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REACTIONS TO TRYPARSAMIDE *

A REVIEW OF TEN YEARS' EXPERIENCE

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TRYPARSAMIDE, the sodium salt of N-phenyl-glycine-amide-*p*-arsonic acid, was synthesized by Jacobs and Heidelberger of the Rockefeller Institute (1919) (1). Brown and Pearce (1919) (2) studied it thoroughly from the toxicological and pharmacological standpoints, and it has been used extensively in the treatment of neurosyphilis since its first trial by Lorenz, Loevenhart, Blackwenn and Hodges in 1922 and 1923 (3, 3A). Despite the wide use of this compound and the massive dosage in which it is employed, its toxicity has been considered of relatively minor importance. Except for a moderate number of toxic amblyopias, exceedingly few untoward systemic reactions were previously encountered. Recently, however, numerous reports have appeared which tend to indicate that reactions to tryparsamide are increasing in frequency and severity (4). In order to gain an accurate estimate of our experience with the toxicology of this drug, we have reviewed the records of all patients treated with it in the Department of Dermatology and Syphilology of the University of Pennsylvania from 1930 to 1939 inclusive.

MATERIAL

Our series consists of 113 patients who received 3,784 injections, and whose age distribution was fairly typical for late syphilis, since most of the patients were in the third and fourth decades. The sex and colour distribution corresponded closely to the findings of Turner (5). The majority of the patients were white males (59). There were 24 white females, 22 coloured males, and

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5 coloured females. Fifty-four of the patients had asymptomatic neurosyphilis; 16 had clinical paresis; 6 had taboparesis (one of these patients, listed below, had primary optic atrophy); 24 had tabes; 4 had primary optic atrophy; 9 had miscellaneous types of neurosyphilitic involvement, and 1 patient had pemphigus; 9 patients had some optic nerve involvement on admission.

LOCAL AND SYSTEMIC REACTIONS

The types of local and systemic reactions to tryparsamide which have been reported * include the following: abscess (6); nausea and vomiting, usually delayed (6, 7, 8, 9, 10, 11); short period of mental confusion with aggravation of the symptoms of paresis (6, 10, 12, 13, 14, 15); fever (9); jaundice (3, 6, 8, 9, 10, 11, 12, 16, 17, 18, 19, 20, 21, 22, 23, 24, 24A); nitritoid reactions (4, 8, 10, 22, 25, 26, 27, 28, 28A); Herxheimer reaction (therapeutic flare-up) (8, 15, 16); œdema (6, 9); loss of weight and mental confusion (14); hæmorrhagic disease (29); conjunctivitis (10); onychoptosis (10); slight renal irritation (30); dermatitis (including "fixed eruption" and herpes zoster) (7, 16, 17, 19, 22, 23, 26, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40 (polysensitivity)); fatal liver necrosis (41).

Our material contained 16 patients who sustained one or more systemic reactions to tryparsamide. There were no local reactions. The reactions we observed included: loss of weight (2 cases); severe nitritoid crisis (4 cases); nausea and vomiting (7 cases); itching and/or patchy dermatitis (4 cases); headaches (1 case); jaundice (1 case); nervousness (1 case); neuralgic pains (1 case).

Although our reaction incidence conforms to the previous impression that tryparsamide is a drug which is relatively reactionless, it is interesting to note that nitritoid reactions, at least in the past five years, have definitely increased in number, since in the period 1930 to 1935 we had but one (in 1932) nitritoid crisis, whereas in the period 1935 to 1939 we encountered three such reactions (in 1938 and 1939). This is not due to the recent increase in the use of tryparsamide, since about the same number of tryparsamide injections were administered in each of the two five-year periods. While this

* This material has been thoroughly compiled by Hinrichsen (42).

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observation is in keeping with the statement that reactions are increasing in frequency and severity, tryparsamide can still be rated as a definitely safe and relatively reactionless drug.

The patients who had dermatitis and/or itching were able, in several instances, to continue tryparsamide. A patient in 1933 exhibited reactions to other anti-syphilitic agents, including tryparsamide: (1) bismuth stomatitis; (2) eczematoid dermatitis of the legs, beginning during tryparsamide therapy and eventuating under neoarsphenamine in an exfoliative dermatitis; (3) chills and fever from arsphenamine).

We attempted to correlate the reaction incidence to tryparsamide with various factors:

1. Type of neurosyphilis.
2. Colour and sex.
3. Year or season.
4. Intercurrent disease.
5. Number of injections in the series.
6. Type or amount of previous treatment.
7. Reaction to previous treatment.

We also considered whether a patient who had received tryparsamide showed decreased tolerance to other treatment after tryparsamide. It is obvious that our results are based on small numbers, but regardless of this possible statistical inaccuracy the analyses of these various factors show the same trend as recorded by other observers.

The type of neurosyphilis has apparently some relationship to the incidence of systemic reactions, since there was about one-half the percentage incidence of systemic reactions in paresis as compared with either asymptomatic neurosyphilis or tabes dorsalis (7 per cent., 18 per cent., 13 per cent. of patients, respectively). It is interesting that two of four patients with primary optic atrophy sustained systemic complications to tryparsamide.

Sex and colour play no apparent rôle in the causation of reactions to tryparsamide, since the reactions occurred more frequently in the groups with more patients. The largest number of reactions occurred among the white men and women, and of the coloured patients only two of the men sustained reactions.

In estimating the effect of the type and amount of previous treatment in predisposing to tryparsamide reactions, we classified the treatment our patients received previous to tryparsamide in accordance with the Co-operative Clinical Group recommendations ("Scheme for treatment appraisal minus time element"). Based on this classification, we found that the type and/or amount of previous treatment had little effect in determining the occurrence of systemic reactions to tryparsamide. For example, the patients who received little arsenical and little heavy metal had relatively similar percentage incidence of reactions as did those who had previously received much arsenical and much heavy metal (17 per cent. as compared with 23 per cent. respectively).

During treatment with tryparsamide, according to our usual routine, a number of patients received other treatment (usually bismuth compounds). When this group was compared with the patients who did not receive concurrent treatment, we found that the incidence of tryparsamide reactions was not apparently affected, since in the group receiving no concurrent treatment there was approximately 14 per cent. reactions to tryparsamide, whereas in the groups receiving various amounts of concurrent treatment, the incidence of reaction was about 16 per cent.

Among our patients there were 7 who sustained reactions during the summer; 6 during the fall; 7 during the winter; and 5 during the spring. In comparing these reactions with the number of injections of tryparsamide administered during the respective seasons (876 in the summer; 930 in the fall; 927 in the winter; and 1,051 in the spring), it was found that the lowest incidence of reactions was in the spring, whereas the highest incidence was in the summer and winter. This trend is in keeping with the reaction incidence noted for other arsenical drugs (43).

In consonance with the general impression among the users of tryparsamide, there seems to have been a recent increase not only in nitritoid reactions, but also in the various other systemic reactions. In our series there were 15 reactions from 1935 to 1939, while there were 10 from 1930 to 1935, whereas during each period the number of injections administered was about the same.

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Our data were totally insufficient to throw light upon the question of intercurrent disease, especially infectious diseases, on the incidence of reactions.

There was no correlation between the type of reaction to tryparsamide or the number of the injection in the series producing the various reactions. Systemic reactions were noted in patients who had received one injection, as well as in one patient who had received 61 injections.

Reaction to previous treatment does not predispose to tryparsamide reactions. In our material, 78 patients had no reaction to any anti-syphilitic drug (including tryparsamide) which they had received. Eighteen patients had had reactions to medicaments previously administered, but no reaction to tryparsamide. Six patients had had reactions to previous drugs and subsequently sustained reactions to tryparsamide. Nine patients had had no reaction to previous therapy, but did react to tryparsamide. Accordingly, of 24 patients who had had reactions to previous treatment, only 6 (25 per cent.) subsequently sustained reactions to tryparsamide, whereas of 15 patients who subsequently developed systemic complications to tryparsamide, only 6 had had reactions to previous therapy.

Our data suggest that tryparsamide therapy does not predispose a patient to reactions to treatment (arsenicals and/or heavy metals) administered subsequent to tryparsamide therapy.

THE EFFECTS OF TRYPARSAMIDE ON THE OPTIC TRACT

The injurious effects of tryparsamide on the optic tract were noted early in the course of the clinical trial of this drug. For example, Pearce (44) noted that 17 of 77 patients treated for trypanosomiasis sustained visual impairment (6 slight, 7 moderate, and 4 marked). Ten of these patients completely recovered, while 3 were left with moderate and 4 with slight impairment of vision.

In the first paper on the treatment of neurosyphilis with tryparsamide, Lorenz, Loevenhart, Bleckwenn, and Hodges (3) found that with 5-gram doses at weekly intervals, 40 per cent. of the patients complained of dimness of vision after four or five weeks. With smaller

doses they found the drug to be therapeutically effective and produced visual symptoms in a much smaller number of cases. According to their experience, 3 grams was the desirable dosage. In 1924 Woods and Moore (45) made an exhaustive study of the visual disturbances induced by tryparsamide. They classified the ocular reactions into subjective and objective reactions. In the former type of reaction the patient complains of dazzling vision, but there are no objective ocular or visual field changes at the height of the reaction or at any other time. In the objective type of reaction, the same patient had the subjective complaints, but in addition the visual fields showed marked changes, consisting of concentric contraction of the form fields. These visual field changes, in the more severe cases, slowly increased to a maximum within three weeks. Eighty per cent. of all visual reactions occurred between the first and fifth dose, and 94 per cent. of the reactions between the first and the tenth dose. This observation has received widespread confirmation by many investigators. Woods and Moore, therefore, stressed the importance of careful observation of the eyes early in the course of treatment, and in the majority of cases the drug can be safely administered if the first five doses are well tolerated. Objective damage to the eyes may occur even with small doses of tryparsamide.

The majority of eye reactions in Woods' and Moore's series occurred in patients with neurosyphilis, although in their series there were 6 cases of ocular damage in patients without neurosyphilis. They found that 22.8 per cent. of their patients with paresis and tabes developed some degree of visual impairment, while patients with other types of neurosyphilis developed these signs or symptoms in only 15.2 per cent. In patients in whom central nervous system disease could be excluded, the incidence of untoward visual phenomena was only 6.1 per cent. In 180 cases of neurosyphilis and post-encephalitic parkinsonian disease, it was 21.1 per cent. Tryparsamide therapy caused visual disturbances in 20 (21 per cent.) of 95 patients with normal eyes before treatment. Twelve additional patients had definite involvement of the optic tract before tryparsamide treatment. This therapy induced visual disturbances in 4 (33 per cent.) of these 12 patients. Two and

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eight-tenths per cent. of the entire series of 241 cases developed permanent visual damage.

In 1936 Sloan and Woods (46) made an extensive review of the literature since 1923 on the effects of tryparsamide on the eye and found 107 subjective reactions and 71 objective reactions among 2,087 cases treated with the drug. They also studied 16 patients in whom objective ocular reactions occurred after tryparsamide therapy; only 1 patient had an acute reaction characterized by rapid loss of vision and resulting in almost complete blindness. This patient gradually improved after forced drainage of the cerebrospinal fluid. The more frequently observed type of reaction (chronic) was characterized by subjective visual symptoms of a mild degree with little or no reduction in the central acuity of vision and no visible change in the fundus, so that evidence of objective ocular damage is practically confined to changes in the visual fields. As a result of their careful observations, Sloan and Woods did not believe that the visual field defects accompanying tryparsamide were due to a reactivation of a latent syphilitic optic atrophy. They believed that patients with normal optic nerves, visual fields, and visual acuity prior to the use of tryparsamide were in little danger of any serious ocular damage from this drug, provided it is permanently discontinued at the first appearance of visual field defects. Continuation of the drug after changes in the fields have occurred may lead to serious visual damage or total blindness.

The incidence of eye complications to tryparsamide, as recorded by various authors, was summarised by Stokes (47), using the available literature up to about 1932. From these statistics the average incidence was found to be 9.2 per cent. and Stokes made the pertinent observation that "the frequency diminishes with the size of the series and the experience of the therapist." He felt that the irreducible minimum of eye complications was about 1-2 per cent.

There have been various theories proposed to explain how tryparsamide affects the optic nerve. One of these theories holds that tryparsamide exerts a direct toxic action. Another is that this drug activates syphilitic processes or induces extension of such processes into the optic nerve. Hinrichsen (42), who has made a most

exhaustive study of tryparsamide in the treatment of syphilis, feels that in favour of the latter assumption is the observation that eye involvement occurs more frequently when there is a pre-existing lesion of the optic nerve. According to her, Sézary and de Font-Reaulx (48) were convinced, as a result of a review of the literature, of the direct toxic action of tryparsamide. Their view is supported by recalling "the clinical observations of optic atrophy occurring in patients treated with atoxyl and tryparsamide, who had neither syphilis nor trypanosomiasis, increased danger with large doses too frequently given, bilateral involvement of the optic nerve, the histologic findings of degenerative rather than inflammatory lesions, and the fact that these changes can be reproduced in animals by giving them pentavalent arsenicals."

In 1924 Young and Loevenhart (49) found œdema of the optic discs in rabbits after the fourth dose of tryparsamide. Five months later there was a hæmorrhagic exudate in the vitreous of these animals. They also found that among the compounds studied only those trivalent and pentavalent organic arsenicals which had an amino group or a substituted amino group in the *para* position to the arsenic produced optic lesions in the rabbits. On the basis of his experimental studies in animals and from post-mortem study of a patient with syphilis in whom sudden blindness had developed after the use of tryparsamide given two and a half years before, Lazar (50) concluded that the optic atrophy is probably syphilitic in origin.

Other studies on this problem in humans (51) have yielded no conclusive information as to the mode of action of tryparsamide on the optic nerve. It is, therefore, not possible from the available evidence to state whether idiosyncrasy to tryparsamide or reactivation of syphilis is the primary factor in causing ocular damage by this drug.

In spite of the fact that some investigators feel that a diseased eye may be more susceptible to tryparsamide, it has not completely deterred others from the use of this drug in case of optic atrophy. In recent articles, Mayer (52) has reported enthusiastically about the actual high percentage of increased visual acuity following treatment with tryparsamide. In view of the often

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conflicting results from visual field tests in patients whose co-operation is not always adequate, the question arises as to whether this improvement may not have been due to an improvement in the patient's mental status. This point of view was taken by Neff (53). Lillie (54) believed that tryparsamide was not contra-indicated by pathologic changes in the fundus, since he believed that syphilis and not tryparsamide is frequently the factor involved in visual complications. O'Leary and Becker (22) noted that subjective complaints, if unheeded, may lead to permanent damage. They made a pertinent observation in that their cases in which the contracted fields were permanent were all the tabetic type.

Cady and Alvis (55) found 1.3 per cent. permanent damage to the optic nerves in patients treated with tryparsamide, who had normal nerves before they were given the drug, but found that 37 per cent. of patients with optic nerve involvement had definite progression of the lesion after the administration of tryparsamide. They, however, felt that patients with subjective symptoms, if not accompanied by objective signs, could be given more tryparsamide with caution. With objective findings they advised stopping the drug for at least a month when it might be safely resumed. Lees (56), in a large experience, found no case, even among those with less marked optic atrophy, in which there was a lessening of the objective signs of atrophy as a result of treatment.

Many other observers (3, 8, 9, 16, 45, 48, 50, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73) have expressed positive opinions as a result of their experience for or against the use of tryparsamide in patients with some degree of optic damage. The majority of the authors are, on the whole, in favour of conservatism.

The state of flux in which this problem exists is exemplified by the fact that two different authors, Mayer (52) and Lazar (50), observing the same group of patients, reached almost opposite conclusions, not so much as a result of difference in observation, but because of a difference in interpretation.

Regardless of the suggestions pro or con, Hinrichsen (42) in her invaluable review has demonstrated from the reports published from 1923 to 1938 that tryparsamide causes about eight times as many permanent ocular

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complications in patients with damaged eyes before treatment as it does in those with normal eyes before treatment. She found that the average amount of permanent injury to the optic nerve in cases where there was no involvement prior to tryparsamide treatment amounted to 2.9 per cent., whereas in cases with optic atrophy, which were treated with this drug, there was an average incidence of 22.7 per cent. of permanent optic damage.

Stokes (47), in his survey, made a useful outline for the preventive methods to be employed with tryparsamide therapy as follows :

“Preventive Measures :

- (a) Insist on the proper ophthalmological control and complete eye examination before visual acuity tests and perimetric fields (not rough tests) during the first series of 10 injections. Check before each injection (fundus examination alone not trustworthy).
- (b) Enlist patient's co-operation if condition permits and protect yourself by explaining risks and symptoms and obtaining consent (some therapists disapprove).
- (c) If co-operation of patient not obtainable, risk is much increased.
- (d) Begin with moderate dose (1 gram) and have preparatory treatment with '606' and bismuth if possible.
- (e) Question the patient each time before injection.
- (f) Have the ophthalmological report at hand before each injection up to the sixth or tenth. Unnecessary except occasionally thereafter.
- (g) Stop treatment immediately if subjective symptoms appear. Do not wait for objective changes.
- (h) Do not treat pregnant women with tryparsamide. We have no knowledge of the effect on the child's eyes.
- (i) Casten (74) has suggested 'forced' spinal drainage as treatment."

These recommendations were followed as much as possible in our material. One recent prophylactic procedure which might be added is the use of vitamin B-12 previous to or along with the injection of tryparsamide.

From our data we sought to obtain information on the following points :

- (1) Whether the type of neurosyphilis affects the incidence of ocular reactions ;
- (2) Whether the state of the optic nerve predisposes to optic damage by tryparsamide ;

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(3) Whether the type or amount of previous treatment predisposes to tryparsamide ocular reactions ;

(4) Whether other treatment during tryparsamide therapy affects eye complication incidence ;

(5) Whether season of year affects the incidence of optic reactions ;

(6) Whether the size of dose of tryparsamide bears any relationship to ocular complications ;

(7) The effect of intercurrent disease on ocular complications ;

(8) The number of injections in the series, giving a tryparsamide ocular complication.

The type of neurosyphilis seems to bear a definite relationship to the occurrences of ocular reactions. As will be noted from Table I, patients with tabes dorsalis are more susceptible to ocular complications than are patients with tabo-paresis or paresis. This may be related to the greater tendency for optic complications in tabes dorsalis. We have no explanation for the high incidence of apparent ocular reactions in patients with miscellaneous types of neurosyphilis (other than tabes dorsalis or paresis). In one patient with non-syphilitic disease (pemphigus), no ocular complaints were noted. In our series 34.5 per cent. of the patients had eye complaints. All these complaints were minor, but this is an unusually high figure and requires explanation. As will be developed later, our criteria for optic nerve ill-effect of tryparsamide were so strict that this figure is by no means representative.

Our data indicate that patients with normal eyes before treatment have a smaller incidence of eye complications under tryparsamide therapy. Among our patients, there were 103 with normal eyes ; 9 with some eye damage (4 with primary optic atrophy) ; and 1 with no data as to the condition of the optic nerve prior to treatment with tryparsamide. Of the 103 patients with normal eyes, 81 cases showed no apparent changes in their visual acuity or restriction of visual fields during tryparsamide therapy. Twenty-two of these 103 cases with normal eyes were affected either subjectively or objectively. Of the 9 cases with some eye damage, 4 were unaffected, while 5 progressed under tryparsamide. Although the number of cases in the second group is relatively small, the trend indicates that eyes showing

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some damage before tryparsamide treatment are definitely predisposed to aggravation under this therapy. There is definite question whether these patients would have become worse without tryparsamide. Accordingly, the exact rôle of this drug in aggravating eye conditions is impossible to evaluate.

TABLE I.—*Relationship of Ocular Complications to Type of Neurosyphilis*

Type of Neurosyphilis	Percent Ocular Complications
Asymptomatic	29.4
Paresis (clinical)	25
Taboparesis	25
Tabes Dorsalis	43.9
Optic Atrophy	25
Miscellaneous (other than those listed)	45.5

On the question of the effect of previous treatment on tryparsamide ocular reactions, our data showed that the incidence of visual damage is greater on the whole in those receiving lesser amounts of treatment prior to tryparsamide than those receiving more prior to the drug. Here, too, the number of patients in the various categories is not sufficiently great to draw broad conclusions. Of patients receiving little-little treatment, 22 had no reactions and 25 had visual complaints. Of those receiving little-much treatment, 10 had no reactions and 4 had visual complaints. In the much-little treatment group, 7 had no reactions, and 3 had reactions. Of those receiving much-much treatment, 15 were free of trouble and 8 had ocular complaints.

The only concurrent treatment usually given to patients during tryparsamide therapy was bismuth. Of those patients who received no supplementary treatment during tryparsamide therapy, 17 had no visual trouble, while 12 had some complaints. Of those receiving varying amounts of bismuth compounds during treatment with tryparsamide, 58 showed no trouble, while 23 had some inconvenience. This would indicate that supplementary treatment during tryparsamide protects rather than predisposes the individual to ocular damage from tryparsamide.

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From 1935 to 1939 there were 17 patients who had either objective and/or subjective ocular complaints, while from 1930 to 1935 there were 15 reactions. This relatively similar incidence of ocular reactions during the two five-year periods, during which about the same number of injections were given, would tend to indicate that ocular reactions have not increased in our series, at least during the past five years. The incidence of ocular complications is least in the spring, but the difference between the various seasons is relatively insignificant.

Our data are too meagre to give any significant information on the question of whether the size of dose or intercurrent disease plays a part in ocular complications.

We concur in the belief, based on numerous other studies, that the incidence of ocular complications appears in the majority of cases early in tryparsamide treatment. However, the occurrence of complications in 7 patients after the fifteenth injection in the series emphasises the fact that one must not relax vigilance, since these complications may occur late in the course of therapy. Thus, of the 37 patients showing the least suspicion or objective evidence of eye complications, 30 were recognized by the fifteenth injection and 7 after the fifteenth injection. Of those whose trouble was recognized before the fifteenth injection, 24 had signs or symptoms by the sixth injection, 2 between the eighth and tenth injection, 5 between the thirteenth and fifteenth injection (1 patient had visual complaints after two different injections). Of the 7 patients whose visual disturbances occurred subsequent to the fifteenth injection, visual trouble was noted on the eighteenth, twenty-first, twenty-fourth, thirty-ninth, fifty-third, and eighty-second injection. In the patient who noted subjective visual disturbances in the eighty-second injection, further tryparsamide therapy was uneventful.

Our experience would seem to indicate that an unusually high percentage of individuals have some trouble with tryparsamide from the ocular standpoint. As noted above, this incidence is undoubtedly higher than the actual because our criteria were exceedingly strict in that we considered the most insignificant complaints or objective changes as important. While this conservatism may occasionally deprive a patient of tryparsamide therapy it has completely prevented per-

manent blindness attributable to tryparsamide in our patients.

It should be emphasized that visual field determinations are of such a subjective character that one may be uncertain as to the results of such a test. Thus, a visual field may be rated as contracted because of improper evaluation, either by the syphilologist or the ophthalmologist. For example, in a woman with central nervous system syphilis, visual fields were normal before each of the first seven injections of tryparsamide. On the eighth injection, a very *slight* contraction was found. Tryparsamide was stopped temporarily, started again, and four additional treatments were given, all with normal visual fields. Sometimes it is impossible, especially with a patient with indefinite optic atrophy, to distinguish between visual field cuts produced by the optic atrophy or by the effects of the tryparsamide. Thus, a man with incomplete optic atrophy showed partial contraction of his visual fields when first examined. Under tryparsamide therapy his visual fields were variable until about six months after tryparsamide was instituted, when a large upper nasal defect appeared in the field of the right eye. There was no loss in visual acuity, and tryparsamide was continued. Ten months later visual fields were repeated with the same resultant picture. Sometimes the visual fields are apparently abnormal because of lack of co-operation and understanding on the part of the patient. We had, for instance, a woman with neurosyphilis in whom on two examinations three years previously contracted visual fields were reported. When tryparsamide was again considered, her visual fields were found to be normal and continued so during the therapy. This woman, apparently through careful instruction, had finally learned to co-operate in accordance with the necessary technique. Another woman with neurosyphilis had a moderately contracted visual field two months before tryparsamide was started. She had the same contraction after the first dose. Tryparsamide was stopped, and five months later the visual field examination was normal. Tryparsamide treatment was resumed, and the visual fields remained normal until the fourth injection, after which the fields again were contracted. This patient was of the type in whom apparently co-operation was variable.

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Another difficulty in interpretation is the fact that the visual fields may vary for some unknown reason and yet not contra-indicate tryparsamide therapy. A man with neurosyphilis in 1932 showed marked bilateral contraction of his visual fields. However, in April of 1933, tryparsamide was started after visual fields were found to be normal. The injections were stopped at the fifth because the visual fields were contracted (May, 1933). In June, 1933, in spite of the fact that the visual fields were contracted, the patient was started on another series of tryparsamide injections, of which he received nine. During this time various degrees of contraction were found. Five months later his visual fields were normal. Another man with neurosyphilis in 1932 had a pronounced bilateral contraction of his visual fields. Four months later two visual field examinations were normal. All these took place before tryparsamide therapy. During the tryparsamide therapy, all subsequent visual fields were normal. The question arises in such cases whether the improvement in mental status actually makes for better co-operation in the visual field examination or whether the visual fields were really variable.

In a very intelligent man with tabes dorsalis, the visual fields in January, 1933, showed only central vision. One week later, the fields were normal. Another week later there were slightly contracted visual fields. Four more visual field examinations over a period of six weeks were normal. After the fourth and fifth injection of tryparsamide, the left nasal field showed a moderate contraction. Tryparsamide was stopped, and all subsequent visual field examinations were normal. In this case the first examination can be discounted because the patient misunderstood instructions, but the variability before tryparsamide on the one examination may not have been significant in view of the subsequent outcome.

From the technical standpoint, it is well to point out that our visual field determinations were not done by the same observer, using the same size test object, the same apparatus, and the same intensity of illumination over a given period of time. Hence, a series of tests made under these variable conditions would undoubtedly be difficult to evaluate.

From this analysis of the difficulty of interpretation of visual field defects, we feel that our incidence of visual

complications is not exact. It is pertinent, however, to repeat that none of our patients, presumably because of our cautious attitude, has developed permanent amblyopia. In one patient with optic atrophy, in whom this drug was employed as a last resort, the vision gradually disappeared permanently to date. There was no rapid failure of vision as might follow a toxic effect. There were no patients in this series who developed fundus changes that could be attributed to the drug.

This series illustrates the freedom from real ocular damage that can be attained with a drug which has a tendency to produce visual damage, if rigid preventative measures such as suggested by Stokes are observed. However, if the drug is stopped at the least evidence of either subjective or objective complaint, it is undoubted that some individuals will be deprived of what might be a useful therapeutic agent.

SUMMARY

Over a period of ten years in 113 patients who had received about 4,000 injections of tryparsamide, it is noted that the systemic reaction incidence to this drug is relatively minor, but that, nevertheless, the incidence of general reactions has had some tendency recently to increase. In contrast to this, the eye complications to tryparsamide, even when a strict system of evaluation is applied, do not seem to have increased in the past five years.

Our data suggest certain defects in the present subjective method of evaluating the toxic ocular effects of tryparsamide therapy on the basis of visual field examination. Since this drug is best used on patients whose mental status is by no means suitable for the visual field test, this test seems to lack dependability in final evaluation of reactions. Our case material suggests that some more objective method is needed. Possibly rigid standardization of the technique of making visual field examinations will overcome these variations.

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