

TREATMENT OF ACTIVE TOXOPLASMIC RETINO-CHOROIDITIS*†

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THE treatment of toxoplasmic uveitis is a widely debated problem (Kaufman, 1965), the main reasons being as follows:

(1) The impossibility of making a definite diagnosis of toxoplasmosis in any particular case (Perkins, 1961).

(2) Conflicting reports on the efficacy and safety of pyrimethamine and spiramycin, the major drugs currently used for treating toxoplasmosis.

(3) Uncertainty about the role of systemic corticosteroids in treatment, which is due to our ignorance of the part played by hypersensitivity in any particular case.

In an attempt to determine the most effective treatment and to elucidate the role of corticosteroids in active toxoplasmic retino-choroiditis, we have analysed the results of various therapeutic regimes in 69 cases (Table).

Conduct of Study

69 attacks of presumed toxoplasmic retino-choroiditis occurred in 54 patients in the 10 years 1958 to 1967; 41 patients had only one attack and thirteen had two or more separate attacks in this time. Diagnosis in each case rested on the typical clinical appearance of an active focal exudative retino-choroiditis, a positive Sabin-Feldman dye test in titres which varied from 1 : 8 to 1 : 2,048, and the exclusion of other likely causes. All the patients had a full blood count, erythrocyte sedimentation rate, Wassermann reaction, Kahn test, haemoglobin estimation, Mantoux test, and chest x ray. The time taken for complete quiescence to be achieved and the number of recurrences of activity following therapy were studied. The criterion of quiescence was a flat, pigmented, white scar without any greyness, fluffiness, or overlying haze. Changes in visual acuity were not taken into account, because this studies the function of only one tiny area of retina and the clarity of the ocular media along the visual axis, and is thus not uniformly helpful in evaluating treatment.

TABLE
SUMMARY OF RESULTS OF DIFFERENT TREATMENT SCHEDULES

Number of Cases	Systemic Treatment	Number of Recurrences	Healing Time (wks)	
			Span	Average
16	Nil	7	4-45	16
21	< 30 mg. prednisone	3	6-35	16+
7	> 30 mg. prednisone	2	2-30	14
14	Steroids + spiramycin	2	3-30	12.5+
11	Steroids + Daraprim	0	3-18	9

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All the patients and controls received topical atropine and corticosteroid drops during the period of active inflammation. Pyrimethamine was given in a loading dosage of 100 mg. followed by 25 mg. daily. The dosage of spiramycin varied from 1 to 4 g. daily in different patients. Of the 28 cases treated with corticosteroids alone, seven were initially given more and 21 less than 30 mg. daily, in divided doses. In all cases treatment was continued until the lesion was completely quiet, except that the corticosteroid dosage was reduced if a lesion showed marked improvement.

Results

These are shown in the Table. Three patients failed to improve on corticosteroids alone (all in the less than 30 mg. daily group) and one on spiramycin plus corticosteroids. In calculating the average time for quiescence in these two groups, the actual period on the drug was used, but the average time was written as 16+ and 12.5+ weeks respectively, instead of 16 and 12.5 weeks. There was no significant difference in the results in patients treated with the various dosages of spiramycin.

Rate of Healing

- (1) Pyrimethamine significantly reduced the healing time when accompanied by large or small doses of corticosteroids, the results being exactly the same in either case.
- (2) Spiramycin had a small effect on reducing healing time.
- (3) Corticosteroids used alone had no significant effect on the rate of healing.

Recurrence Rate

There were no recurrences in the eleven cases treated with pyrimethamine (2 to 6 years' follow-up, average 4½), whereas spiramycin had a recurrence rate of 14 per cent. (0 to 4 years' follow-up, average 2), corticosteroids alone 18 per cent. (0 to 9 years' follow-up, average 4½), and no treatment at all 44 per cent. (0 to 9 years' follow-up, average 7). The high percentage in the untreated group may be due to the longer follow-up period.

Discussion

Pyrimethamine and spiramycin are both concentrated in the cells of the retina and can therefore act against intra-cellular toxoplasma (Kaufman, 1961; Chodos and Habegger-Chodos, 1960). Beverley (1958) showed that systemic pyrimethamine used alone produced a 100 per cent. cure rate and systemic sulphonamides alone an 80 per cent. cure rate in experimental mouse toxoplasmosis, but that both drugs had to be given in dangerously high dosages to achieve this effect. However, the two drugs greatly potentiate each other's action when used in combination because they affect different sites on the metabolic pathway, sulphonamides preventing the synthesis of folic acid and pyrimethamine its utilization. Also, Frenkel and Hitchings (1957) showed in both mice and man that moderate dosages of folic acid inhibit the toxic side-effects of pyrimethamine and sulphadiazine without interfering with their efficacy against toxoplasmosis. Pyrimethamine is, therefore, usually combined with a sulphonamide and folic acid in treating toxoplasmosis. Kaufman, Remington, Melton, and Jacobs (1959) showed, however, that slow-growing strains of *Toxoplasma gondii* were relatively resistant to pyrimethamine, and Kaufman and Geisler (1960) and TenPas and Abraham (1965) have stressed the necessity for frequently repeated blood examinations in patients on pyrimethamine therapy. In addition to the actual

danger of thrombocytopenia and leucopenia, Chodos and Habegger-Chodos (1960) found unpleasant side-effects in all their twenty pyrimethamine-treated patients, and Fajardo, Furgiuele, and Leopold (1962) noted such symptoms in 55 per cent. of their forty patients. Spiramycin is free from such side-effects and a number of workers have shown it to be effective in toxoplasmosis in experimental animals, although high doses are needed (Bogacz, 1954; Garin and Eyles, 1958; Giles, Jacobs, and Melton, 1964). Whilst many reports have been published on the treatment of ocular toxoplasmosis in man, the only large comparative series are those of Chodos and Habegger-Chodos (1960) and Fajardo and others (1962). Chodos and Habegger-Chodos treated twenty patients with pyrimethamine and sulphonamides and 77 patients with spiramycin; they concluded that the two regimes were equally effective, but that spiramycin was the drug of choice because of the absence of side-effects. In a later communication (1961), the same authors stated that spiramycin plus systemic corticosteroids was no more effective than spiramycin alone. Fajardo and his co-workers, however, found that lesions in forty patients treated with a pyrimethamine, sulphonamide, and corticosteroid combination became quiescent in an average of 9.5 weeks as against 20 weeks for 41 patients treated with spiramycin plus corticosteroids. Our figures in the pyrimethamine-treated patients correspond closely to those of Fajardo's group, and also to those of Ghosh, Levy, and Leopold (1965), who obtained quiescence in an average of 10 weeks in ninety patients treated with a pyrimethamine, sulphonamide, and corticosteroid combination and of 9 weeks in ten patients treated with pyrimethamine and sulphonamides only. Our results with spiramycin show it to have some effect in toxoplasmosis, although this is less than that of pyrimethamine. We found it to be virtually free from side-effects.

The role of systemic corticosteroids in therapy has also aroused controversy. Beverley (1958) suggests three possible causes for acute exacerbations of toxoplasmic retino-choroiditis: a local proliferation of the organism following the rupture of a cyst, a hypersensitivity reaction to toxoplasma cyst contents, and a hypersensitivity reaction to products of tissue breakdown. Systemic corticosteroids would be indicated in retino-choroiditis in the second and third groups, but might be contraindicated in the first. Beverley's theory has not been greatly disputed, but it is difficult to differentiate between these three types of inflammation clinically. Our results indicate that corticosteroids have little, if any, effect on healing, and are thus again in agreement with those of Fajardo and his co-workers, who found an average healing time of 13 weeks in six patients treated with 12 mg. methylprednisolone daily.

Reports in the literature on recurrence rates after various therapeutic regimes are also conflicting. Chodos and Habegger-Chodos (1961) found a 5 per cent. recurrence rate in spiramycin-treated patients followed up for one year. Fajardo and his co-workers found an equal recurrence rate of 7.5 per cent. in their two groups in a follow-up period of 0 to 3 years, but Canamucio, Hallett, and Leopold (1963) found recurrences in 16 per cent. of 45 patients treated with a pyrimethamine, sulphonamide, and corticosteroid combination and in 30 per cent. of 61 patients treated with spiramycin plus corticosteroids. Our finding that pyrimethamine therapy is followed by a lower recurrence rate is thus in agreement with that of Canamucio's group. This difference in recurrence rates with different treatments lends support to the theory that at least some recrudescences are due to activity by toxoplasma organisms themselves rather than to a mere antigen-antibody reaction, since in the latter case one might expect equal recurrence rates with any type of therapy.

Conclusions

- (1) Pyrimethamine is the most effective drug in common use against active toxoplasmic retino-choroiditis.
- (2) Spiramycin is relatively ineffective in treatment.
- (3) Systemic corticosteroids have no effect on healing, irrespective of dosage and of whether they are used alone or in combination.
- (4) Because of its dangers and unpleasant side-effects, there is a case for undertaking treatment with pyrimethamine only in patients with lesions which might otherwise result in permanent impairment of vision. Less severe cases may be treated with spiramycin as out-patients.
- (5) Where pyrimethamine therapy is necessary it should be given in combination with sulphonamides and folic acid, because of the reduction in toxicity and side-effects with this combination—at least until other drugs such as penimepicycline (François, Jadin, Wesy, and van de Castele, 1964; Amalric and Bessou, 1964) have been shown to be equally efficacious and safe.

Summary

Analysis of treatment in 69 cases of active toxoplasmic retino-choroiditis shows that pyrimethamine is the most effective drug in our armamentarium, reducing the average healing time from 16 to 9 weeks, and being followed by a lower recurrence rate than other treatments. Spiramycin is relatively ineffective. Systemic corticosteroids alone or in combination do not influence the speed of healing or the recurrence rate.

Where the possibility of permanent visual impairment makes active treatment imperative, this should be given as a combination of pyrimethamine, sulphonamides, and folic acid.

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REFERENCES

- AMALRIC, P., and BESSOU, P. (1964). *Rev. Oto-neuro-ophthal.*, **36**, 89.
- BEVERLEY, J. K. A. (1958). *Trans. ophthal. Soc. U.K.*, **78**, 109.
- BOGACZ, J. (1954). *Bull. Soc. Path. exot.*, **47**, 903.
- CANAMUCIO, C. J., HALLETT, J. W., and LEOPOLD, I. H. (1963). *Amer. J. Ophthal.*, **55**, 1035.
- CHODOS, J. B., and HABEGGER-CHODOS, H. E. (1960). "Antimicrobial Agents Annual—1960", p. 459 (Published 1961).
- (1961). *Arch. Ophthal. (Chicago)*, **65**, 401.
- FAJARDO, R. V., FURGIUELE, F. P., and LEOPOLD, I. H. (1962). *Ibid.*, **67**, 712.
- FRANÇOIS, J., JADIN, J., WERY, M., and VAN DE CASTEELE, J. (1964). *Ann. Oculist. (Paris)*, **197**, 72.
- FRENKEL, J. K., and HITCHINGS, G. H. (1957). *Antibiot. and Chemother.*, **7**, 630.
- GARIN, J. P., and EYLES, D. E. (1958). *Presse méd.*, **66**, 957.
- GHOSH, M., LEVY, P. M., and LEOPOLD, I. H. (1965). *Amer. J. Ophthal.*, **59**, 55.
- GILES, C. L., JACOBS, L., and MELTON, M. L. (1964). *Arch. Ophthal. (Chicago)*, **71**, 119.
- KAUFMAN, H. E. (1961). *Amer. J. Ophthal.*, **52**, 402.
- (1965). Annual review—the uvea. *Arch. Ophthal. (Chicago)*, **73**, 417.
- and GEISLER, P. H. (1960). *Ibid.*, **64**, 140.
- , REMINGTON, J., MELTON, M. L., and JACOBS, L. (1959). *A.M.A. Arch. Ophthal.*, **62**, 611.
- PERKINS, E. S. (1961). "Uveitis and Toxoplasmosis", p. 66. Churchill, London.
- TENPAS, A., and ABRAHAM, J. P. (1965). *Amer. J. med. Sci.*, **249**, 448.