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Effect of repeated ivermectin treatments on ocular onchocerciasis: evaluation after six to eight dosings

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Abstract In 26 villages (1987 population 12,302), hyperendemic for savanna onchocerciasis in North Cameroon, ivermectin was distributed annually between 1987/89 and 1995. Each year until 1992, ophthalmologic examinations were performed before treatment. A final examination was made in 1995. The effects of ivermectin on ocular onchocerciasis were assessed by following (a) the ophthalmologic indices in three cohorts of males recruited before treatment in 1987, 1988 and 1989, who were treated and examined annually, and (b) the indices recorded yearly in the cross-section of males aged 15-19 years. The indices in 1995 from patients who had received up to eight doses were compared with those calculated before treatment in individuals of similar age. In the cohorts, the prevalences of microfilariae in the anterior chamber (MFAC) and of punctate keratitis (PK) recorded in 1995 were markedly reduced; there was a non-significant decrease in sclerosing keratitis (SK), and a significant worsening in the fundus indices in the cohorts. The cross-sectional analysis showed significant decreases in the prevalences of MFAC, PK and SK, and a significant increase in the mean visual acuity; there was no significant change in any fundus index. The findings suggest that repeated ivermectin treatment does not prevent the appearance of initial retinal lesions or the worsening of existing retinal lesions.

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Key words Onchocerciasis; ocular lesions; ivermectin; keratitis; visual acuity; Cameroon

Introduction *Onchocerca volvulus*, the cause of human onchocerciasis, is a filarial worm which parasitizes more than 17 million people, 99% of them living in rural areas of Africa. The pathogenic stages of this parasite, the microfilariae (mf), live in the dermis and all the ocular tissues. Their presence, accumulation and death cause the dermal and, above all, the ocular complications of the disease. The ocular lesions may lead to blindness, and some 200,000 persons in Africa are blind because of onchocerciasis.¹

For some 10 years, most onchocerciasis control has been based on large-scale distributions of ivermectin. Numerous studies demonstrated that a single dose of ivermectin brings about a rapid and long-term reduction in the microfilarial load in the skin, and that the drug can be distributed safely on a large scale without a special monitoring strategy except in those areas where *Loa* filariasis is also endemic. Many studies have been conducted to investigate the effect of ivermectin on ocular onchocerciasis. The results of phase II and III trials, conducted on small numbers of subjects, showed that a single dose of ivermectin markedly reduced the number of mf in the anterior chamber of the eye,²⁻⁶ and suggested that some severe and potentially blinding anterior segment lesions, such as sclerosing keratitis and iridocyclitis, may also be improved by ivermectin treatment.⁷⁻¹⁰ In contrast, relatively few data are available on the effect of ivermectin treatment on the posterior segment onchocercal lesions, i.e. optic nerve disease and chorioretinitis. The first studies suggested that ivermectin treatment did not result in either an exacerbation or an improvement of pre-existing fundus lesions,^{7,11-14} although in some cases ivermectin appeared to prevent the appearance of early retinal lesions.¹⁵ Long-term follow-up of patients demonstrated that repeated ivermectin treatments may reduce the incidence of onchocercal optic nerve disease (OND),¹⁶ or even bring about a regression of the OND.¹⁷

A phase IV trial of ivermectin against onchocerciasis was conducted from 1987 to 1995 in the Vina valley (North Cameroon). One objective of this study was to evaluate the effect of repeated annual ivermectin treatments on onchocercal ocular lesions, and to assess the potential of the drug to prevent some of them. The effects of the two first treatment rounds have been reported previously.¹⁸ This paper reports the results recorded after 6-8 distributions.

Patients and methods

STUDY AREA The Vina valley has been described in detail previously.^{18,19} Briefly, it lies in a Sudan-savanna area and is limited on the north and on the south by two ranges of mountains rising up to 1,920 m. The study area was located in the downstream half of the valley, between the villages of Ndok on the west and Bogdibo, near the boundary with Chad, on the east. This zone includes the town of Touboro, whose population is about 10,000 persons, and 26 villages that lie on a road that runs along the left bank of the Vina River (Fig. 1). The total popu-

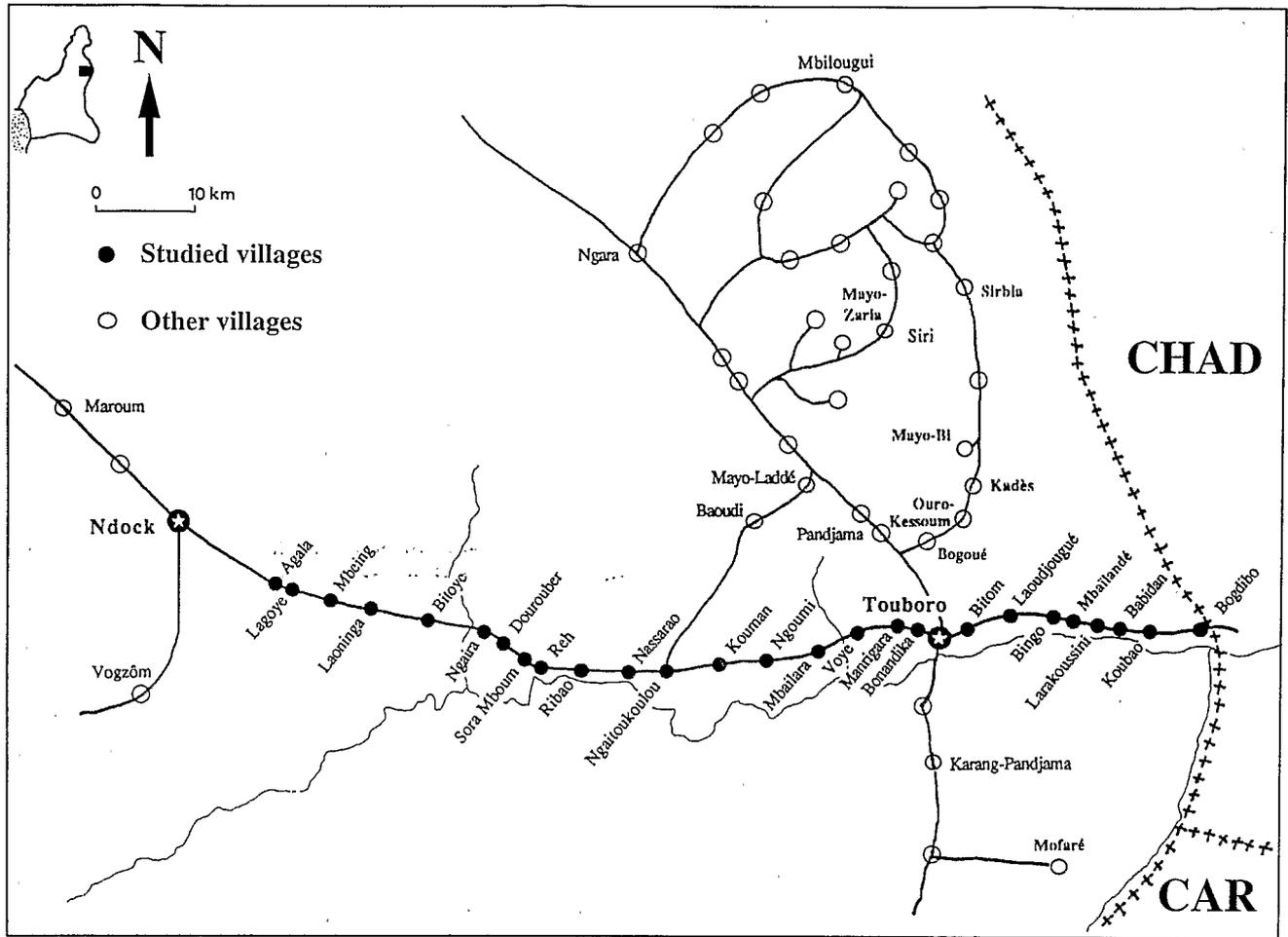


Fig. 1. Map of the Vina Valley.

lation recorded in these villages during the nationwide census of 1987 was 12,302 people. The major occupations are subsistence agricultural farming and cultivation of cotton.

The Vina valley is part of the vast Vina-Pende-Logone onchocerciasis focus, which extends across Cameroon, the Central African Republic, and Chad. In this area, the disease causes severe ocular complications.²⁰ Parasitologic examinations were performed before the first ivermectin distribution, using the method recommended by the Onchocerciasis Control Programme in West Africa (OCP).^{18,19} Two classical indices used in OCP were calculated to evaluate the initial levels of endemicity in the study area: the age- and sex-standardized prevalence of skin mf in people 5 years of age and older (PMF),²¹ and the community microfilarial load (CMFL), i.e. the Williams' geometric mean number of mf per skin snip among adults 20 years of age and older.²² These surveys showed that all the 26 villages of the study area were hyperendemic for onchocerciasis (i.e. with a PMF $\geq 60\%$). However, differences were found between the villages, both the prevalence and intensity of infection tending to increase gradually from west to east: in the eight villages located between (and including) Agala and Sora Mboum (total population in 1987: 2,683), the CMFL ranged from 20 to 40 mf per skin snip (mf/ss); in the ten villages located between Reh and Bonandika (total popula-

tion: 4,817), the CMFL ranged from 50 to 120 mf/ss; and in the eight villages located between Bitom and Bogdibo (total population: 4,802), the CMFL exceeded 150 mf/ss.¹⁹ No vector control operation had ever been conducted in the area. Ivermectin was available only through the distributions organized by the team involved in the present study, and no diethylcarbamazine had been available since 1987.

TREATMENT The five villages located between Bonandika and Ngoumi were treated for the first time in 1987; a second round was organized in these communities six months later in 1988, and then treatments were distributed annually until 1995. The 13 villages located between Kouman and Agala were treated for the first time in 1988, and then annually until 1995. The eight villages located between Bitom and Bogdibo were treated annually from 1989 to 1995. All treatments were distributed free of charge by mobile teams.

The treatment was given at a dose of 150 µg/kg of body weight. Pregnant women, mothers breastfeeding babies less than one month of age, children less than 5 years of age, and patients with severe clinical illness were excluded from treatment. The reactions were monitored and treated by mobile teams during the 48 hours following the distribution.

STUDY POPULATION AND EXAMINATION SCHEDULE At the outset of the study, just before the first ivermectin treatment, the ophthalmologic examinations were limited to males 15-45 years of age. This choice was based on the conclusions of former studies suggesting (1) that the incidence of first severe ocular lesions due to onchocerciasis was maximal, and their progression more rapid, in this age group;^{23,24} and (2) that the risk of appearance of a new lesion was proportional to the microfilaridermia in those individuals aged 10 to 45.²⁵ The 15-45 years age group was thus particularly appropriate to assess the effect of the post-treatment reduction in the microfilarial load on the evolution of severe onchocercal ocular lesions.

Every year until 1992, ophthalmologic examinations were carried out just before ivermectin distribution. In 1993 and 1994, ivermectin treatment was not preceded by an ophthalmologic examination but a final and full eye examination was made in 1995. At each round, all the persons from whom pre-treatment ophthalmologic data were available were convened to be re-examined, even if they had turned 45 years. At the same time, the residents of the villages who had just reached 15 years of age, and who had presumably already received one or more doses of ivermectin, were prompted to attend a first ophthalmologic examination. This was done in order to conduct an analysis of cross-sectional groups of patients (see below) and a particular effort was made to achieve a high examination coverage among these individuals; this included detailed explanations on the objective of the cross-sectional study, on the usefulness of the data obtained from their ocular examination, and on the importance of avoiding the possible bias that could be associated with a low participation.

As outlined above, the treatment area, which included only five villages in 1987, was extended in 1988, and again in 1989. Each year from 1987 to 1989, a new cohort was recruited, consisting of males 15-45

years of age who received their first dose of ivermectin and underwent their first (pre-treatment) ophthalmologic examination. These cohorts were named cohort 1987, 1988, and 1989, respectively. Although parasitologic examinations were not performed on all the patients who underwent ophthalmologic examinations, the parasitologic results obtained before the outset of the study strongly suggest that the patients belonging to the cohort 1989 were initially more heavily infected than those belonging to the two other cohorts; and that, conversely, the persons belonging to the cohort 1988 probably harbored lower microfilarial loads than the others.

OPHTHALMOLOGIC EXAMINATIONS The full name and age of every patient was recorded before examination. Visual acuity, including pin-hole acuity, was measured separately for each eye, using a Snellen illiterate E chart at 5 m distance. The optotypes were designed on a decimal scale. For measuring visual acuity below 1/10, the subject was placed successively at 4 m, 3 m, 2 m, and 1 m from the chart, until he was able to read the larger optotype; the visual acuity corresponding to these distances was recorded as 0.8/10, 0.6/10, 0.4/10 and 0.2/10, respectively. When the patient was not able to read the larger optotype at a distance of 1 m, he was asked if he had light perception or not. The visual fields were not tested.

Ophthalmologic examinations were performed by one ophthalmologist in 1987, and, at each subsequent round, by four ophthalmologists out of a team of six. A session was organized before each round to standardize both the methods of examination and the definitions of lesions. For the posterior segment lesions, the standardization was done using fundus photographs taken during the previous examinations, and examined independently by the different examiners. The lesions were graded in a blind manner by each ophthalmologist, and then the grades for a given lesion were compared. Agreement between the different examiners was measured using the kappa statistic.

Anterior segment examination was done using a Haag-Streit slit-lamp, with $\times 25$ magnification. It was performed after the subjects had sat with their heads lowered between their knees for at least 3 minutes in order to facilitate and standardize counting of mf in the anterior chamber (MFAC). The number of MFAC and the number of corneal stromal opacities corresponding to punctate keratitis (PK) were counted in each eye. The mf in the cornea were recorded as present or absent, but not counted. Details on the severity of sclerosing keratitis (SK), iritis, and cataract were recorded. The ocular pressure was measured by applanation tonometry after the examination of the anterior segment. Posterior segment examination was carried out using direct ophthalmoscopy after pupil dilatation with tropicamide.

GRADING OF SIGNS AND LESIONS The results of the examinations were recorded on a standardized form with alternative obligatory replies (no: 0 – yes: 1). This form included sections corresponding to all the possible ocular signs or lesions possibly related to onchocerciasis. MFAC and PK counts were scored as 0 when 0; 1 when one to four; 2 when five to 19; and 3 when greater than 20. An SK was scored as 1 when the

lesion involved the nasal or temporal periphery or both; as 2 when the lesion was semilunar but did not cover the pupil area, and as 3 when the lesion covered the pupil area. For the chorioretinal lesions, both the location (in the macular region, temporal to the macula, nasal to the macula, in the peripapillary region, in other sites, and diffuse lesions) and the severity of the lesions were recorded. With regard to the latter point, the changes were defined as follows: (a) mottled appearance (corresponding to early disturbance of the retinal pigment epithelium (RPE)); (b) confluent atrophy of the RPE; (c) tigroid appearance (corresponding to a combined atrophy of the RPE and choriocapillaris allowing a view of the choroidal vessels that still appeared normal in color and diameter); (d) large areas of atrophy of the RPE and choriocapillaris, with sclerosis of the underlying choroidal vessels which appeared as pale or whitish chords. In the analysis, changes (c) and (d) were amalgamated as advanced chorioretinitis. The possible changes in the optic disc were the following: pallor, swelling, and optic atrophy (OA). The presence of vascular sheathing was also recorded. The assessment of a difference between a disc pallor and an OA may sometimes be subjective. For statistical analysis, it was thus decided that an OA would be defined by the presence of a disc pallor accompanied by a vascular sheathing and a pinhole visual acuity less than 1/10.

INDICES USED FOR STATISTICAL ANALYSIS

Prevalence of blindness and low 'community mean visual acuity' Blindness was defined according to the World Health Organization's criteria, i.e. as an acuity less than 1/20 in the better eye. In addition, a "community mean visual acuity" (CMVA) was calculated to compare the visual acuity between groups of subjects. This was done following a three-step procedure. Firstly, for each eye, the value recorded for analysis was as follows: when the visual acuity was $x/10$, with $x \geq 1$, the value used was x (x thus ranging from 1 to 10); for visual acuity equal to 0.8/10 or 0.6/10, the value used was arbitrarily 0.1; for visual acuity equal to 0.4/10 or 0.2/10, the value used was arbitrarily 0.05; the values corresponding to perception of light and no perception of light were arbitrarily 0.01 and 0.001, respectively. Secondly, for each subject, an individual mean visual acuity was defined as the geometric mean of the values recorded for each eye. Thirdly, at the community level, the CMVA was defined as the geometric mean of the individual mean visual acuities.

Prevalence of lesions Prevalences were calculated for some onchocercal ocular signs and lesions: presence of MFAC, punctate keratitis, sclerosing keratitis, chorioretinitis, and optic atrophy. The different stages of sclerosing keratitis were not taken into account in analysis because the number of patients showing this type of lesion was small. The data on iritis were not analyzed for the same reason.

Scores The main objective of the study was to evaluate the effect of ivermectin on the posterior segment lesions, i.e. chorioretinal and OND. As the severity of these lesions depends on two characteristics, namely their stage of evolution (early or advanced, following the appearance of

the lesion) and their extent, we tried to combine these two types of data by calculating a chorioretinal score and an optic disc score for each eye. Specific software programs were created to calculate the scores.

The stage of evolution of a chorioretinal lesion was scored as 2 for an early disturbance (mottling appearance) or a confluent atrophy of the RPE, as 3 for a tigroid appearance, and as 4 when there was an atrophy of the RPE and the choriocapillaris, accompanied by sclerosis of the choroidal vessels. The extent of the lesion was scored as 1 when it was limited to the areas temporal to the macula, nasal to the macula, or in the peripapillary area, as 2 when it concerned the macula, and as 3 when the lesions were diffuse. For a given eye, the score was calculated as follows: (score of appearance \times 2/3) + (score of location \times 1/3). A greater weight was given to the score of appearance because it was assumed that the effect of ivermectin, if present, would become apparent on the pathologic evolution earlier than on the extent of the lesion. For a given patient, the chorioretinal score was the arithmetic mean of the scores calculated for each eye. At the community level, a mean retinal score was calculated. This was defined as the geometric mean of the individual scores. With regard to the optic disc, a swelling or pallor was scored as 2, a non-excavated optic atrophy was scored as 4, and the presence of vascular sheathing was scored as 1. For a given patient, the optic disc score was the arithmetic mean of the scores calculated for each eye. At the community level, a mean optic disc score was calculated, which was defined as the geometric mean of the individual scores.

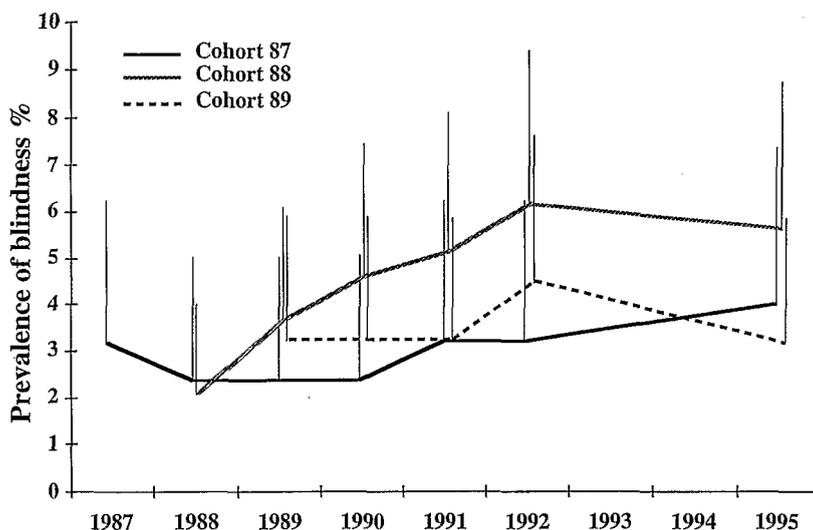
DATA ANALYSIS All data were entered into a microcomputer with the software package DBase IV®. This was done in the evening of the examination day, so that the few patients whose records were incomplete or inconsistent could be readily re-examined the following day. Those patients in whom one of the eyes could not be, or was not, examined were excluded from analysis; this exclusion procedure was done separately for the anterior and the posterior segments of the eye.

The effect of repeated ivermectin treatments was assessed in two ways. The first way consisted of following up the indices within the three cohorts, while the second consisted of following up the indices recorded each year in the cross-section of males aged 15-19 years. The cohort analysis included only those patients who received ivermectin and underwent ophthalmologic examination every year. The cross-sectional method was aimed at comparing the indices obtained in patients who were of similar age, but were different regarding history of previous ivermectin treatment. In particular, the indices obtained in 1995 from patients who could have received up to 8 successive annual treatments were compared with the indices calculated from data recorded before treatment (1987-1989) in individuals of the same age group.

Results

STUDY POPULATION In 1995, the numbers of individuals who had received all the possible doses of ivermectin, and in whom the anterior segments of both eyes were examined at each examination round, were 125 in cohort 1987, 191 in cohort 1988 and 140 in cohort 1989 (total

Fig. 2. Prevalence of blindness in the three cohorts.



for the three cohorts: 456 persons); the numbers of individuals who had received all the possible doses of ivermectin, and in whom the posterior segments of both eyes were examined at each examination round, were 114 in cohort 1987, 180 in cohort 1988 and 130 in cohort 1989 (total for the three cohorts: 424 persons). With regard to the cross-sectional study, 352 males were 15-19 years old at their first ocular examination. In 1995, the number of males examined who belonged to this age group was 156.

LONGITUDINAL COHORT ANALYSIS Figures 2-7 show the evolution of the indices within the three cohorts from the start of the study up to the last examination round in 1995. If one combines the results recorded from the patients in the three cohorts, the blindness rate increased from 1.75% (before the first distribution) to 3.29% in 1995 (Fig. 2); this increase was not significant ($p > 0.10$). In the same interval, the community mean visual acuity (CMVA) decreased from 6.69 before the first treatment to 5.87 in 1995 (Fig. 3); this decrease was also not significant ($p > 0.20$).

The prevalence of MFAC decreased dramatically after the two first distributions, after which the curve showed a plateau between 1992 and 1995 (Fig. 4). The difference between the initial prevalence of MFAC (36.40%) and the value recorded in 1995 (5.26%) was highly significant ($p < 10^{-3}$). The prevalence of PK also decreased (from 44.96 to 24.56%) between the first and the last examination round (Fig. 5); although the decrease observed was more progressive than for the prevalence MFAC, it was also highly significant ($p < 10^{-3}$). The prevalence of sclerosing keratitis tended to decrease between the pre-treatment and the last examination (from 10.31% to 8.33%), but this was not significant ($p > 0.30$).

The prevalence of OA increased significantly ($p < 10^{-3}$), from 0.47% before the first treatment to 5.44% in 1995 (Fig. 6). A significant increase was also recorded for the optic disc score, from 1.02 at the first examination round to 1.54 in 1995 ($p < 0.05$). Among all the patients who had normal optic discs before the first treatment, 114 showed abnormalities in 1995. Most of these new lesions were unilateral pallor of

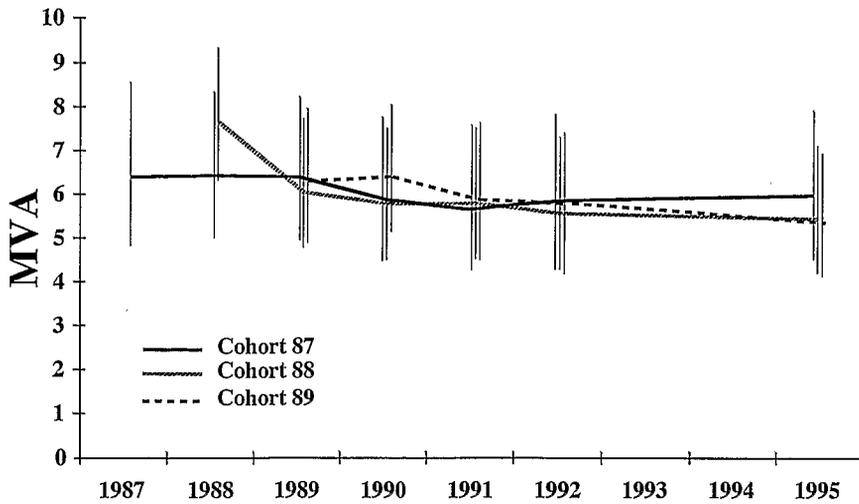


Fig. 3. Mean visual acuity (MVA) in the three cohorts.

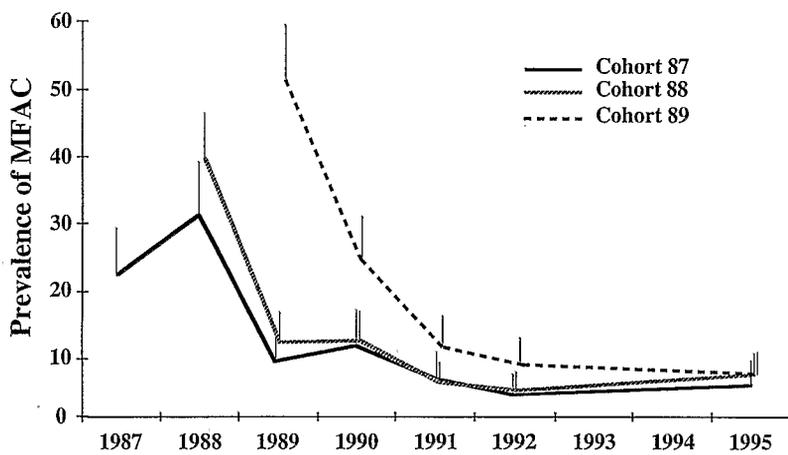


Fig. 4. Prevalence of microfilariae in the anterior chamber of the eye (MFAC) in the three cohorts.

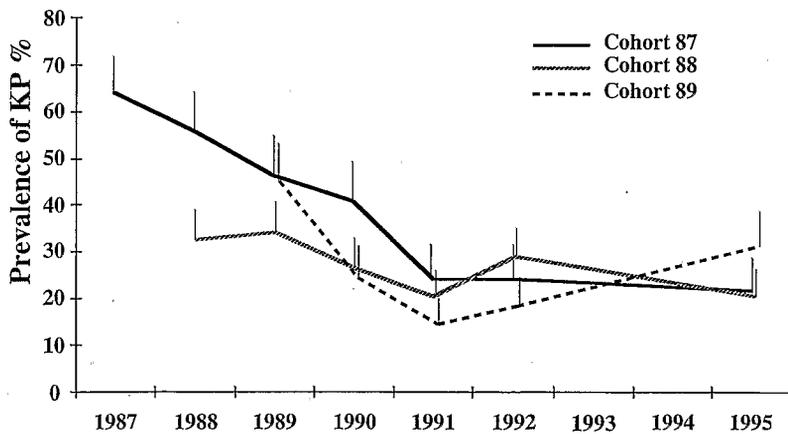


Fig. 5. Prevalence of punctate keratitis (PK) in the three cohorts.

the disc, but 31 patients showed more serious lesions; for six of them, the new lesions were accompanied by a marked decrease in visual acuity, which was less than 0.2/10 for at least one eye.

Initially, the prevalence of chorioretinal lesions of all types in the cohorts was 14.86%; in 1995, it increased to 46.46%; this difference was highly significant ($p < 10^{-9}$). The mean annual incidences of chorioretinal

Fig. 6. Prevalence of optic atrophy in the three cohorts.

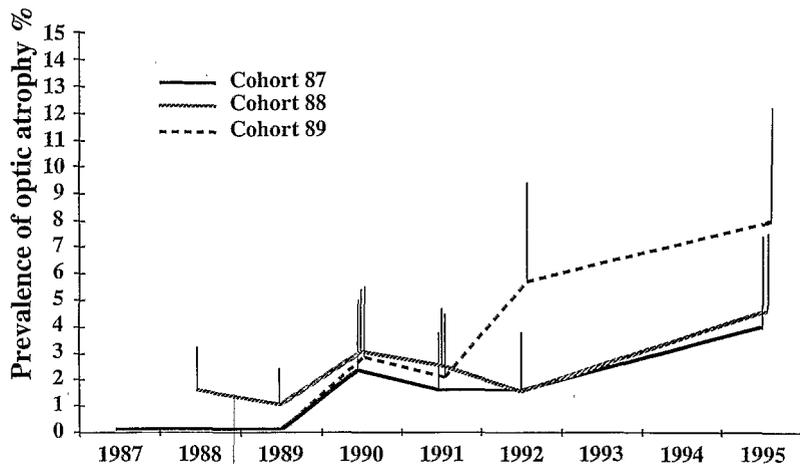
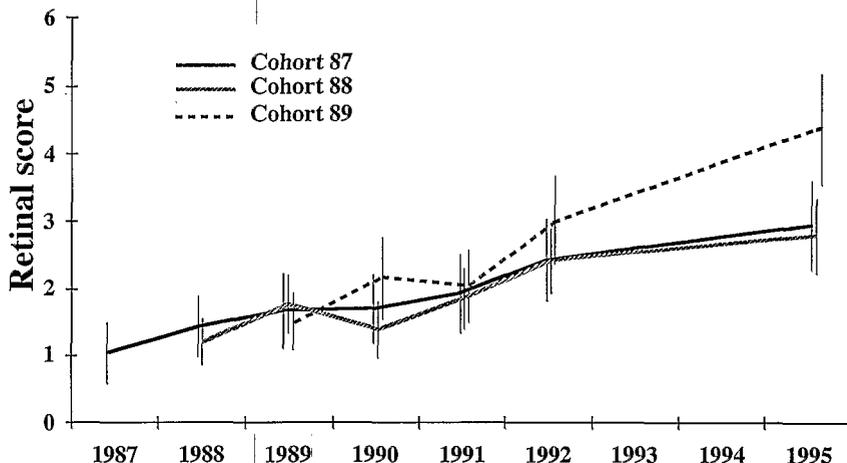


Fig. 7. Retinal score in the three cohorts.



lesions of all types between the first examination and 1995 were 4.89%, 3.79%, and 9.13%, in cohorts 1987, 1988, and 1989, respectively; and the difference observed was consistent with the difference of endemicity in the villages where the three cohorts were recruited (see above). The prevalence of advanced chorioretinitis in the cohorts was initially 2.36% and increased to 13.92% in 1995; the difference was highly significant ($p < 10^{-9}$). The chorioretinal score increased significantly ($p < 10^{-3}$), from 1.12 at the first examination round to 3.24 in 1995 (Fig. 7). The worsening included both an extension of the lesions and a progression in the pathological process, as assessed by the clinical appearance. New lesions of the macula were found in 77 patients.

CROSS-SECTIONAL ANALYSIS At the first examination round, the blindness rate among males aged 15-19 years was 1.70%. In 1995, the blindness rate in the males belonging to this age group was 0.64%; this decrease was not significant ($p > 0.25$). However, it is noteworthy that no blind person was recorded in 1995 among all the males aged 15-19 years who were examined in the villages located west of Touboro, i.e. the less heavily infected communities where the CMFL ranged between 20 and 150 mf/ss. At the first examination, the CMVA in the cross-sectional

group was 7.10; this index increased significantly to 9.12 in 1995 ($p < 10^{-2}$).

The prevalence of MFAC decreased dramatically, from 43.18% in 1987/89 to 6.41% in 1995; the difference was highly significant ($p < 10^{-3}$). A significant decrease was also found in the prevalence of PK (45.74% at first examination round and 19.87% in 1995; $p < 10^{-3}$) and the prevalence of SK (8.24% in 1987/89 and 1.28% in 1995; $p < 10^{-3}$).

The prevalence of OA decreased from 1.07% in 1987/89 to 0.64% in 1995; this difference was not significant ($p > 0.55$). Similarly, the optic disc score decreased non-significantly from 0.71 to 0.41 between 1987/89 and 1995 ($p > 0.05$). The chorioretinal score increased from 0.76 at the first examination round to 0.99 in 1995; the difference was also not significant ($p > 0.20$). Similarly, the prevalence of advanced chorioretinitis in males aged 15-19 years did not change significantly ($p > 0.05$) between the first examination round (1.42%) and 1995 (1.92%).

Discussion This paper provides the results of a long-term study (8 years) on the effect of repeated doses of ivermectin on ocular onchocerciasis. It was performed in a Sudan-savanna area of Cameroon where onchocerciasis is hyperendemic, with CMFL exceeding 100 mf/ss in the majority of the villages. The objectives were similar to those of other trials carried out in areas where onchocerciasis has a different epidemiological pattern, i.e. the Asubende focus (Ghana), a Guinea-savanna area where the initial CMFL was 65.7 mf/ss and where vector control activities were carried out intermittently during the first three years of ivermectin distribution; the Kaduna focus (Nigeria), a Guinea-savanna focus where the initial CMFL was 3.2 mf/ss; the Bo focus (Sierra Leone), a degraded forest area where the initial CMFL was 7.9 mf/ss; and the Rumpi Hills focus (west Cameroon), a rain-forest area where the initial CMFL was 53.6 mf/ss. A comparison of the results obtained in the different sites is important to predict the impact of the large-scale ivermectin distribution programs that are being implemented as part of the African Programme for Onchocerciasis Control launched in 1996.

In the studies carried out in Sierra Leone and Nigeria, a control group of patients receiving placebo during 2 and 3 years, respectively, was included in the trial. For ethical reasons, no control group was included in the trial conducted in the Vina valley, and it was thus impossible to evaluate directly the effect of the treatment on the natural history of ocular onchocerciasis. However, the analysis on cross-sectional groups allowed us to assess the potential of repeated ivermectin treatments in preventing the appearance of some onchocercal lesions.

In the Vina valley study, cohort analysis was limited to those individuals who received all the possible doses of ivermectin. These patients corresponded to 35.9% of the total number recruited at the baseline examination performed before the first distribution. The cohort analysis was restricted to this population in order to be sure that it would be conducted on a homogeneous group with regard to regularity of treatment. In addition, as the results obtained during the phase II and III trials on the posterior segment lesions were not clear, it was decided to focus the analysis on an evaluation of the optimal effect of ivermectin (i.e. annual treatments) on ocular onchocerciasis. By making this choice,

TABLE I. Comparison of the pre-treatment data recorded on the patients belonging to the cohorts, and on a group containing all the males 15-45 years of age, who were examined before their first treatment but who subsequently attended less than half of the distributions (= "non-assiduous" patients).

Ophthalmologic indices	Cohort patients	"Non-assiduous" patients	p*
Number of patients	456**	172***	
Blindness rate (%)	1.75	5.81	< 0.05
Mean visual acuity	6.69	4.22	< 10 ⁻²
Prevalence of MFAC**** (%)	36.40	44.77	NS
Prevalence of punctate keratitis (%)	44.96	47.67	NS
Prevalence of sclerosing keratitis (%)	10.31	18.6	< 0.05
Prevalence of optic atrophy (%)	0.47	1.74	NS
Optic disc score	1.02	1.63	NS
Prevalence of chorioretinal lesions (%)	14.86	16.99	NS
Prevalence of advanced chorioretinitis (%)	2.36	7.84	< 10 ⁻²
Chorioretinal score	1.12	1.91	< 10 ⁻²

* NS = not significant

** For posterior segment lesions: 424 subjects

*** For posterior segment lesions: 153 subjects

**** MFAC = Microfilariae in the anterior chamber of the eye.

we accepted the possibility that the patients who participated in all the distribution rounds might not be representative of the total population examined, and thus that the results might be biased for various reasons: for example, individuals with severe visual impairment might have been inclined to participate more assiduously in the treatments, whereas those who did not show any symptom might have had less reason to attend the examination, and might have missed or refused the examination and treatment rounds; besides this, investigators might have made a particular effort to re-examine those patients who showed the most serious lesions at the previous examination rounds. To verify whether such a bias existed, we compared the pre-treatment data recorded, on the one hand, on the patients belonging to the cohorts (and who were thus present at all examination and treatment rounds), and on the other hand on a group containing all the patients who were examined before their first treatment but who subsequently attended less than half of the distributions (Table I). This analysis showed that the blindness rate, the retinal score, and the prevalence of advanced chorioretinitis were significantly higher, and the mean visual acuity was significantly lower, in the "non-assiduous" group than in the cohorts; however a more detailed analysis demonstrated (1) that this difference was due to some 12 patients who had severe ocular onchocerciasis at the outset of the study, and who abandoned the trial because they did not feel any improvement after the first treatment, (2) and that the initial ocular situation of the other "non-assiduous" patients was not significantly different from the situation recorded in the individuals of the cohorts. Consequently, one may assume that the decision to limit the analysis to those patients who participated in all examination rounds did not significantly affect the validity of the conclusion. For analysis, the results recorded on the three cohorts were combined because the trends observed within each of them were similar, and because we assumed that the effect of 6, 7 or 8 annual treatments on ocular onchocerciasis would not be significantly different.

No information was recorded about the treatments taken previously by the patients who reached 15 years of age and who were examined for the first time in the course of the trial, as part of the cross-sectional study. Uncertainties thus exist regarding the number of doses received by the patients in the cross-sectional group examined at the last examination round. However, the marked decrease observed in 1995 in the prevalence of MFAC and PK among the males aged 15-19 years, as compared with the indices recorded in 1987-1989, indicates that the patients belonging to this age group examined in 1995 probably attended most of the distributions. This assumption is important as part of the results regarding the posterior segment lesions.

Several methods have been proposed to calculate the mean visual acuity of a series of patients. As emphasized by Evans,²⁶ the method to utilize "depends on the context of specific application". The method defined in the present study aimed at maximizing the contribution of the poor visual acuity samples. This was done empirically by replacing, in the calculations, the visual acuities below 1/10 by very low values. The validity of the method in the context of the present trial was checked by studying the relationship between the CMVA and the community microfilarial load recorded in 17 villages of the Vina valley, and it was found that the two indices were very closely correlated ($r=-0.73$; $p<10^{-3}$). In addition, the CMVA and the blindness rate were also closely correlated ($r=0.87$; $p<10^{-4}$).

As stated above, the calculation of a chorioretinal score permitted us to take into account simultaneously the stage of the chorioretinal lesions and their extent. In addition, this index was calculated so that the role of the early lesions was minimized; this is important because this type of lesion may be the subject of variation in assessment between different observers or between the examination rounds (see below). As for the CMVA, the validity of the chorioretinal score was checked by evaluating its relation with the CMFL in 17 villages of the Vina valley. The correlation coefficient was found to be highly significant ($r=0.65$; $p<10^{-3}$).

The recording and grading of some ocular signs related to onchocerciasis, particularly the early stages of posterior segment lesions, may be the subject of inter-observer variation. This could be all the more true in areas where a proportion of patients show intraretinal deposits (IRDs), which are lesions whose relationship to onchocerciasis is still unclear. Semba *et al.*¹³ demonstrated that two types of IRDs could be distinguished: "white IRDs", which change rapidly within months and are most numerous in patients with severe chorioretinal lesions, and "shiny IRDs", which in contrast do not appear to change in number or location and do not seem more numerous in patients with other chorioretinal lesions. Fundus photographs taken in the Vina valley indicated that more than two types of lesions can be grouped under the term "IRDs", and, for most of them, uncertainties existed regarding their relationship to onchocerciasis. Sessions were organized by the ophthalmologists before each examination round in order to restate the definition criteria of the various lesions observed in the study area and to reach a consensus so that inter-observer variation was reduced to a minimum. In addition, "quality control tests" were performed during the examination round

itself: at each round, a random sample of volunteer patients was examined twice. The inclusion of these patients in the line was done without the knowledge of the ophthalmologists, and the second examination was performed either by the same ophthalmologist after an interval of several days, or by another ophthalmologist. In all cases, the results recorded at both examinations were very similar.

The great care taken to reduce the inter-observer variation did not enable us to avoid another phenomenon that probably occurred in the Vina valley as the study proceeded, namely an "inter-round variation" of assessment. Over time, it appears that the ophthalmologists improved the accuracy of their diagnoses and recording. It is likely that some signs that are not classically included in the clinical picture of ocular onchocerciasis, such as the IRDs, were under-recorded during the first examination rounds. Subsequently, as it became obvious that these signs were common in the study area, the ophthalmologists might have been inclined to regard them as related to onchocerciasis, and to record them systematically on the form. The existence of such a phenomenon might explain why, as part of the cross-sectional study, the chorioretinal score tended to increase as the study proceeded. It should also prompt further research on the relationship between atypical chorioretinal lesions and onchocerciasis, and the development of a detailed grading system similar to the one proposed for onchodermatitis.²⁷

The blindness rate and the mean visual acuity did not change significantly in the cohorts within the 6-8 years of the study. In contrast, the increase in the CMVA in the cross-sectional groups suggests that repeated ivermectin treatment may prevent loss of visual acuity related to onchocerciasis in males aged 15-19 years. Besides the advantage of being closely correlated with the community microfilarial load (see above), the CMVA seems in addition to be a sensitive index for detecting relatively minor variation in visual acuity within a group of individuals. Improvement in the visual acuity has also been reported from western Cameroon.¹⁰

With regard to the anterior segment signs, an improvement was found in all groups and for all indices. The marked decrease in the prevalence of MFAC and prevalence of PK within the cohorts and between cross-sectional groups confirmed the data reported over many years from other studies. In addition, the present study demonstrated that after 6 to 8 distributions, the prevalence of SK had decreased (although not significantly) within the cohorts. This confirms previous longitudinal results, reported from Ghana after two distributions and from Sierra Leone after four treatments, which suggested that SK may regress after repeated ivermectin treatments.^{9,17} Besides this, the present study demonstrated that repeated ivermectin treatments bring about a marked decrease in the incidence of new SK. This result was expected because the development of SK is related to a massive presence of microfilariae in the cornea (MFC),²⁸ and because ivermectin treatment brings about a decrease in the number of MFC.

With regard to the posterior segment lesions, all the indices increased significantly within the cohorts. The increase in the prevalence of chorioretinal lesions within the cohorts indicates that the retinal lesions may continue to appear and to progress despite repeated annual treat-

ments. Similar results have been reported from the trial conducted in Sierra Leone.¹⁷ The annual incidences of chorioretinal lesions of all types recorded in the cohorts 1987 and 1988 were higher than the one recorded (2.65%) during an ophthalmologic longitudinal study carried out between 1970 and 1975 in the same area of North Cameroon on untreated patients 10 years of age and older.^{25,29,30} The worsening of the chorioretinal lesions has also been demonstrated qualitatively in the cohorts defined in the present article, using successive fundus photographs of chorioretinal lesions.³¹ These results should be considered in the light of the current views concerning the pathogenesis of onchocercal chorioretinal disease, which suggest that the retinal pathology is initiated by the presence of local microfilariae, whereas the extension of the lesions does not require their presence.³² This would explain why the decrease in the microfilarial loads following ivermectin treatment did not result in an interruption of the pathologic process started prior to the outset of the study, and particularly the increase in the prevalence of advanced chorioretinitis in the cohorts. In addition, the increase in the prevalence of early retinal lesions in the cohorts, and the fact that the chorioretinal score did not change significantly with time in the cross-sectional groups, suggest that the pathological process in the retina is initiated early in life, i.e. before the age of 15. This supports the conclusion of a report of the World Health Organization, in which it was assumed that the impact of ivermectin on posterior segment lesions, particularly chorioretinitis, would take many years to become manifest.³³

In the Vina valley, the prevalence of OA continued to increase within the cohorts despite repeated treatments. New lesions of the optic disc appeared in 25% of the patients, and some of them showed a decrease in their visual acuity. Such a worsening has been reported from the trial conducted in Kaduna (Nigeria),¹⁶ but has not been found in Sierra Leone where, in contrast, OA showed significant improvement in appearance.¹⁷ The latter result was all the more unexpected because the improvement concerned not only early (optic disc pallor) but also advanced lesions (totally white optic disc), and the authors admitted that "it is unlikely that there was real improvement in optic disc pallor". With regard to the cross-sectional study, the prevalence of OA was found to decrease between the initial and the last examination rounds in the Vina valley. The difference was not significant, but this trend was in agreement with the results obtained in Nigeria and Sierra Leone, which demonstrated that repeated ivermectin treatments bring about a reduction in the incidence of OND.^{16,17} The observations reported from the Kaduna study indicate that ivermectin treatment may also reduce the incidence of visual field deterioration, particularly among those patients with pre-existing OA.³⁴ As the visual fields were not tested in the Vina valley, we could not confirm this very promising result. Besides this, the annual incidence rate of OA in the three cohorts of the Vina valley was 0.75%. This value was lower than the annual incidence rates recorded in North Cameroon on untreated patients 10 years of age and older (1.98%).^{25,29} It was also lower than the incidence rates found in Kaduna among the patients who did not receive treatment (2.7%), and those who were treated repeatedly with ivermectin (1.6%). The lower value recorded in North Cameroon might be due to the fact that in this area the last ex-

TABLE 2. Comparison of the ophthalmologic indices recorded before treatment (1987/1989) and in 1995. (MFAC = microfilariae in anterior chamber ; 0 = no significant change ; + = significant improvement ; - = significant worsening).

Ophthalmologic indices	Changes in the three cohorts	Comparison between cross sectional groups
Blindness rate	0	0
Mean visual acuity	0	+
Prevalence of MFAC	+	+
Prevalence of punctate keratitis	+	+
Prevalence of sclerosing keratitis	0	+
Prevalence of optic atrophy	-	0
Optic disc score	-	0
Prevalence of advanced chorioretinitis	-	0
Chorioretinal score	-	0

aminations were performed after a higher number (6 to 8) of treatments and/or because the criteria used to define an OA were different between the studies.

The results of the present study are summarized in Table 2. On the whole, there was an agreement between these results and the ones reported from the few other longitudinal studies on the long-term effect of repeated ivermectin treatments on ocular onchocerciasis. It is possible that the differences regarding the initial level of endemicity in the study areas, and the pathogenicity of the local parasitic strain, may account for the minor variations in the results obtained in the different studies. Repeated ivermectin treatments may prevent the appearance of two blinding onchocercal lesions: sclerosing keratitis and OND. In some cases, they may bring about a regression of pre-existing sclerosing keratitis; but uncertainties still exist regarding the effect of repeated treatments on pre-existing OND. The most disappointing results concern the effect of ivermectin on chorioretinal lesions. This is probably due to the specific pathogenic process leading to this type of lesions. One may assume that a decrease in the prevalence of chorioretinitis would appear only after a long time, and only if the exposed residents are treated repeatedly from a young age, i.e. before the invasion of the retina by the microfilariae that initiate the pathologic process. This hypothesis could be confirmed by continuing the ophthalmologic follow-up of the populations that participated in the studies conducted in Cameroon, Ghana, Nigeria and Sierra Leone.

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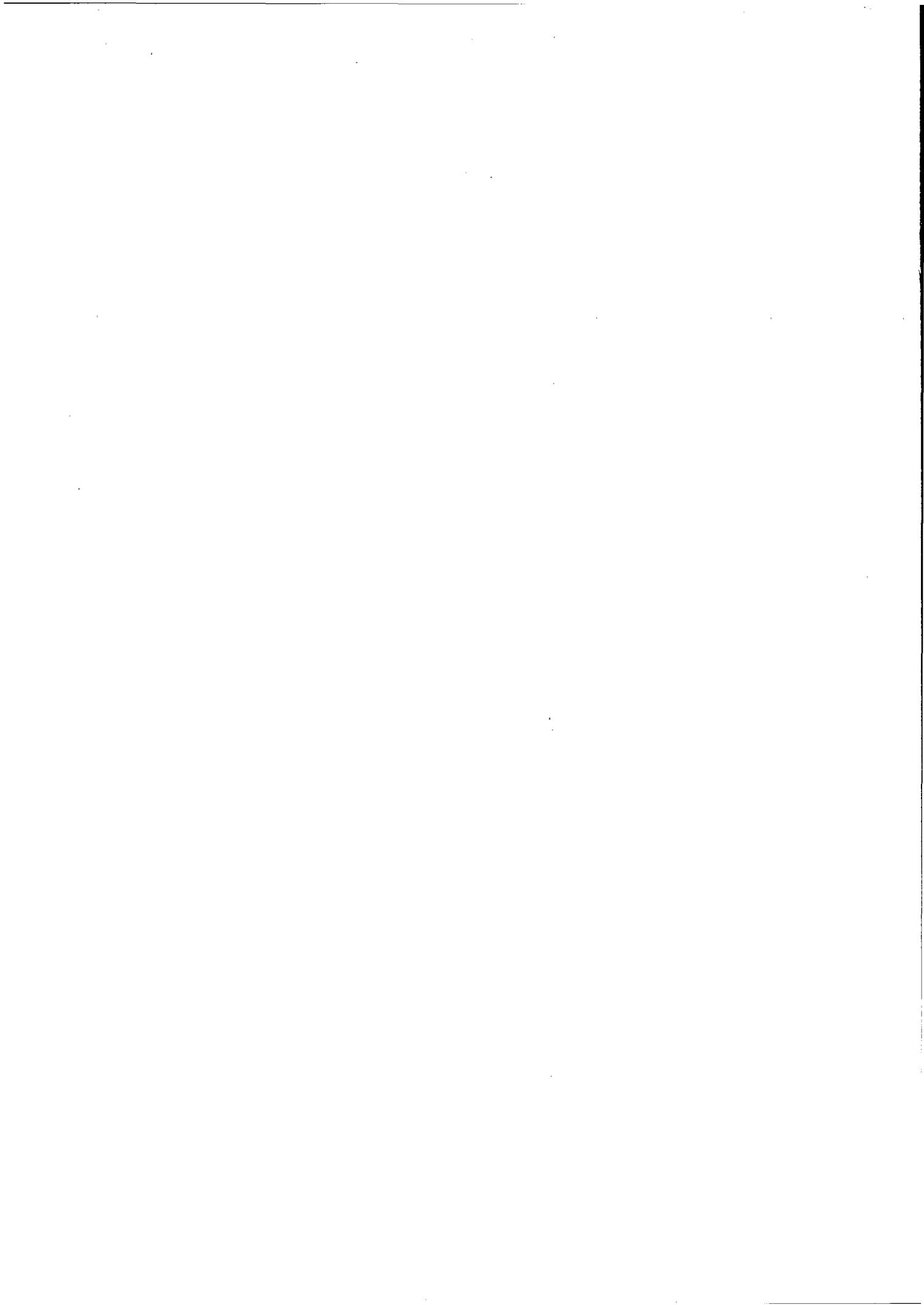
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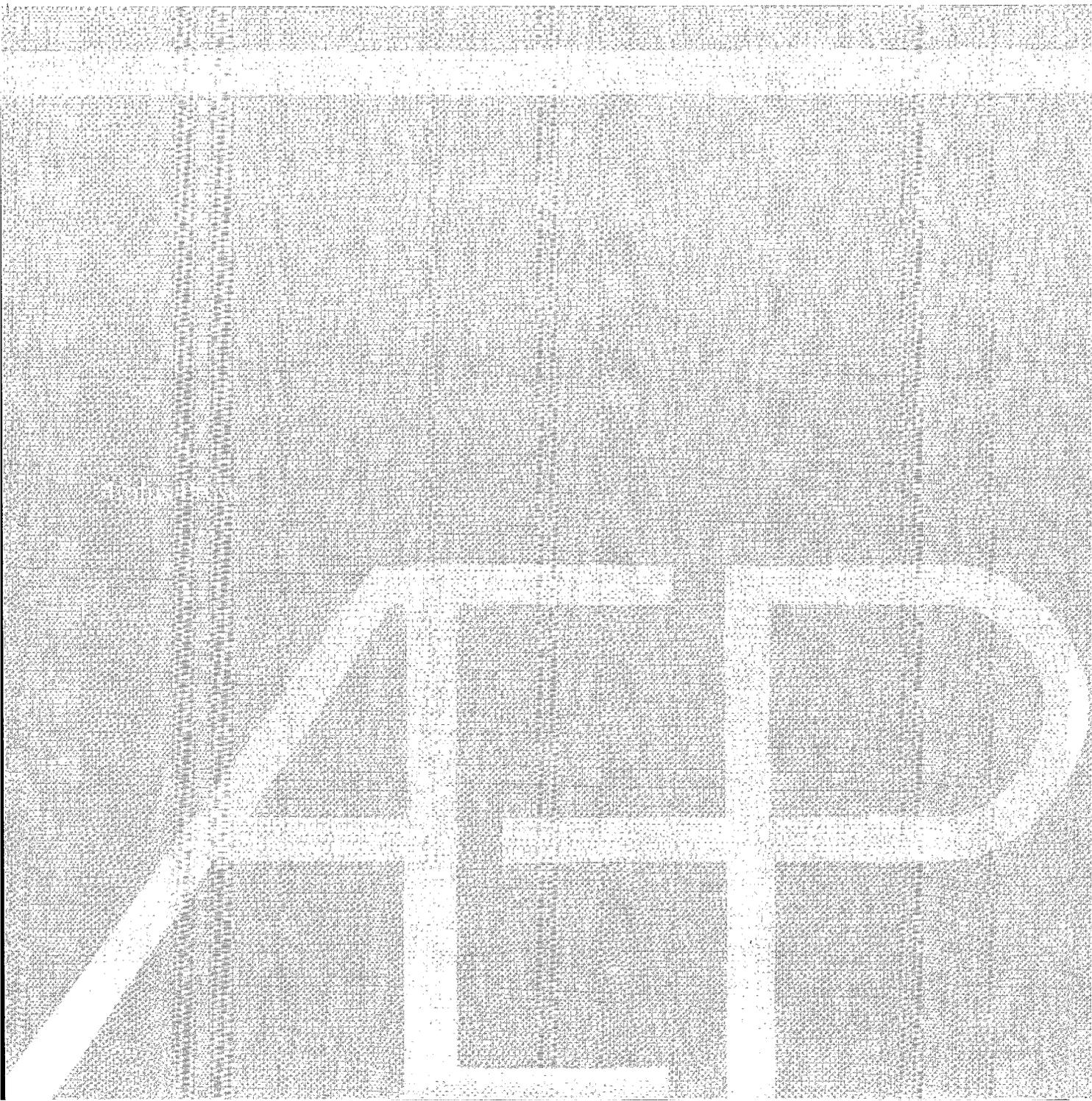
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