 417 sera were reported from Chamblee, Georgia, as being adequate for testing. Specimens broken in transit or bacterially contaminated or otherwise unsuited for testing were excluded. Of the 417 sera studied, 242 were negative to both TPI and FTA-ABS tests, 175 were positive to one of these two specific tests, and 115 were reactive to both of these tests. In other words, of the total of 417 sera, 41.9% showed a reactive test, whereas 58.1% were nonreactive.

Of the group of 175 sera with a reactive response, 115 or 65.7% reacted to both the TPI and FTA-ABS tests. Forty-nine of the reactive sera were detected only by the FTA-ABS test or were nonreactive to the TPI test. Thus, 49 of 175, or 28% of the reactive group, were nonreactive to the TPI test. Eleven of the 175 reactive sera were found to be reactive to the TPI test but nonreactive to FTA-ABS test. Thus, only 6.3% of the reactive cases were detected by the TPI test that would have been overlooked by the FTA-ABS test.

The standard reagin test (VDRL) was also performed on each of these sera. Of the 175 patients reactive to TPI and/or FTA-ABS tests, the VDRL was reported to be reactive (including weakly reactive responses) in 142 or 81% of the cases. Hence, 20% of the cases of late syphilis were seronegative as here defined.

The fact that 28% of the reactive group were serologically detected only by the FTA-ABS test is quite important, for these cases would have been missed even if the TPI test had been done. Dr. W. H. Taylor of our laboratory has recently reviewed our data and has found at least 82 cases to date which are nonreactive to VDRL, nonreactive to TPI, but reactive to FTA-ABS tests. The significance of this serologic syndrome (false negative TPI but reactive FTA-ABS tests) is therefore considerable. This is not stated to deprecate the TPI test, however, for the latter has stood the test of time and

is used throughout the world as the test by which all specific treponemal tests must be compared. Certainly the TPI test will detect the great majority of cases of late syphilis that are missed by the ordinary reagin tests. Dr. M. Brittain Moore, Jr., recently analyzed the data of the Tuskegee group and found that in a 30-year follow-up of 300 Negro men with untreated syphilis 97% reacted to FTA-ABS, 91% to TPI, 51% to VDRL, 21% to RPCF, and 19% to FTA-200 tests. The significance of this is readily apparent—for the diagnosis would be missed, serologically speaking, in one half the cases if only the VDRL test were used, and in nearly 80% of the cases if one used the Reiter protein complement fixation and the FTA-200 tests, both of which are being commonly performed by state health departments today. It is critical that one not confuse the FTA-200 test, which is poor in the detection of late syphilis, with the FTA-ABS test, which is excellent in the same group of cases!

Several cases will now be documented to illustrate numerous of the serologic syndromes which have been encountered.

*Case 1* (E. S.). This 73-year-old white male was seen on April 11, 1964, through the courtesy of Dr. M. B. Morgan. Two or three months previously, the patient had become aware of horizontal diplopia which had persisted. This was noted primarily with distant vision. No headache or other neurologic symptoms were present with the diplopia, and there were no other complaints. Dr. Morgan examined the patient, noted Argyll Robertson pupils, and kindly allowed us to see the patient as well. There was no history of diabetes.

Twenty years previously, the patient had been treated in Boston for syphilis. He stated that he had received heavy metal injections weekly for 18 months. Several spinal fluid examinations had been performed during that time. The patient stated that he had

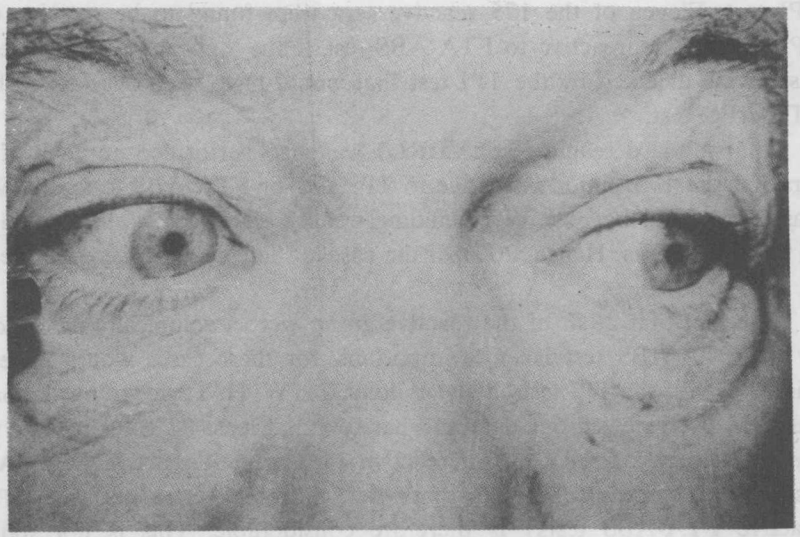

**Fig. 1-1.** Case 1 (E. S.). Fixing at distance, with the light on the right eye.

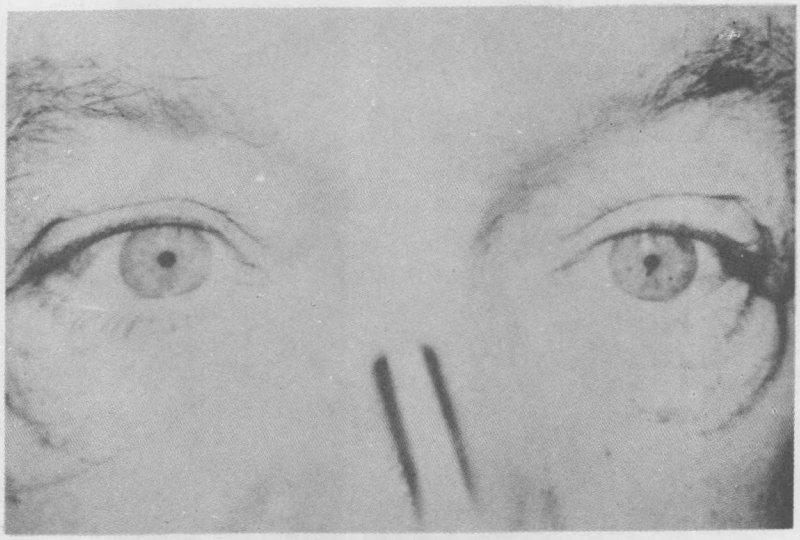

**Fig. 1-2.** Case 1 (E. S.). Fixing at near (April 11, 1964).

experienced serologic conversion to nonreactivity within a year of this therapy and had had no reactive reagin tests since, to his knowledge. There was no history of penicillin therapy at any time.

Ophthalmologic examination showed the corrected vision to be 20/25 in the right eye and 20/20 in the left eye. Classic Argyll Robertson pupils were present. The only other positive finding was minimal right abducens paresis. Intraocular pressure was 21 in the right eye and 25 in the left eye (applanation). Schiøtz values at the same time were 6.5/7.5 = 20.1 mm. in both eyes. Thirty minutes after the patient had drunk a quart of water in the nonfasting state, applanation tensions were 26 and 28. Biomicroscopy revealed marked iris atrophy in both eyes. The fundi were not remarkable.

Serologic studies revealed the following:

| | |
|---|---|
| 4-13-64 | serum VDRL, nonreactive |
| 4-14-64 | TPI, reactive |
| 4-14-64 | FTA-ABS, weakly reactive |

The impression was right abducens paresis, subsiding perhaps on a vascular basis, and Argyll Robertson pupils, with a history of syphilis treated with heavy metals.

*Comment.* Classic Argyll Robertson pupils were noted in this patient on eye examination. If the history of syphilis had not been revealed by the patient, a nonreactive serum VDRL test might have caused one to overlook the diagnosis. However, since there was a history of syphilis and heavy metal therapy for 18 months, and since both specific treponemal tests were reactive, there was no doubt that the pupils were associated with seronegative late syphilis.

*Case 2* (338627). This 54-year-old Negro woman was admitted to Jackson Hospital on April 12, 1964, with symptoms suggesting acute brainstem infarction. She had been well until the day of entry when she had suddenly developed headache, malaise, vomiting, vertigo, tinnitus, decreased hearing, and paresthesias. When she was examined in the hospital, patchy alopecia was noted on her scalp. A murmur of aortic insufficiency was heard, and her blood pressure was 180/80 mm. Hg. Fluoroscopy revealed a fusiform aneurysm of the ascending aorta.

Eye examination revealed corrected visual acuity of 20/20 in both eyes. The pupils showed classic light-near dissociation. Thus, the right pupil reacted nil to direct light,

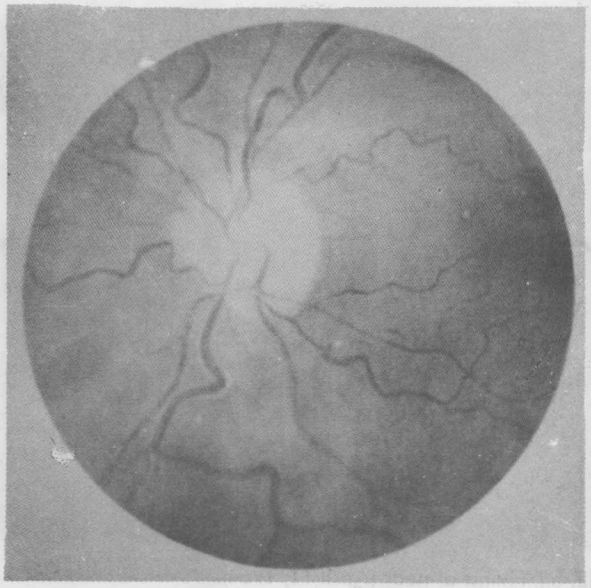

**Fig. 1-3.** Case 2 (W. E. S., 338627). This patient had patchy alopecia, Argyll Robertson-like pupils, aortic insufficiency, fusiform aneurysm of the ascending aorta, and perivenous sheathing in the fundi. This is the fundus of the left eye on April 14, 1964. The reagin test was nonreactive, but both specific treponemal tests were reactive.

but 3-4 + to near. The left pupil reacted only a trace to direct light, but again had a good 3-4 + response to near. Ophthalmoscopy revealed clear media and minimal blurring of the discs, arteriolar tortuosity was present, and definite sheathing was seen along the veins going out to midperiphery in both eyes (Fig. 1-3).

Because of the perivascular sheathing, hemoglobin eletrophoresis was made and revealed hemoglobin-A only. A sickle cell preparation was negative. Lumbar puncture revealed an opening pressure of 260 mm., clear colorless fluid, no cells, and a negative Pandy test.

Serologic studies revealed the following:

4-12-64 VDRL, nonreactive
4-12-64 TPI, reactive
4-12-64 FTA-ABS, reactive

*Comment.* Patchy alopecia, Argyll Robertson-like pupils, aortic insufficiency, fusiform aneurysm of ascending aorta, softening of the brainstem, and perivenous sheathing in the fundi were present in this woman, who had a nonreactive reagin test. The specific treponemal tests were both reactive, however, and confirmed the clinical evidences of late syphilis.

*Case 3* (A-16305). This 67-year-old white man was seen at the Coral Gables Veterans Administration Hospital on March 19, 1964. He had been hospitalized because of progressive urinary difficulty. A transurethral prostatectomy had been done in the hospital, but there was little symptomatic improvement. The patient was seen in neurologic consultation by Dr. Kenneth Kahn who noted classic Argyll Robertson pupils and early signs of tabes dorsalis. The patient admitted having had lightning pains and some difficulty with his gait and balance for several years. He denied any history of syphilis, however.

On eye examination, the corrected visual acuity was 20/20-1 in the right eye and 20/30 + 2 in the left eye. Classic Argyll Robertson pupils were noted. The pupils were thus small and a bit irregular; the left was slightly larger than the right. Neither pupil reacted to light but both responded nicely to the near reflex (Figs. 1-4 and 1-5). Visual fields were within normal limits to 1/330 white in both eyes. The eyes were white, motility was normal, and the fundi were not remarkable.

March 5, 1964, lumbar puncture had revealed normal pressure, no cells, clear fluid, protein 36 mg.%, and a nonreactive VDRL test.

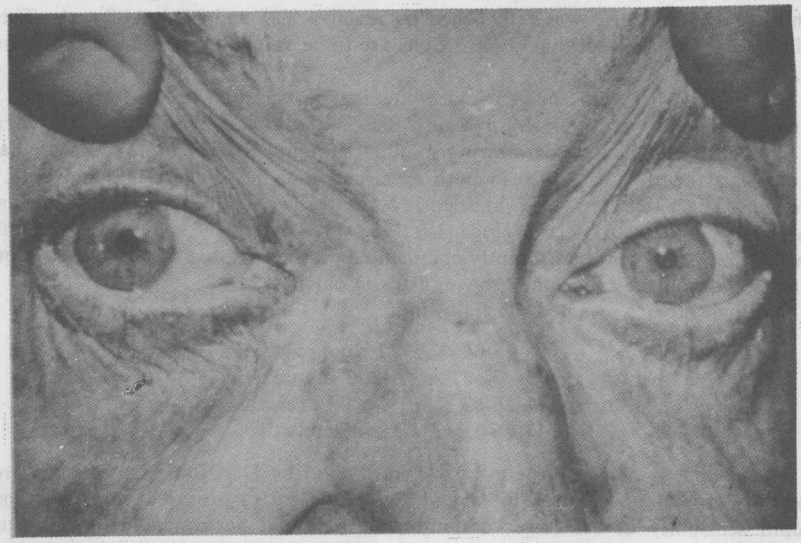

**Fig. 1-4.** Case 3 (H. G. A., A-16305). Patient with tabes dorsalis, fixing at distance.

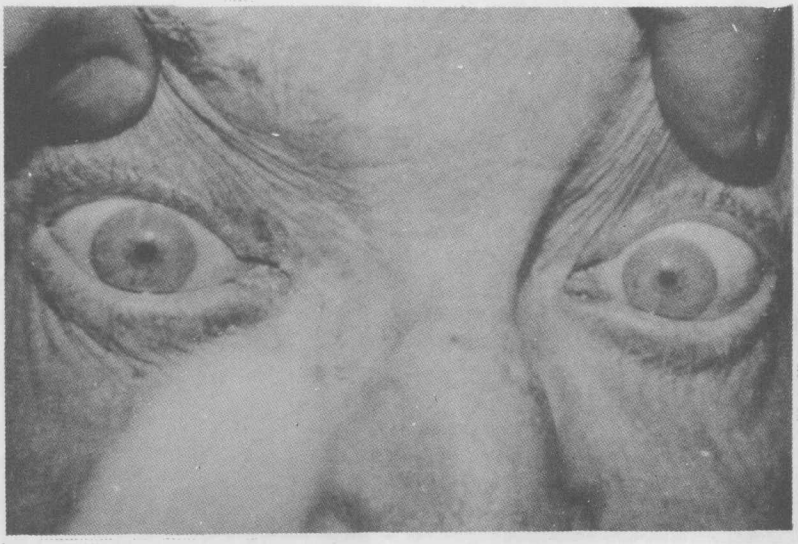

**Fig. 1-5.** Case 3 (H. G. A., A-16305). Patient with tabes dorsalis fixing at near.