Neuro-ophthalmological study of late yaws and pinta

II. The Caracas Project

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There are three major forms of treponemal disease in man: syphilis, due to *Treponema pallidum*; yaws, due to *Treponema pertenue*; and pinta, due to *Treponema carateum*. The spirochaetes that cause these diseases are morphologically indistinguishable. Furthermore, the diseases cannot be differentiated by any definite histopathological, serological, immunological, or therapeutic methods. The only two known ways of differentiating these treponematoses are (1) clinical criteria and (2) experimental infection of laboratory animals or human volunteers.

Ocular and neurological manifestations in late syphilis are of common occurrence and well recognized, whereas yaws is said to involve only the skin, mucous membranes, and osseous structures, and pinta to involve only the skin. To answer the specific question whether neuro-ophthalmological involvement occurs in late yaws or pinta, a cooperative study was initiated by the Department of Ophthalmology of the University of Miami School of Medicine and the National Institute of Venereology in Caracas, Venezuela. A team of investigators flew from Miami to Caracas in August, 1969, to investigate a group of 123 patients; there were three ophthalmologists, two neurologists, two internists, one epidemiologist, one dermatologist, one veterinarian, one serologist, and one ophthalmic photographer.

All of the 123 patients, who were identified by number only, were examined in the same way by the research team. They had been personally pre-selected by Dr. Rafael Medina, director of the National Institute of Venereology of Venezuela, to include three groups of cases: late yaws, late pinta, and controls. The controls were Venezuelans matched by age, sex, and culture, and included individuals with and without other forms of nontreponemal disease. No history was taken by the examining members of the team, and thus the only person aware of the clinical diagnoses was Dr. Medina. Approximately forty patients a day were

examined for 3 days. At the suggestion of the epidemiologist, the patients were numbered from 150 to 272, so that the memorizing of numbers would be reduced to a minimum. The studies performed on each patient are listed below.

Because of the large volume of data being obtained, there were rare instances in which the findings on some patients were incomplete. The complete data are presented in the Supplementary Tables A to E (see pp. 238 to 251), so that individual cases are available for review.

Various laboratories cooperated in this study. All serological tests and the routine cerebrospinal fluid studies were done at the National Institute of Venereology in Caracas. The immunofluorescent smears were examined in a double-blind manner by Dr. C. W. Israel and Mrs. E. K. Walter in Miami. Quantitative cerebrospinal fluid immunoglobulin determinations were performed by the Neurology Department, Jefferson Medical College in Philadelphia, through the courtesy of Dr. Norman J. Schatz.

The specific points of clinical interest emphasized in the examinations were as follows:

- I Blood tests
 - (1) VDRL (Venereal Disease Research Laboratory reagin test)
 - (2) TPI (*Treponema pallidum* immobilization test)
 - (3) FTA-ABS (Fluorescent treponema antibody absorbed test)
- II General physical examination
(inspection, chest, abdomen, blood pressure)
- III Neurological examination
(mental status, cerebellar signs, peripheral neuropathy, other abnormalities)
- IV Dermatological examination
(inspection of all patients stripped, with photographs of all lesions and punch biopsy of selected lesions)
- V Neuro-ophthalmological examination
(visual acuity at distance with E game, both with and without pin-hole aperture; external eye examination, with photographs of all pupillary

reactions; slit-lamp examination of any questionable anterior segment changes; dilated indirect ophthalmoscopy and fundus photographs of all patients)

VI Aqueous humour paracentesis (dark-field and fluorescent antibody smears)

VII Lumbar puncture
(description, cell count, Pandy, total protein, colloidal gold curve, CSF VDRL test, immunoglobulins, fluorescent antibody smears).

Findings

The volume of data obtained in the study is so large that it is presented in the supplementary tables, and the text is restricted to a summary of the findings and documentation of selected interesting patients. The magnitude of the investigative problem with regard to immunofluorescent smears bears mention. Smears of aqueous humour and cerebrospinal fluid were made on each patient in Caracas, air-dried, fixed in acetone, and then brought back to Miami. Dr. C. W. Israel and Mrs. E. K. Walter examined these slides with the immunofluorescent antibody stain for *Treponema pallidum* in a double-blind manner. They thus knew nothing whatever of the clinical or other laboratory findings in these cases. One hour was allotted to each slide for examination under oil immersion microscopy, and two to four slides per patient were usually scrutinized before a report was submitted. Because of time and financial restrictions, it was decided at the beginning of the project that only one year could be given to the immunofluorescent survey. In the year following the project, the two examiners completed the immunofluorescent study of the aqueous humour from 62 patients, cerebrospinal fluid from 56 patients, and both of these fluids from 48 patients. Thus the aqueous humour only was studied from fourteen cases, and the cerebrospinal fluid only from eight cases. The exact findings in all cases studied are listed in the Tables. The data on these 62 cases will constitute the final summary of immunofluorescent studies.

After the clinical, serological, and cerebrospinal fluid studies had been completed, Dr. Medina supplied a complete list giving his clinical diagnosis in each case. Before the data are discussed, eighteen cases of particular interest will be described in detail.

Case reports

Case 152, a 25-year-old woman, had 20/20 vision in both eyes. Some white spots were seen on her face. There was a Marcus Gunn pupil in the left eye. The fundi were normal but for equivocal macular changes. The serum VDRL, TPI, and FTA-ABS tests were all reactive. The cerebrospinal fluid revealed 2 white cells,

protein 21 mg. per cent., immunoglobulins over 11 per cent., nonreactive VDRL, and 2332211000 colloidal gold curve. Fluorescent antibody smears of the spinal fluid were negative, but revealed non-fluorescing spiral forms in the aqueous humour. The clinical diagnosis from Dr. Medina showed that this patient had been previously experimentally infected with *Treponema Fribourg-Blanc*.

COMMENT A young woman experimentally infected with *Treponema Fribourg-Blanc* revealed an absolute elevation of the immunoglobulins in the cerebrospinal fluid and an abnormal pupillary reaction in the left eye.

Case 153, an 80-year-old man, showed changes in the pupils and optic discs equivocal for his age. Neurological examination revealed a right Babinski response and a mild sensory neuropathy. All three blood tests were reactive, but the cerebrospinal fluid was negative. Fluorescent antibody smears of the aqueous humour revealed non-fluorescing spiral forms, but one treponeme was found in the aqueous humour which definitely stained with anti-*T. pallidum* globulin (Fig. 1). The clinical diagnosis in this case was late yaws due to natural infection.

FIG. 1 *Treponeme in the aqueous humour of Case 153, a patient with late yaws, stained with the fluorescent antibody stain for T. pallidum*

COMMENT A treponeme of excellent morphology which stained with the fluorescent antibody stain for *T. pallidum* was found in the aqueous humour of a white and quiet eye of an elderly man with known late yaws.

Case 154, a 42-year-old man, had 20/50 vision in both eyes, and showed definite light-near dissociation of the left pupil. Neurological examination was normal except for some rotary nystagmus seen on looking down and to the right. The serum VDRL test was reactive, but both the TPI and FTA-ABS tests were nonreactive. The cerebrospinal fluid was normal. Fluorescent antibody smears of aqueous humour revealed non-fluorescing spiral forms (Fig. 2, overleaf). The clinical diagnosis was that the patient had been previously experimentally infected with *Treponema Fribourg-Blanc*.

FIG. 2 Oil immersion photomicrograph of non-fluorescing spiral form in aqueous humour of Case 154, a patient previously experimentally infected with *Treponema Fribourg-Blanc*

COMMENT Light-near dissociation of the pupil was seen in a patient previously infected with *T. Fribourg-Blanc*, and a non-fluorescing spiral form was found in the aqueous humour.

Case 157, a 44-year-old woman, had a normal eye examination, but showed mild dementia, ataxia, and a snout reflex on neurological examination. Serum TPI and FTA-ABS tests were reactive. The spinal fluid had 4 white cells, protein 22 mg. per cent., nonreactive VDRL, and 1111220000 colloidal gold curve, but had an IgG level greater than 11 per cent. Non-fluorescing spiral forms were found in the aqueous humour of this

FIG. 3 Non-fluorescing spiral form found in aqueous humour of Case 157, a patient with late *yaws* due to natural infection

FIG. 4 Another non-fluorescing spiral form from aqueous humour of Case 157

patient (Figs 3 and 4). The clinical diagnosis was late *yaws* due to natural infection.

COMMENT This patient with known *yaws* showed an abnormal neurological examination, had an elevated immunoglobulin G in the cerebrospinal fluid, and showed non-fluorescing spiral forms in the aqueous humour.

Case 158, a 54-year-old female, showed an inflammatory lesion of the external eye (pingueculitis), definite light-near dissociation of the pupils, and perivascular scarring in the left optic fundus. Neurological examination of this patient was normal. Serum TPI and FTA-ABS tests were both reactive. The cerebrospinal fluid examination was normal. Fluorescent antibody smears revealed non-fluorescing spiral forms in the aqueous humour.

COMMENT This patient with a natural infection of late *yaws* revealed inflammatory lesions in the eyes and had abnormal pupils.

Case 169, a 41-year-old woman, had 20/20 vision in both eyes and the ophthalmological examination was negative. Some skin lesions were seen on the face. The neurological examination, however, revealed a suck-and-snout reflex, and evidence of moderate peripheral neuropathy. The serum VDRL test was reactive, but both TPI and FTA-ABS tests were nonreactive. The cerebrospinal fluid showed cells nil, protein 15 mg. per cent., and nonreactive VDRL, but a 1233331000 colloidal gold curve.

This patient had been selected by Dr. Medina as a control. The finding in Fig. 5 (opposite) was from an FA smear of cerebrospinal fluid, and may be an artefact.

Case 171, a 37-year-old woman, had normal general physical and neurological findings. Ophthalmological examination revealed 20/20 vision bilaterally and a slight injection of the eyes, and the discs were equivocally pale. These ocular signs were minimal, but the laboratory

FIG. 5 FA smear of cerebrospinal fluid from Case 169. This patient was a clinical control, but had a reactive serum VDRL test and an abnormal neurological examination. This apparent spirochaete may be an artefact

data were of great interest. All three serological tests (VDRL, TPI, and FTA-ABS) were nonreactive. The cerebrospinal fluid was normal. Despite this, immunofluorescent smears of aqueous humour from the patient's right eye revealed more than 12 spirochaetes of perfect morphology for *Treponema pallidum*, and these all stained with the immunofluorescent stain. Six of these treponemes

are seen in Figs 6 to 10. The clinical diagnosis from Dr. Medina was late yaws due to natural infection.

COMMENT There were slightly injected eyes and borderline disc pallor with normal routine blood and cerebrospinal fluid tests. However, numerous *spirochaetes* positive to FA stain were found in the aqueous humour of the right eye. This is the first demonstration of *spirochaetes* in the human eye in late yaws. Treponemes were seen in

FIG. 6 Treponeme from aqueous humour of Case 171, a healthy woman with seronegative late yaws. These organisms stained with FA stain

FIG. 7 Treponeme from aqueous humour of Case 171

FIG. 8 *Treponeme* from aqueous humour of Case 171

FIG. 9 Another spirochaete which stained with FA stain from the aqueous humour of Case 171. Note the perfect morphology of these organisms

FIG. 10 Two treponemes from the aqueous humour of Case 171, a patient with late seronegative yaws

seroreactive late yaws in Case 153, but this patient was an example of *seronegative late yaws*.

Case 174, a 60-year-old man, was of great interest on clinical examination in that a large central perforation of the bony palate (Fig. 11, opposite), pointed to a diagnosis of late yaws. Ophthalmological examination revealed 20/50 vision in the right eye and 20/30 in the left. The fundi showed definite evidences of previous inflammation with old pigmented peripapillary scarring in both eyes (Figs 12 and 13, opposite). A pigment clump in the periphery of left eye attested to this.

Laboratory studies revealed nonreactive serum TPI and FTA-ABS tests, but the cerebrospinal fluid contained 6 lymphocytes/cu. mm., protein 38 mg. per cent., and a 1111100000 colloidal gold curve, and the cerebrospinal fluid VDRL test was reactive. One slide of aqueous humour from the right eye was negative for organisms on FA stain.

COMMENT The clinical diagnosis of *late yaws* due to natural infection in this patient was confirmed by a large *palatal perforation*. Although the patient was seronegative to TPI and FTA-ABS blood tests, he had six leucocytes

FIG. 11 Large perforation of the palate in Case 174, a 60-year-old man with late seronegative yaws. Examination of the cerebrospinal fluid gave a reactive CSF VDRL test

FIG. 12 Right eye of Case 174. Note peripapillary scarring from previous inflammation

FIG. 13 Left eye of Case 174, a patient with late yaws. Note evidence of former inflammation around the optic nerve head

in the spinal fluid and showed a *reactive cerebrospinal fluid VDRL test*. Definite abnormalities in the optic fundi of this patient indicated former inflammation.

Case 175, a 47-year-old man, had a normal eye examination, except for cups in the optic discs which were suspicious either for glaucoma or congenital cupping. Neurological examination was otherwise normal. The clinical diagnosis of this patient was that of a healthy control, but laboratory tests revealed that the VDRL, TPI, and FTA-ABS tests were all reactive. The cerebro-

spinal fluid was normal. FA smears of the aqueous humour revealed non-fluorescing spiral forms (Fig. 14, overleaf).

COMMENT A healthy control revealed reactive VDRL, TPI, and FTA-ABS tests, showed cupping of the optic discs on clinical examination, and had non-fluorescing spiral forms in the aqueous humour.

Case 178, a 53-year-old man, had normal ocular and neurological examinations. All three blood tests were

FIG. 14 *Non-fluorescing spiral form in aqueous humour of Case 175. This patient was a control case, but was seroreactive to the VDRL, TPI, and FTA-ABS tests*

nonreactive, and the cerebrospinal fluid was normal. The clinical diagnosis by Dr. Medina was late syphilis. FA smears of aqueous humour from the right eye revealed non-fluorescing spiral forms (Fig. 15).

Case 182, a 58-year-old man, had a visual acuity of counting fingers at 1 ft. in the right eye, and 20/70 in the left. He informed the examiners that he had a 'corneal madre buba' or primary yaw of the cornea in the right eye! Fig. 16 shows the external appearance of his eyes, and Fig. 17 shows the abnormal fundus in the right eye. Neurological examination revealed slight cerebellar signs, mild ataxia, and some tremor of the hands. All three blood tests were reactive. The cerebrospinal fluid was normal

FIG. 15 *Non-fluorescing spiral form in aqueous humour of Case 178. The patient was said to have late syphilis, but clinical examinations gave normal results and all three blood tests were nonreactive*

except for an IgG greater than 11 per cent. FA smears were negative.

COMMENT *Corneal madre buba* or primary yaw of the cornea was found in this patient. He had *mild neurological signs*, was *seroreactive* to all tests, and had an *elevated CSF IgG level*.

Case 203, a 32-year-old woman, presented with acute inflammation in the left eye. The visual acuity was 20/100 in the right eye and 20/50 in the left. Slit-lamp biomicroscopy revealed an acute interstitial keratitis in the left eye (Figs 18 and 19, opposite). The clinical diagnosis was congenital syphilis. All three blood tests were reactive.

FIG. 16 *Corneal madre buba (primary yaw) in the right eye of Case 182. The patient's mother had active yaws at time of his birth and inoculation of the cornea occurred at that time, and he had active disease for first 6 months of his life*

FIG. 17 Fundus photograph of right eye of Case 182, showing corneal madre suba

The spinal fluid had 8 lymphocytes, protein 40, 1111100000 gold curve, and a reactive CSF VDRL test. FA smears were negative.

COMMENT This patient with known *congenital syphilis* was brought in to serve as a control for the project. She developed an *acute interstitial keratitis* in the left eye a day before the return visit. The CSF VDRL test was reactive.

Case 221, a 56-year-old woman, had a visual acuity of 20/25 in the right eye and 20/30 in the left, but showed definitely abnormal fundi with disc pallor and perivascular sheathing. Neurological examination showed slight cerebellar signs and rather marked evidence of peripheral neuropathy. Serum TPI and FTA-ABS tests were reactive. The cerebrospinal fluid was normal. The clinical diagnosis was yaws due to natural infection.

COMMENT A patient with late yaws showed definite *ophthalmoscopic abnormalities* with marked perivascular sheathing.

Case 249, a 69-year-old woman, had the most marked bilateral optic atrophy of any patient seen during the study. The best corrected visual acuity was 20/70 in both eyes. The discs showed unequivocal atrophy. Furthermore, neurological examination revealed evidence of dementia and the right ankle jerk was absent. The serum VDRL, TPI, and FTA-ABS tests were reactive. The cerebrospinal fluid revealed two non-fluorescing spiral forms, but was otherwise normal. One slide of the aqueous humour of the right eye was FA negative. The patient had had a natural infection with yaws many years before.

FIG. 18 Left eye of case 203, showing active acute interstitial keratitis due to congenital syphilis. This patient was a control case

FIG. 19 Left eye of Case 203, with darker exposure. This allows one to see the epithelioid cells at the back of the cornea in this case of active interstitial keratitis

COMMENT A seropositive patient with late yaws revealed unequivocal *primary optic atrophy* in both eyes.

Case 251, a 24-year-old woman, showed definite abnormalities on neuro-ophthalmological examination. Definite light-near dissociation of the pupils was present, and the discs were pale, more so on the right. Clinical examination was otherwise normal. Serum VDRL, TPI, and FTA-ABS tests were all reactive. The spinal fluid was of interest in that it contained 20 white cells per cu. mm., but the protein was 27 mg. per cent., the CSF VDRL was nonreactive, and the colloidal gold curve 0110000000. FA smears of aqueous and spinal fluid were negative.

COMMENT There was *light-near dissociation* of the pupils and *optic atrophy*, all three blood tests were reactive, and

FIG. 20 Skin changes of late pinta on the hand of Case 255. This patient also had interstitial keratitis (Fig. 21)

the cerebrospinal fluid was abnormal with a pleocytosis of 20 lymphocytes/cu. mm. Dr. Medina had put this patient in to serve as a positive control, for she had known recent syphilis.

Case 255, a 50-year-old woman, was of great interest in that she had typical skin changes of late pinta (Fig. 20), and also classical interstitial keratitis in both eyes on slit-lamp examination (Fig. 21). The visual acuity was 20/50 in the right eye and 20/25 in the left. There was moderate optic atrophy as well as the biomicroscopic evidence of interstitial keratitis. Neurological examination revealed that she was confused, showed definite cerebellar ataxia, had a snout reflex, and had 3+ peripheral neuropathy-like changes.

All three blood tests were reactive. The cerebrospinal fluid was normal and FA smears negative.

COMMENT This patient with late pinta had interstitial keratitis in both eyes. Definite abnormalities were found on neurological examination in addition to early disc pallor. All three serological tests were reactive.

FIG. 21 Corneal changes seen in Case 255, with late pinta. Slit-lamp examination revealed typical interstitial keratitis with ghost vessels and active blood flow in deeper layers of corneal stroma of both eyes

Case 258, a 30-year-old man, had 20/20 vision in both eyes but showed slightly irregular pupils with some light-near dissociation. The neurological examination was negative. All three blood tests were reactive. The cerebrospinal fluid was normal. Skin lesions were noted on the knee (Fig. 22). A biopsy of this area revealed a spirochaete on examination with Krajiian silver stain (Fig. 23, opposite). Dr. Medina later revealed that the patient had been given an experimental inoculation with pinta.

COMMENT Experimental pinta in this patient with irregular pupils was associated with skin lesions near the knee and a spirochaete was found on biopsy.

Case 259, a 19-year-old man, had bilateral 20/20 vision but showed interesting yellow-tan spots around the maculae in both eyes (Fig. 24, overleaf). Neurological examination revealed that he was confused and showed evidence of peripheral neuropathy. All three blood tests were reactive. The cerebrospinal fluid was normal. The clinical diagnosis was pinta due to natural infection.

COMMENT A subtle maculopathy was evident on ophthalmoscopic examination of a patient with known late pinta.

Case 268, a 40-year-old man, had normal visual acuity but old pigmented inflammatory lesions were seen in the left eye, along with some perivascular sheathing in the fundi. Neurological examination was normal. All three blood tests were reactive. The cerebrospinal fluid was clear, but contained 9 lymphocytes, protein 40 mg. per cent., nonreactive CSF VDRL, and 0023100000 colloidal gold curve; the IgG level was greater than 11 per cent. The clinical diagnosis was late yaws due to natural infection.

COMMENT A patient with late yaws showed evidence of inflammatory retinopathy. The cerebrospinal fluid contained 9 white cells and the IgG level was elevated.

FIG. 22 Skin lesions on knee in Case 258, a patient with an experimental inoculation with pinta. One of these areas was biopsied (Fig. 23)

FIG. 23 Krajiian silver stain of skin biopsy from Case 258

FIG. 24 Fundus photograph of Case 259, a natural infection with pinta. Subtle yellow-tan spots were seen around the macula in both eyes.

Discussion

Examination of this group of 123 patients known to comprise cases of late yaws, late pinta, and matched controls was performed with emphasis on the neuro-ophthalmological findings. After all the data had been obtained, the clinical diagnostic code was provided by Dr. Medina. This revealed that the total group contained 71 cases of late yaws, 11 cases of late pinta, and 41 negative and positive controls, including 21 individuals in good health, five experimentally inoculated with *Treponema Fribourg-Blanc*, and fifteen with known syphilis. Many correlations can be made with the data provided in the Supplementary Tables, and the interested researcher is invited to use them. Certain obvious conclusions can, however, be drawn.

There is no question but that eye lesions may be present in the patients with late yaws. These include the type of defects that might not previously have been detected without refined diagnostic techniques and equipment. Moderate disc pallor with 20/50 to 20/70 vision in elderly individuals, light-near dissociation of the pupils, peripheral perivascular sheathing, and pigmentation in the optic fundi were definitely found in patients with late yaws.

One might question whether the yaws was causally related to the neuro-ophthalmological lesions found in these cases. They were those known to be consistent with a diagnosis of late syphilis, another tre-

ponematoses. The patients involved in this study, however, came from areas highly endemic for yaws and pinta, in which syphilis was otherwise virtually unknown, and all had been followed for years by Dr. Raphael Medina and personally selected by him. Dr. Medina is the world authority on the non-venereal treponematoses, having had more personal experience with clinical yaws and pinta than virtually any other living physician. Of great interest was the fact that treponemes found in the aqueous humour of two patients with late yaws (Cases 153 and 171) were morphologically excellent and stained with the fluorescent antibody stain for *Treponema pallidum*. This is the first demonstration of the presence of spirochaetes in the human eye in late yaws. It should be noted that in both cases the eyes were clinically white and quiet. One of these two cases was seronegative and the other seroreactive.

Non-fluorescing spiral forms were found in the aqueous humour in fifteen cases. The clinical diagnosis was yaws in seven cases, *T. Fribourg-Blanc* infection in three, syphilis in two, pinta in one, and two were controls. One of the control cases (175) was reactive to all three blood tests, however. The non-fluorescing spiral forms were found for the most part in the aqueous humour specimens (15 cases), and were described in the cerebrospinal fluid in only one (Case 249). There is a real possibility that these spiral forms were artefacts. They were longer than pathogenic treponemes, thinner, and more tightly wound, with more uniform spirals. The aqueous humour specimens were obtained in disposable sterile plastic tuberculin syringes, whereas the spinal fluid specimens were in clean glass sterile Wassermann tubes. One might wonder if the non-fluorescing spiral forms were plastic shavings in the syringes. Because a new syringe was used for each case and because such non-fluorescing spiral forms are not ordinarily encountered with these syringes, photographs of several of these forms are provided in this paper to serve for study by other investigators. One should be cautious in interpreting the significance of non-fluorescing spiral forms. However, the organisms seen in Cases 153 and 171 were unquestionably true treponemes, on the basis of both morphology and staining characteristics.

The cerebrospinal fluid immunoglobulins were of interest in these patients. The IgG expressed as a percentage of total protein is not valid in cases with total proteins of less than 20 mg. per cent. In such cases, only an absolute IgG elevation (*i.e.* greater than 3.2 mg. per cent.) is significant. In this study there were nineteen cases with cerebrospinal fluid protein levels greater than 20 mg. per cent. which had an IgG percentage greater than 11 per cent.

These are listed in the Supplementary Tables. These nineteen cases included ten patients with late yaws, five with known syphilis, and two with experimental *T. Fribourg-Blanc* infection, and two controls. There was only one patient with a total CSF protein less than 20 mg. per cent., yet with an absolute elevation of spinal fluid IgG (Case 257). This patient had late yaws due to natural infection. Therefore, among twenty cases with elevated cerebrospinal fluid immunoglobulin levels, there were eleven cases of yaws. No case of pinta showed an elevated CSF IgG value. A count of five lymphocytes per cu. mm. or more in the spinal fluid was noted in eleven cases. The highest relative lymphocytic pleocytosis found was twenty cells, and this was in Case 251, a patient with known syphilis. White cells varying from 5 to 10 per cu. mm. were found in ten patients, six of whom had late yaws, whereas four were control patients. It should be emphasized that several of the control patients showed clinical signs of other diseases. The Supplementary Tables present all the clinical findings in such cases. Other CSF findings, however, were pertinent. The CSF VDRL test was reactive in five cases—two of syphilis (151 and 203), and three of late yaws (174, 252, and 270). Case 174 was previously cited as having a palatal perforation, being seronegative to both TPI and FTA-ABS tests, and yet having a reactive CSF VDRL test. This was a good example of seronegative late yaws. There is therefore no question that abnormalities have been found in the cerebrospinal fluid in several patients with late yaws. These have included modest lymphocytic pleocytosis, abnormal colloidal gold curves, and raised IgG levels.

The abnormal findings in the ocular and neurological examinations were mostly found in late yaws. Primary corneal yaws was seen in one case. Abnormal pupils, perivascular sheathing, and optic atrophy were seen in patients with late yaws. The clinical findings in patients with late pinta were less impressive, but the number of pinta cases was smaller. The most outstanding finding in pinta was concomitant interstitial keratitis in Case 255. A subtle yellow-tan perimacular retinopathy was seen in two or three patients with pinta, but this may have been a familial or abiotrophic process which was coincidental in these individuals. The importance of fundus photographs in documenting eye changes in such cases is evident.

Summary

A cooperative study of a group of 123 patients consisting of cases of late yaws, late pinta, and matched controls, was performed with emphasis on the neuro-ophthalmological findings. Ocular and neurological abnormalities were not found in cases of pinta,

with the single outstanding exception of one patient with pinta and bilateral interstitial keratitis. However, several patients with late yaws showed neuro-ophthalmological abnormalities. These consisted of light-near dissociation of the pupils, perivascular pigmentation, and vascular sheathing in the optic fundi, as well as moderate disc atrophy. These findings were often subclinical and required refined instrumentation for discovery, but their significance in the field of treponematoses is evident. Some abnormalities were noted in the cerebrospinal fluids of patients with late yaws. Elevated immunoglobulin G levels were found in the cerebrospinal fluids of eleven cases of late yaws, despite the presence of normal total protein levels in these fluids.

The most significant finding was the detection of spirochaetes in the aqueous humour of two patients with late yaws. These organisms stained with the fluorescent antibody stain for *T. pallidum*. One of the patients was seroreactive and the other was seronegative. Seronegative late yaws with a reactive cerebrospinal fluid reagin test was also observed.

This study is the first to report the presence of treponemes in the human eye in late yaws.

Étude neuro-ophthalmologique dans le pian tardif et la pinta

Le projet de Caracas

SOMMAIRE

Une étude coopérative de neuro-ophthalmologie fut entreprise sur un groupe de 123 malades atteints de pian tardif, de pinta tardive et de témoins appropriés. Dans les cas de pinta, il ne fut pas trouvé d'anomalie oculaire ou neurologique, avec une seule exception frappante d'un malade pintique présentant une kératite interstitielle bilatérale. À l'inverse, plusieurs malades atteints de pian tardif présentèrent des anomalies neuro-ophthalmologiques. Celles-ci consistaient en dissociation de la réponse de la pupille à l'éclairement de près, en une pigmentation péri-vasculaire et en engainements des vaisseaux du fond d'oeil aussi bien qu'en une atrophie discal modérée. Ces constatations furent souvent sub-cliniques et il fallut une instrumentation perfectionnée pour les découvrir. Cependant, leur importance dans le domaine des tréponématoses est évidente. On nota quelques anomalies dans le liquide céphalo-rachidien de malades ayant un pian tardif. Dans 11 cas de pian tardif, le LCR montrait une élévation du taux de l'immunoglobuline G, bien que le taux total des protéines fut normal dans ces liquides.

La constatation la plus importante fut celle de spirochètes dans l'humeur aqueuse de 2 malades ayant un pian tardif. Ces organismes présentaient le phénomène de la fluorescence avec l'anticorps préparé pour *T. pallidum*. Un des malades était séro-positif, l'autre séro-négatif. On a également observé, en cas de pian tardif, séro-négatif, une positivité du LCR.

Ceci est la première publication rapportant la présence de tréponème dans l'oeil humain en cas de pian tardif.

SUPPLEMENTARY TABLE A Ophthalmological findings

Case no.	Visual acuity			Pupils		Corneae		Disks		Fundus		Other findings	Eyes		
	R	L		N	L-N-D	A	N	Oncho	IK	A	N			IF	A
	20/25	20/50													
150				×			+			×		R 4th nerve palsy Impression R pupil smaller than left R 4th nerve paresis	Abnormal		
151	20/20	H.M.		×					gl.		×	History of glaucoma On 4 per cent. pilocarpine 3 times a day L corneal opacity since birth	Abnormal		
152	20/20	20/20		×					×		×	Maculae ± Impression Marcus Gunn pupil L White spots on face	Abnormal (L pupil)		
153				±			+		±				±		
154	20/50	20/50		×			×		×		±	Impression Definite L L-N D	Abnormal pupils ± fundi		
155	20/70	20/50			±		+		±		+		Abnormal fundi		
156	20/20	20/25					×		×		+	Perivascular pigment clump in L lower nasal artery	Abnormal fundi		
157	20/20	20/20		±			×		×		×		Normal (± pupils)		
158	20/50	20/50		+				+	×		×	Definite L-N D L pingueculitis and petivascular scarring	Abnormal		
159				±			×		×		×	L classic Duane's syndrome ± L-N D Otherwise N Possibly microfilari in aqueous	Abnormal (Duane's)		
160	20/50	20/50		±			×		±		×		± (pupils and disc)		
161	20/20	20/50		×			×		± I +		×	N except ± pallor L disc and one small pigment spot in R upper nasal artery	Abnormal to ± Another observer noted 1 + optic atrophy L disc		
162	20/30	20/50		×			×		×		×	L Epipapillary membrane	Normal		
163				×				4 +	×		×	N except corneal onchocercal changes	Normal (corneal oncho)		
164				×			×		×		×	Scared little 13-yr-old-girl	Normal		
165	20/40	20/40		×			×		×		×	Axenfeld's syndrome on slit lamp Arteriolar sclerosis	Normal		
166	20/20	20/20		×			×		±		×	Normal to one examiner Borderline disc pallor to another	Normal		

Key: R = Right
L = Left
N = Normal
A = Abnormal

Oncho = Onchocerciasis
IK = Interstitial keratitis
OA = Optic atrophy

IF = Inflammatory changes
Pilo = Pilocarpine
L-N-D = Light-near dissociation

Case no.	Visual acuity		Pupils		Corneae		Discs		Fundi		Other findings	Eyes
	R	L	N	L-N D	N	Oncho	N	OA	N	IF		
167	20/20	20/25	+		×	×	×	×	×		Anisocoria, R larger Definite L-N D Few onchocercal spots	Abnormal (pupils)
168	20/50	20/50		×			×		×	×	Slight perivascular pigmentary clumping in fundi ± Marcus Gunn on L	±
169	20/20	20/20	×		×		×		×		Some skin lesions on face Eyes normal	Normal
170	20/25	20/25		±			×			±	R facial asymmetry L upper nasal peripheral pigment spot	±
171	20/20	20/20	×		×			±	×		Eyes slightly injected Discs a little pale	Normal to ± discs
172	20/20	20/20	×		×		×		×	×	2 discrete metallic inflammatory lesions above L macula Some depigmentation on face	Abnormal (fundi)
173	20/20	20/20							×		Fundi normal	
174	20/50	20/30	×			w-b	×			×	Peripapillary scarring both eyes Pigment clump left eye Waite-Beetham lines	Abnormal (fundi)
175	20/20	20/20	×		×		gl		×		One examiner reported Elschnig No. 2 cups Another reported glaucoma: R 3-5, L 4/5-5; appplanation R 20, L 17 mm. Hg Patient to return for glaucoma examination	N except for enlarged cups
176	20/70	20/150		×	×		×			×	Classic retinitis pigmentosa-like changes Abnormal pupils 2+ Marcus Gunn L	Abnormal
177	20/30	20/30	×			×	×		×		Iris hamartoma L White spots on hands Fundi normal	Normal
178	20/30	20/25	×			×	×		×		N except one old onchocercal scar on cornea in slit lamp	Normal
179	20/20	20/20	×			×	±		×		N except ± disc pallor	Normal disc pallor ±
180	20/20	20/20		×	×		×		×		Equivocal anisocoria only	Normal
181	20/80	20/80	×		×		×			×	Disc pallor Macular scar Perivascular pigmented lesions Old scars on hands and feet	Abnormal (fundi)
182	1/200	20/70		×			×		×		R corneal madre buba	Abnormal
183	20/50	20/70		±		4+	×		×	×	L large pigmented lesion around a vessel at 1.30 o'clock	Abnormal (fundi)

Case no.	Visual acuity		Pupils		Corneae		Disks		Fundus		Other findings	Eyes
	R	L	N	L-N-D	A	N	Oncho IK	A	N	IF		
184	20/70	20/70	×			×			×		Cupping noted, more on L Periphery negative Tension 5/5.5 R 4/5.5 L	Abnormal (vision)
185	20/40	20/70		×			×		×		Old nummular corneal scars seen in slit lamp, more on R 1.5 + Marcus Gunn L ± disc pallor	Abnormal
186	20/70	20/70		+			+			×	R cornea onchocercal changes Definite L-N D Three peripheral chorio-retinal lesions	Abnormal (pupils and fundi)
187	20/20	20/20	×			×			×		Skin lesions of tinea	Normal
188	20/70	6/200	×				×		×		Tension 3/5.5 R 3.5/5.5 L	Abnormal (disks)
189	20/120	20/50	×	+			×			×	L one paramacular lesion	Abnormal (pupils) Fundus ±
190	20/25	20/30		+		×			×		Larger cup R disc R one small scar at 5.45 o'clock Closest to true Argyll Robertson pupils so far seen in Venezuela	Abnormal (pupils)
191	20/20	20/25	×			×			×		L ± disc pallor Otherwise normal except one small round pigmentary spot R upper nasal quadrant	Normal to ±
192	20/30	20/25		+		×			×		L ± temporal pallor Very suspicious L-N D	Abnormal
193	20/70	20/50	×					×	×		More cupping L Tension R 5.5/5; L 3.5/5.5 Referred to glaucoma clinic	Abnormal (cornea and cupping)
194	20/50	20/50	×			×				×	Definite primary optic atrophy, L more than R Peripheral pigmentation R	Abnormal (optic atrophy)
195	20/70	20/25		±		×			×		L pupil slightly irregular Borderline pallor R disc	± (pupils and disks)
196	20/25	20/20		a		×				×	Severe frontal bossing R pupil larger One scar above in R eye Full dentures	Abnormal
197	20/20	20/20	×			×				±	Sheathing of vessels on R disc Subtle pallor more on L	±
198	20/20	20/20	×			×			×			Normal
199	20/20	20/20	×			×			×		Slight pannus above R	Normal
200	20/20	20/20	×			×			×		? little temporal pallor	Normal to ± disc

Case no.	Visual acuity		Pupils		Corneae		Disks		Fundus		Other findings	Eyes
	R	L	N	L-N D	A	N	Oncho	IK	A	N		
201	20/20	20/20	×			×				×		Normal
202	20/20	20/20	×			×				×		Normal
203	20/100	20/50		×				×			×	Abnormal
204	20/20	20/20	×	×		×			+	×		Abnormal (optic atrophy)
205	20/50	12/200	×			×			×			Abnormal (congenital syphilis)
206	20/20	20/20	×			×			±		×	Abnormal (pupils)
207	20/50	20/30	×			×			×		×	Abnormal (pupils and fundi)
208	20/25	20/20	×			×			±			Normal
209	20/25	20/25	×			×			×			Normal
210	20/50	20/30	×			×			±			± pupils and discs
211	20/100	C.F.5		×				+		×		Abnormal
212	20/20	20/20		±		×			×	×		± Pupils to normal
213	20/20	20/20	×			×			×	×		Normal
214	20/50	20/30		±		×			×	×		± pupil
215	20/30	20/30		+		×			×		×	Abnormal (pupils)
216	20/40	20/30	×			×			±	×		Normal to ± discs
217	20/50	20/50		+		×			±		×	Abnormal
218	20/20	20/20	×			×			±			Normal to ±
219	20/25	20/20		±		×			×	×		Normal
220	anoph	20/70		×		×			gl.			Abnormal (glaucoma)

Case no.	Visual acuity		Pupils		Corneae		Discs		Fundi		Other findings	Eyes
	R	L	N	L-N D	A	N	Oncho	IK	A	N	IF	A
221	20/25	20/30	×			×					×	Abnormal (fundi) pupils ±
222	20/20	20/20	×			×				×		Normal to ± disc
223	20/20	20/20	×			×					±	± to normal
224	20/20	20/20	×			×				×		Normal
225	20/20	20/20	×			×				×		Abnormal (fundi)
226	20/20	20/20	×			×				×		Normal
227	20/20	20/25		×		×				×		Abnormal (fundi and pupils)
228	20/20	20/20	×			×				×		Normal
229	20/20	20/20		×		×				×		Abnormal (pupils)
230	20/25	20/25	×			×				×		Normal
231	20/20	20/20	×			×				×		±
232	20/20	20/20	×			×				×		Abnormal (discs)
233	20/20	20/20			±	×				×		±
234	20/30	20/20	×			×				×		Abnormal (optic disc R)
235	20/20	20/20		×							×	Abnormal (pupils) Fundi ±
236	20/20	20/20			±	×					×	Normal to ± (pupils and sheathing)
237												Normal
238	20/20	20/20			±	×				×		Normal
239	20/20	20/20			±	×				×		Normal

Case no.	Visual acuity		Pupils		Corneae		Discs		Fundi		Other findings	Eyes
	R	L	N	L-N D	A	N	Oncho IK	A	N	IF	A	
240	20/20	20/20	×			×			×		Asteroid R Thin lateral brows R disc pale L perivascular cupping	Abnormal (fundi)
241	20/50	20/30		×		×			×		Pupils slightly irregular Definite L-N D	Abnormal (pupils)
242	20/30	20/30	×	×		×			×		Definite L-N D	Abnormal (pupils)
243	20/50	20/30	×	×		×			×		Discrete yellow spots Some lens changes	Abnormal (fundi)
244	20/20	20/20		×		×			×		Optic atrophy R 2 + L 1 + 'Justice girdle' both eyes	Abnormal (fundi)
245	20/70	20/20			×	×			×		Congenital coloboma R disc with artery of hyaloid canal Sensory R exotropion R Marcus Gunn pupil	Abnormal
246	20/20	20/20		×		×			×		L-N D	Abnormal (pupils)
247	20/20	20/20		±		×			×		Suspicious pallor of discs One observer thought them probably normal	±
248	20/30	20/50		×		×			×		Definite L-N D Optic atrophy	Abnormal
249	20/70	20/70		×		×			×		Worst case of optic atrophy seen R L 2 +	Abnormal (optic atrophy)
250	20/50	20/30		×		×			×		Suspicious L-N D Few onchocercal spots Fundi hard to see, probably normal	Abnormal (pupils)
251	20/30	20/30		×		×			×		L-N D Disc pallor, more on R	Abnormal (pupils) Discs ±
252	20/20	20/20		±		×			×		Little bird eyes Shallow anterior chambers Deep cupping Tension 5.5/7.5 R 5.25/7.5 L 23.8 mm. Hg R 25 mm. Hg L Given pilocarpine 4 per cent. three times a day both eyes	Abnormal (glaucoma) Sent to glaucoma clinic
253	20/50	20/50		+		×			×		Pupils pathological L disc ± pallor	Abnormal (pupils)
254	20/30	20/30	×			×			×		Normal except slight disc pallor R	± disc

Case no.	Visual acuity			Pupils			Corneae			Disks		Fundus			Other findings	Eyes
	R	L		N	L-N	D	A	N	Oncho	ID	A	N	IF	A		
255	20/50	20/25		×					4+		×				Marked interstitial keratitis both eyes Optic atrophy R 1-2+ ; L trace Pinta scars	Abnormal (IK and optic atrophy)
256	20/20	20/20					±	×			×	×			Pupils sluggish	Normal
257	20/20	20/20		×				×			×	×			Some 'justice girdle' L only	Normal to ± fundi
258	20/20	20/20			×			×			±	×			L-N D Pupils slightly irregular ? Temporal pallor	Abnormal
259	20/20	20/20					±		×		×		×		L cornea old trauma scar Disks pale, right more Yellow-tan spots around maculae	Abnormal
260	20/20	20/20		×				×			±	×			? Temporal pallor both eyes Some peripapillary changes	±
261				×				×							Silent lithe 12-year-old Indian girl Vision apparently normal but would not co-operate in E test	
262	20/20	20/20		×				×								
263	20/25	20/20			×			×			±	×			R pupil slightly irregular updrawn at 4.30 o'clock Optic atrophy R 2+, L 1.5+	Abnormal
264	20/20	20/20		×				×			±	×			Discs suspicious Bounding pulse Tension 6/5.5 both eyes	
265	20/50	20/30			×			×			×	×			L-N D Optic atrophy, more on L	Abnormal
266	20/70	20/30		×				×			±		×		One observer thought discs suspicious of glaucoma Other thought normal Old chalazion right upper lid	± discs
267	20/50	20/25		×				×			×	×			Some lens changes	Normal
268	20/20	20/20			×			×			±		×		L Two pigmented inflammatory lesions Slight pallor L Sheathing 2+ L	Abnormal (fundus and pupils)
269	20/20	20/20		×				×			×	×			Congenital tortuosity of vessels Skin lesions on neck Equivocal Pupils	Normal
270	L.P.	20/20			×				×		×	×			R cornea huge scar with flat anterior chamber L Marcus Gunn pupil L definite primary optic atrophy	Abnormal (optic atrophy)
271	20/25	20/25		×				×			×	×				Normal
272	20/20	20/20		×				×							R 2+ L 3+ to light	

SUPPLEMENTARY TABLE B *Neurological findings*

Case No.	0-1-2-3* Mental status	0-1-2-3 Cerebellar	0-1-2-3 Neuropathy	Other findings	Impression
150	+2 (I)	0	0	None	Confusion for time and place
151	0	+3	0	Palmomental reflex Shoulder girdle atrophy	Left arm ataxia Cervical arthritis
152	Not seen				
153	0 (I)	0	1	Right Babinski sign	Mild sensory neuropathy
154	0	0	0	Nystagmus, rotational, down, right	None
155	0	2	1	None	Unsteady wide-based gait Ataxia Mild neuropathy
156	0	0	0	None	Normal
157	1 (I)	1	0	Migraine +4 Snout reflex	Mild dementia Finger-to-nose wavering
158	0	0	0	None	None
159	0	0	2	Duane's retraction syndrome	Peripheral neuropathy
160	0 (I)	0	0	None	
161	0 (‡L)	0	0	Snout reflex	
162	1 (I)	0	0	None	
163	0	0	1+	None	Mild sensory neuropathy
164	1 (I)	0	0	None	
165	0	0	0	None	
166	(±)	0	1	None	Mild sensory neuropathy
167	0	1	0	None	Finger-to-nose wavering
168	0	0	±	R Babinski sign ±	
169	0	0	2	Snout-suck reflex	Peripheral neuropathy
170	2	0	0	Snout reflex	Dementia
171	0	0	0	None	Normal
172	0	0	1±	None	Normal
173	0 (I)	0	0	R facial paresis	
174	0	0	0	Hole in palate	
175	1 (I)	0	1+	Cupping discs	
176	0	0	0	Friedreich's foot Retinitis pigmentosa-like fundi Overactive reflexes	Family history of ataxia
177	0 (I)	1	0	Overactive knee jerks	
178	0	1	0	None	
179	0	0	1+	Pallor optic discs	
180	0	0	0	R facial paresis, lower	
181	2	3	0	Spastic legs Gross leg ataxia	Memory poor

*(I) Illiterate (‡L) Semi-literate (±) Doubtful

<i>Case No.</i>	<i>0-1-2-3-*</i> <i>Mental status</i>	<i>0-1-2-3</i> <i>Cerebellar</i>	<i>0-1-2-3</i> <i>Neuropathy</i>	<i>Other findings</i>	<i>Impression</i>
182	0	1	0	Tremor of hands	Mild ataxia
183	0	0	0	Depressed ankle jerk Suck reflex	
184	2 (I)	0	+3	Overactive jaw jerk	Peripheral neuropathy confusion
185	0	2+	3	None	Peripheral neuropathy, moderate to severe
186	3	0	0	Snout	Dementia
187	1	0	0	None	
188	0	0	0	None	
189	0	0	0	Babinski signs	
190	1	0	3+	None	Peripheral neuropathy, moderate to severe
191	0	0	0	None	
192	0	0	1+	None	Mild neuropathy
193	1 (I)	0	0	None	
194	3+	3+	0	Suck reflex	Dementia Cerebellar ataxia
195	0	0	0	None	
196	0	0	0	None	
197	0	0	0	None	
198	0	0	0	None	
199	0	0	0	None	
200	0	0	0	None	
201	0	0	0	None	
202	0	0	0	None	
203	Not seen				
204	0 (I)	0	0	None	
205	0	0	1+	Saddle nose Congenital syphilis	Mild neuropathy
206	0	0	0	None	
207	0	0	0	None	
208	1+ (I)	1	0	Language problem Left Babinski sign	Ataxia Mild aphasia Diffuse encephalopathy
209	0	0	0	None	
210	0	0	0	None	
211	0	0	0	None	
212	3+	0	1+	None	Mild confusion Mild neuropathy
213	0	0	0	None	
214	0	0	0	Hysterical weakness and numbness left arm	Hysteria

Case No.	0-1-2-3-* Mental status	0-1-2-3 Cerebellar	0-1-2-3 Neuropathy	Other findings	Impression
215	0	0	0	None	
216	0	0	0	None	
217	0	1+	3+	Ankylosed ankle Attacks of screaming Confusion	Ataxia Neuropathy
218	0	0	1	None	Mild neuropathy
219	0	0	0	None	
220	2+	2+	0	None	Ataxia Confusion
221	0 (I)	1+	3+	Polyuria	Perhaps diabetic
222	1+	0	0	Disc pallor	
223	0	0	0	None	
224	0	0	2+	Undernourished	Peripheral neuropathy
225	0	0	0	None	
226	0	0	0	None	
227	0	0	0	None	
228	0	0	0	None	
229	0	0	0	None	
230	0	0	0	None	
231	0	0	0	None	
232	0	0	0	± pallor	
233	0	0	0	None	
234	0	0	+3	None	Peripheral neuropathy, moderate to severe
235	0	0	0	None	
236	0	0	0	None	
237	Not seen				
238	0	0	0	None	
239	0	0	1	Absent knee and ankle jerks	Peripheral neuropathy
240	0	0	0	None	
241	0	0	0	None	
242	0	0	0	None	
243	1+	0	2+	None	Moderate neuropathy
244	2+	1+	3+	None	Confusion Neuropathy
245	0	0	0	None	
246	0	0	0	None	
247	2+	0	0	None	

<i>Case No.</i>	<i>0-1-2-3* Mental status</i>	<i>0-1-2-3 Cerebellar</i>	<i>0-1-2-3 Neuropathy</i>	<i>Other findings</i>	<i>Impression</i>
248	2+	0	2+	None	Confusion Neuropathy
249	2+	0	0	Absent R ankle jerk	
250	0	0	3+	Snout-suck reflex	Moderate neuropathy
251	0	0	0	None	
252	1+ (I)	0	+1	Overactive knee jerk Palmomental reflex Snout reflex	Dementia Mild neuropathy
253	3+	0	3+	None	Dementia Neuropathy
254	0	0	0	None	
255	2 (I)	2+	3+	Snout reflex	Confusion Ataxia Neuropathy
256	1+ (I)	0	0	None	
257	0	0	0	None	Snout reflex
258	0	0	0	None	
259	3+	0	4+	None	Confusion Neuropathy
260	0	0	0	None	
261	0	0	0	None	Pinta
262	0	0	0	None	
263	3+ (I)	2+	2+	None	Confusion Ataxia Neuropathy
264	0	0	0	None	
265	0	0	0	None	
266	2 (I)	0	1+	Slow and clumsy	Confusion Mild neuropathy
267	1 (I)	0	0	None	
268	0	0	0	None	
269	0	0	0	None	
270	3+	0	0	None	Confusion Dementia
271	1+ (I)	0	1	None	Mild neuropathy
272	1+	0	1+	None	

SUPPLEMENTARY TABLE C *Fluorescent antibody data*

Case no.	Cerebrospinal fluid	Aqueous humour	Case no.	Cerebrospinal fluid	Aqueous humour
150	negative	NFSFs	187	negative	negative
151	negative	NFSF	188	1 questionable	negative*
152	negative	NFSFs	189	negative	negative
153	negative	NFSFs and FSF	190	negative	negative
154	negative	NFSFs	191	negative	—
155	negative	NFSF	192	negative	negative
156	negative	NFSFs	193	negative	negative
157	negative	NFSFs	194	negative	negative
158	negative	NFSFs (tight spirals)	195	negative	negative
159	negative	NFSFs	196	negative	negative
160	negative	negative	197	—	negative
161	negative	negative	198	negative	—
162	negative	NFSFs	199	—	negative
163	negative	negative	200	negative	negative
164	negative	—	201	negative	negative
165	negative	NFSFs	202	negative	NFSFs
166	negative	negative	203	—	negative
167	negative	negative	204	—	negative
168	negative	negative	205	—	negative
169	negative	—	206	—	negative
170	suspicious	negative	209	—	negative
171	negative	FSF	210	—	negative
172	negative	negative	211	—	negative
173	negative	negative	212	—	negative
174	—	negative	213	—	negative
175	negative	NFSFs	217	—	—*
176	negative	negative	244	negative	negative
177	negative	negative	245	negative	—
178	negative	NFSFs	249	NFSF	—
179	negative	negative	251	negative	negative
180	negative	negative	254	negative	—
181	1 possible	negative	255	negative	negative
182	negative	negative	258	—	—†
183	—	negative	259	negative	negative
184	negative	—	260	—	—*
185	negative	negative	268	—	negative
186	negative	negative			

*Skin biopsy Krajan negative

†Skin biopsy, 1 possible

SUPPLEMENTARY TABLE D

Summary of total protein findings

The IgG in percentage of total protein is not valid in cases with total protein less than 20 mg. per cent. In these cases, only an absolute IgG elevation (3·2 per cent.) is significant

I Nineteen fluids with total protein greater than 20 mg per cent. and with per cent. IgG greater than 11 per cent.:				
151	181	198	215	
156	182	200	220	
157	185	202	266	
162	186	211	268	
165	196	214		
II One fluid with total protein less than 20 mg per cent. with absolute elevation of IgG (3·2 mg per cent.):				
257				
III Fluids with total protein greater than 20 mg per cent. and IgG greater than 3·2 mg per cent. but not greater than 11 per cent.:				
None				
IV Seventeen fluids showing no significant elevation either in absolute IgG or in percentage of total protein:				
152	190	218	250	
155	193	226	263	
158	201	228		
159	205	236		
160	213	243		

SUPPLEMENTARY TABLE E Summary of CSF and serological findings in 123 patients

Case No.	Sex	Age (yrs)	Cerebrospinal fluid					Serology			Diagnosis
			Cells	Protein	VDRL	Pandy	Colloidal gold	VDRL	TPI	FTA-ABS	
150	M	52	—	21	NR	—	1111100000	R	R	R	Pinta, natural
151	M	58	2	43	R	+	1111110000	R	NR	R	Late syphilis
152	F	27	2	21	NR	—	2332211000	R	R	R	Experimental <i>Treponema Fribourg-Blanc</i>
153	M	80	—	19	NR	—	0011111100	R	R	R	Yaws, natural
154	M	42	2	21	NR	—	1111100000	R	NR	NR	Experimental <i>Treponema Fribourg-Blanc</i>
155	M	71	2	19	N	—	1111100000		NR	NR	Yaws, natural
156	M	45	—	38	NR	+	1222100000	NR	NR	NR	Experimental <i>Treponema Fribourg-Blanc</i>
157	F	44	4	22	NR	+	1111220000		R	R	Yaws, natural
158	F	54	—	17	NR	+	0111000000		R	R	Yaws, natural
159	F	54	—	38	NR	+	0111100000	R	NR	NR	Yaws, natural
160	F	52	2	29	NR	—	0111100000	R		R	Control
161	M	49	2	38	NR	+	1111100000	NR	NR	NR	Yaws, natural
162	F	57	2	27	NR	+	1212221000	R	NR	R	Yaws, natural
163	M	38	2	10	NR	—	1111100000	NR	NR	NR	Control
164	F	12	2	11	NR	—	0000000000		NR	NR	Control
165	M	43	1	24	NR	+	0111110000		NR	NR	Control
166	F	30	8	13	NR	—	1110000000	NR	NR	NR	Control
167	M	49	—	19	NR	—	1111000000	R	R	R	Yaws, natural
168	M	65	8	19	NR	—	0011100000	R	NR	R	Yaws, natural
169	F	41	—	15	NR	—	1233331000	R	NR	NR	Control
170	F	48	2	16	NR	—	0111100000	R	NR	R	Yaws, natural
171	F	37	2	15	NR	—	1111000000	NR	NR	NR	Yaws, natural
172	M	29	2	14	NR	—	1111000000	NR	NR	NR	Control
173	M	22	4	16	NR	—	1111100000	R	R	R	Yaws, natural
174	M	60	6	38	R	—	1111100000		NR	NR	Yaws, natural
175	M	47	—	15	NR	—	1111100000	R	R	R	Control
176	M	33	2	15	NR	—	1110000000	R	R	R	Congenital syphilis
177	M	42	—	30	NR	—	1110000000	R	R	R	Pinta, natural
178	M	53	—	16	NR	—	0000000000	NR	NR	NR	Late syphilis
179	M	18	—	16	NR	—	1111000000	NR	NR	NR	Congenital syphilis
180	F	23	—	11	NR	—	1000000000	R	R	R	Congenital syphilis
181	M	69	2	26	NR	—	0011111100	NR	R	R	Yaws, natural
182	M	58	2	20	NR	—	0011222000	R	R	R	Yaws, natural
183	F	46	—	16	NR	—	0112200000	NR	NR	R	Yaws, natural
184	F	36	2	14	NR	—	1111000000	R	R	R	Yaws, natural
185	M	85	—	29	NR	+	0000000000		NR	R	Yaws, natural
186	F	50	—	27	NR	—	1111100000	NR	NR	R	Yaws, natural
187	M	36	2	16	NR	—	0011110000	NR	NR	NR	Control
188	M	73	1	14	NR	—	0001110000	R	R	R	Pinta, natural
189	F	56	2	16	NR	—	0011222000	NR	NR	NR	Control
190	F	41	2	27	NR	—	0011221000	R	R	R	Yaws, natural
191	F	41	—	12	NR	—	1111100000		NR	R	Pinta, natural
192	F	42	2	11	NR	—	1111000000	NR	NR	NR	Control
193	M	48	4	26	NR	—	0011110000	R		R	Yaws, natural
194	F	56	—	12	NR	—	1111100000	R	R	R	Yaws, natural
195	F	39	—	12	NR	—	0000000000	R	NR	R	Yaws, natural
196	F	58	2	25	NR	—	1112220000	R	R	R	Late syphilis
197	F	42	—	21	NR	—	1111110000	NR	NR	NR	Yaws, natural
198	F	24	2	30	NR	+	1221100000	NR	NR	NR	Control
199	M	37	3	22	NR	—	0011111100	R	R	R	Yaws, natural
200	M	15	—	26	NR	+	1110000000	R	NR	R	Late syphilis
201	F	18	—	22	NR	—	1110000000	R	R	R	Yaws, experimental
202	F	42	—	28	NR	+	1120000000	R	R	R	Yaws, natural
203	F	32	8	40	R	+	1111110000	R	R	R	Congenital syphilis
204	F	45	2	14	NR	—	0000000000	NR	NR	NR	Yaws, natural
205	F	24	—	12	NR	—	1111000000	R	R	R	Congenital syphilis
206	F	37	2	16	NR	—	1111100000	R	R	R	Yaws, natural
207	F	48	—	16	NR	—	1120000000	R	R	R	Yaws, experimental
208	M	13	6	20	NR	—	1111000000	NR	NR	NR	Control
209	F	42	—	12	NR	—	0111100000	NR	NR	NR	Yaws, experimental
210	F	40	2	15	NR	—	0011111100	NR	NR	R	Yaws, natural
211	F	29	2	28	NR	+	0011110000		R	R	Congenital syphilis
212	F	26	—	12	NR	—	1111000000	R	R	R	Yaws, natural
213	F	15	6	19	NR	—	1110000000	R	R	R	Yaws, experimental

R = reactive
NR = nonreactive

Case No.	Sex	Age (yrs)	Cerebrospinal fluid					Colloidal gold	Serology			Diagnosis
			Cells	Protein	VDRL	Pandy			VDRL	TPI	FTA-ABS	
214	F	20	2	29	NR	+		0000000000	R	NR	NR	Experimental <i>Treponema</i>
215	F	29	3	24	NR	-		2211000000	R	R	R	<i>Fribourg-Blanc</i>
216	F	23	2	19	NR	-		1111000000	R	R	R	Congenital syphilis
217	F	66	-	12	NR	-		0111100000		R	R	Congenital syphilis
218	F	32	-	12	NR	-		0110000000	NR	NR	NR	Pinta, natural
219	F	25	2	13	NR	-		0011110000		R	R	Control
220	F	65	2	30	NR	+		1111100000	R	R	R	Experimental <i>Treponema</i>
221	F	56	-	13	NR	-		0000000000		R	R	<i>Fribourg-Blanc</i>
222	F	33	2	15	NR	-		1110000000	R	R	R	Yaws, natural
223	F	16	-	16	NR	-		1110000000	R	R	R	Yaws, natural
224	M	11	1	25	NR	-		0001110000		NR	NR	Pinta, natural
225	M	48	2	21	NR	-		0000000000	R	R	R	Control
226	M	40	2	14	NR	-		1111100000	R	R	R	Yaws, natural
227	F	23	-	15	NR	-		0110000000	R	R	R	Syphilis, recent
228	F	19	2	15	NR	-		0000000000			NR	Yaws, natural
229	F	10							R	R	R	Yaws, experimental
230	M	18	4	19	NR	0		0111000000		NR	NR	Yaws, natural
231	M	34	-	14	NR	-		0000000000	R	NR	R	Control
232	M	17	-	14	NR	-		0111000000		NR	NR	Yaws, experimental
233	M	40	-	12	NR	-		1111000000		R	R	Yaws, natural
234	F	32	-	15	NR	-		0011000000	NR	NR	NR	Experimental <i>Treponema</i>
235	M	38	2	12	NR	-		1111000000	R	R	R	<i>Fribourg-Blanc</i>
236	M	39	-	19	NR	-		0011000000	R	R	R	Control
237	M	27							NR	R	R	Yaws, natural
238	M	37							R	R	R	Yaws, natural
239	F	47	-	19	NR	+		0011000000	NR	R	R	Yaws, natural
240	F	33	-	19	NR	-		1111100000	R	R	R	Yaws, natural
241	F	36	5	30	NR	-		0112110000	NR	NR	NR	Control
242	F	51	3	19	NR	-		1111100000	R	R	R	Yaws, natural
243	F	55	3	20	NR			0000000000	R	R	R	Yaws, natural
244	F	67							R	R	R	Yaws, natural
245	F	43	±	15	NR	-		1111000000	NR	NR	R	Yaws, natural
246	F	33	2	28	NR	-		0111100000	NR	NR	NR	Control
247	F	24	5	12	NR	-		1111100000		NR	NR	Control
248	F	59	1	14	NR	-		0111000000	R	R	R	Yaws, natural
249	F	69	1	15	NR	-		1111000000	R	R	R	Yaws, natural
250	F	53		40	NR	-		0211211000	NR	NR	NR	Yaws, natural
251	F	24	20	27	NR	-		0110000000	R	R	R	Syphilis, recent
252	F	50	10	40	R	-		2332200000	R	R	R	Yaws, natural
253	F	50	1	19	NR	-		0111000000	R	NR	NR	Yaws, natural
254	F	42	2	18	NR	-		1111000000	R	R	R	Yaws, natural
255	F	50	-	25	NR	-		1111000000	R	R	R	Pinta, natural
256	M	50	1	35	NR	-		0111000000	R	NR	R	Yaws, natural
257	M	41	-	16	NR	-		0110000000	R	R	R	Yaws, natural
258	M	30	-	30	NR	-		0111000000	R	R	R	Pinta, experimental
259	M	19	-	24	NR	-		1111000000	R	R	R	Pinta, natural
260	M	12	1	25	NR	-		0011000000	R	R	R	Pinta, natural
261	F	13							R	R	R	Pinta, natural
262	M	34	-	25	NR	-		0111000000	R	R	R	Yaws, natural
263	M	44	1	16	NR	-		0110000000	R	R	R	Yaws, natural
264	M	36	4	16	NR	-		1111000000	R	NR	R	Yaws, natural
265	M	44	-	16	NR	-		1111100000	R	R	R	Yaws, natural
266	M	59	3	36	NR	+		0232000000	R	NR	R	Yaws, natural
267	M	49	3	26		-		0211100000		R	R	Yaws, natural
268	M	40	9	40	NR	-		0021100000	R	R	R	Yaws, natural
269	M	36	1	32	NR	-		0011200000		NR	R	Yaws, natural
270	M	40	7	45	R	+			R	R	R	Yaws, natural
271	M	50	2	28	NR	-		0011111100	R	R	R	Yaws, natural
272	M	16							NR	NR	NR	Control