ACETARSOL IN THE TREATMENT OF LATE CONGENITAL SYPHILIS AMONGST MENTAL DEFECTIVES.

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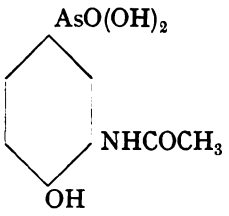
THE treatment of congenital syphilis, in spite of the advances in the general treatment of syphilis in the last thirty years, still leaves much to be desired. Veeder, after treating some 500 cases of congenital syphilis in St. Louis between 1912 and 1920, came to the conclusion that the results of treatment were most unsatisfactory, and that very little was to be gained by the treatment of the syphilitic child. He advocated the treatment of the parents to prevent the birth of syphilitic children. Nabarro is of opinion that the criterion of cure should be the complete cessation of any symptoms of activity and a normal blood and cerebro-spinal fluid. He has not been able to fix any limit of time after which he can regard the patient as cured. He mentions a case of his which relapsed with interstitial keratitis after having had a negative Wassermann reaction for eight years. Ambrose King doubts whether congenital syphilis is ever really cured; he states that "cases had been seen in which manifestations of congenital syphilis appeared only after the lapse of a number of years, and others in which active lesions occurred, but with a negative Wassermann".

At Caterham Hospital, where approximately 10% of mentally defective children were found to be heredo-syphilitics, many had received specific treatment, but the final results could only be described as poor. In 1933 I reported a case of a boy with congenital syphilis who had received prolonged treatment from an early age, in spite of which he developed meningo-vascular syphilis with hydrocephalus and interstitial keratitis. He died at the age of 17, and a post-mortem examination showed widespread lesions attributable to congenital syphilis.

In institutions where large numbers of patients are treated, ease of administration of drugs is desirable. In this respect acetarsol, which is administered by mouth, has obvious advantages over the arseno-benzene derivatives given by injection. Children dread the weekly pricking, which may easily cause psychological upset. For this reason, if for no other, treatment by an oral preparation of arsenic is to be welcomed, if results are at all comparable.

COMPOSITION, PROPERTIES AND HISTORY OF DRUG.

Acetarsol (B.P. Addendum 1936), also known as orarsan, stovarsol, spirocid, osarol and acetarsone, is 3 acetyl-amino 4 hydroxyphenyl arsonic acid, and is represented by the following graphic formula :



It belongs to the pentavalent series of arseno-benzene derivatives, being allied to the better-known tryparsamide. Of a white amorphous appearance, it is practically tasteless and almost insoluble in water, but somewhat soluble in alkaline solutions. Its arsenical content is 27·2%, which compares with 20% in neosalvarsan and 32% in salvarsan. Originally prepared by Ehrlich in 1909 (preparation 594), it was discarded after trial as being too toxic. In 1921 the drug was examined again by Fourneau and his co-workers and renamed " Fourneau 190 ". Levaditi and Nabarro-Martin in 1922 reported that monkeys and rabbits with primary sores were cured by stovarsol administered orally, following which 80 syphilitic patients were treated. In 30 with primary syphilis the chancre disappeared in from 5 to 15 days. Good results were also obtained in secondary and tertiary lesions, but probably owing to the short period of treatment (about 15 days), there were frequent relapses. Sézary and Barbé treated 125 unselected cases of general paralysis (1921–1929), and obtained good results in those with mania and expansive delusions. In 34 of this type 17 were able to resume work and 4 derived benefit. Serological reactions were improved in 34% of total cases.

MacQueen found that spirocid had many advantages over N.A.B. in the treatment of infected Arabs in Palestine.

Stovarsol has also been used in the treatment of yaws, malaria and amœbiasis, but it has been used most successfully in congenital syphilis. Maxwell and Glaser, Abt and Traisman all report very favourably on the action of this drug in congenital syphilis. Nabarro used it in the treatment of a number of congenitally syphilitic infants in residence at St. Margaret's Hospital, several of whom had become serologically negative. It was, however, too early to say whether they were cured. He states, " If it should turn out eventually that stovarsol can cure congenital syphilis, this will be a very distinct advance over treatment by injections ". The plan of dosage he used was that outlined by Prof. Hamburger and his assistant, Dr. Alois Bratusch-Marrain, who is of opinion that the treatment of congenital syphilis with

spirocid is superior to that with neosalvarsan. The Wassermann reaction disappears more quickly and there is better intellectual development. In prolonged treatment it is easier of administration, especially to out-patients. Given in the following manner, toxic reactions due to any hypersensitiveness to the drug are minimized:

For the first 7 days, 0·005 grm. (gr. $\frac{1}{12}$) per kgrm. body-weight daily.
,, following 7 days 0·01 ,, (gr. $\frac{1}{6}$) ,, ,, ,,
,, ,, ,, 0·015 ,, (gr. $\frac{1}{4}$) ,, ,, ,,
,, ,, 42 days 0·02 ,, (gr. $\frac{1}{3}$) ,, ,, ,,

There is then an interval of 4 to 6 weeks, followed by other similar courses until the Wassermann reaction has become negative three times. Even then it is recommended that further half-yearly courses be given for safety. Davidson and Birt, following the method recommended by Maxwell and Glaser, report excellent results in the treatment of congenital syphilis with stovarsol at the Out-patients' Department of the Winnipeg Children's Hospital. Of 27 patients who had been treated for over 7 years by other methods, only 6 Wassermann reactions became negative as compared with 14 changed from positive to negative, and 2 reduced to doubtful in 2 years in a group of 23 treated with stovarsol. They claim that "the decided increase in the percentage of cases cured is enough in itself to assure this drug a permanent place in the therapy of congenital syphilis".

Treatment of Congenital Syphilis at Caterham Hospital (L.C.C.).

In the spring of 1934 it was decided to treat with acetarsol a heterogeneous group of mental defectives suffering from late congenital syphilis. The diagnosis of congenital syphilis was based on (1) family history with, in some instances, blood Wassermann reaction of the mother, (2) physical signs, and (3) serological tests.

The group consisted of 29 cases of both sexes and all ages. As far as known, the majority had not received any prior specific treatment. The duration of treatment was about $2\frac{1}{4}$ years. A control group of 12 other cases received no treatment during that time.

For convenience in analysis the 29 cases are divided into two groups—(1) those with normal cerebro-spinal fluids, and (2) those with abnormal cerebro-spinal fluids, hereafter referred to as Groups A and B respectively. The control group is designated Group C.

Dosage.

The scheme of dosage was mainly that recommended by Bratusch-Marrain, with modifications to suit individual cases. For instance, it was found inadvisable for the maximum dose to exceed gr. 5 (grm. 0·33) *t.d.s.* A few cases were treated with minimal doses only. The daily dose was split into

approximately three equal parts, these being administered crushed in water, half an hour before the principal meals.

Experimental Observations.

When taken orally, does acetarsol reach the blood and cerebro-spinal fluid; if so, in what concentration? This was answered by direct experiment. Through the kind co-operation of Dr. S. A. Mann, of the Central Laboratory of the L.C.C. mental hospitals, and of Dr. J. J. Fox, of the Government Laboratory, to both of whom I am indebted, the arsenical content of samples of blood and cerebro-spinal fluid of Case No. 24 was determined.

Case No. 24.—H. V. B—, male, æt. 27. Family history: 4th child of 8. Two were born dead, 2 died in early infancy, and 1 has recently been admitted to a mental hospital suffering from juvenile general paralysis.

Signs: Frontal bossing, hypoplastic teeth, absent xiphoid appendix. Spastic right hemiplegia. Pupils react to light poorly. Marked tremor of tongue and lips. Ataxia. Slurred speech.

He has been showing slow mental and physical deterioration for the last 10 years and is a typical example of juvenile general paralysis.

The experiment was carried out between the 3rd and 4th courses of acetarsol, when his body-weight was 49 kilos. The first specimen of blood and cerebro-spinal fluid was taken in the morning. Gr. 20 (grm. 1·3) of acetarsol was then given orally, crushed in water, on an empty stomach. Further samples of blood and cerebro-spinal fluid were then taken at the following times with the appended results:

Sample.	Time.	As_4O_6 parts per million.
1	Cerebro-spinal fluid 10.40 a.m.	Less than 0·4.
2	,, 11.50 a.m.	,, ,, 0·4.
3	,, 12.50 p.m.	Approximately 0·4.
4	,, 2.0 p.m.	Less than 0·4.
5	,, 4.30 p.m.	Approximately 1.
6	,, 10.40 a.m. (next day)	Less than 0·4.
1	Blood from arm vein 10.40 a.m.	0·9
2	,, ,, 11.50 a.m.	1·8
3	,, ,, 12.50 p.m.	3·5
4	,, ,, 2.0 p.m.	5·2
5	,, ,, 4.30 p.m.	9·3
6	,, ,, 10.40 a.m. (next day)	21·1

These findings would appear to indicate non-penetration of the drug into the cerebro-spinal fluid. The rise in the 4.30 p.m. specimen was due to slight blood contamination. The arsenical content of the systemic blood on the

other hand rises from 0·9 to 21·1 parts per million in 24 hours, clearly showing absorption from the alimentary tract.

Serological Reactions.

These were carried out at the Central Pathological Laboratory of the London County Mental Hospitals. Specimens of blood and cerebro-spinal fluid were examined before and at the end of every course. The blood-serum was examined by the Wassermann reaction and the macro-Meinicke clarification reaction (M.K.R.). The cerebro-spinal fluid was examined for increase of cells and protein and the Wassermann reaction and Lange's colloidal gold test were done. The technique used was that of Mann and Partner.

Briefly, for the Wassermann reactions, the figure following the first plus indicates the number of units of complement (1 unit equals approximately 0·01 c.c. of pure guinea-pig serum) absorbed by 1 c.c. blood-serum or cerebro-spinal fluid. The plus following the figure indicates that a further absorption of complement would take place if the range of dilution of serum or cerebro-spinal fluid were extended.

For the macro-Meinicke clarification test (M.K.R.) four tubes are set up. A positive reaction is indicated by complete clarification of at least one tube.

Group A.

This consisted of 19 cases (5 males and 14 females); 12 of these were under 26 years, and 7 over. Case No. 19, a female aet. 48, had active lesions but negative serology. Of 17 cases showing positive Wassermann reactions prior to treatment, 8 became negative, 7 were reduced in strength, and 2 were unchanged after treatment. The M.K.R. reaction was more resistant; of 18 positives, 6 became negative, 6 were reduced in strength, and 6 were unchanged. The corresponding figures for the control group (C) were: Wassermann reactions positive, 7; became negative, 1; reduced in strength, 0; unchanged, 4. M.K.R. positive, 10; became negative, 1; reduced in strength, 2; unchanged, 7.

In Group A there was no increase of positivity after treatment, but in Group C over approximately the same time, 4 negative Wassermann reactions and one doubtful became positive, 2 increased in strength. Though the control group is not exactly comparable in respect of age and sex to the treated group, the difference in the final serological reactions is so marked as to leave little doubt as to the drug's influence.

It will be noted that as many as 5 out of 6 who were finally both Wassermann and Meinicke negative were under 20 years of age. This would appear to indicate better serological response to treatment in the younger members of this group.

TABLE I.—*Group A : Cases with Normal Cerebro-spinal Fluid before, during and after Treatment.*

Case No.	Sex.	Age.	Grade.	Number of courses.	Before treatment. Blood.		After treatment. Blood.		Weight in kg.		Hb in grm. per 100 c.c. blood.		Highest eosinophil count. (%).	Toxic reactions.	Clinical results (improvement).		Remarks.
					W.R.	M.K.R.	W.R.	M.K.R.	Before treatment.	After treatment.	Before treatment.	After 3rd course.			Physical.	Mental.	
1	M.	12	Imb.	4	+15	++	—	—	34·5	45·4	12·8	12·0	23·4	..	Good	Good	..
2	,,	17	,,	6	—	++++	—	—	42·0	43·3	12·8	13·9	3·6	..	Moderate	*Nil*	..
3	,,	18	,,	6	+30+	++++	+30+	++++	48·6	54·2	13·1	12·3	6·3	..	Good	,,	..
4	,,	20	,,	7	+30+	++++	—	+	46·4	48·6	13·3	13·2	3·4	..	,,	Moderate	..
5	,,	25	F.-m.	5	+6	++++	—	—	51·3	54·6	..	..	..	..	,,	Good	..
6	F.	20	Imb.	6	+30+	++++	—	+++	55·9	56·2	11·8	12·8	2·0	Dermal	Very good	Moderate	Minimal dosage.
7	,,	30	,,	6	+30	++++	—	+++	37·7	39·0	12·8	14·2	3·0	,,	Moderate	,,	..
8	,,	14	,,	7	+30+	++++	+15+	+++	30·5	34·9	11·8	12·5	1·0	..	Good	,,	..
9	,,	33	F.-m.	6	+30+	++++	+30	++++	58·0	60·7	..	..	..	..	,,	,,	Active signs.
10	,,	32	,,	7	+30+	++++	+30+	++++	60·5	62·6	10·2	12·3	2·0	Herpes	,,	,,	..
11	,,	31	,,	7	+15+	++++	+6	+++	72·7	68·4	11·8	13·8	1·7	Lungs	Very good	Good	..
12	,,	14	Imb.	7	+30+	++++	+15+	++++	28·2	34·0	10·2	12·6	3·1	Dermal	,,	Moderate	Minimal dosage.
13	,,	17	,,	7	+30+	++++	+15	+++	53·6	57·0	10·2	11·8	5·0	,,	Good	Good	..
14	,,	13	,,	5	+30+	++++	—	—	46·8	39·0	12·8	13·0	3·0	Pharyngitis	,,	Moderate	..
15	,,	31	,,	7	+30+	++++	+15+	++++	60·5	64·0	12·8	13·0	1·0	Dermal	Very good	,,	..
16	,,	17	,,	7	+15+	++++	—	—	54·3	53·1	11·6	12·6	0·6	,,	,,	Good	..
17	,,	59	,,	5	+30	++++	+6	++++	59·7	56·6	13·0	12·8	2·8	..	Died	..	Aplastic anæmia.
18	,,	16	,,	5	+30	++++	—	—	35·4	35·8	..	..	..	..	Good	Good	..
19	,,	48	,,	4	—	—	—	—	45·4	48·8	12·7	13·9	0·7	..	,,	Moderate	Active signs.

Imb. = Imbecile. F.-m. = Feeble-minded (Moron). W.R. = Wassermann reaction (+30+ = strongly positive; +6 = weakly positive). M.K.R. = Macro-Meinicke clarification reaction (++++ = strongly positive).

TABLE II.—*Group B: Cases with Abnormal Cerebro-spinal Fluid before Treatment.*

Case No.	Sex.	Age.	Grade.	Number of courses.	Time (before or after treatment).	Blood.		Cerebro-spinal fluid.				Weight in kgrm.	Hb. in grm. per 100 c.c. blood.	Highest eosinophil count. (%).	Toxic reactions.	Clinical results (improvement).		Remarks.
						W.R.	M.K.R.	W.R.	Cells.	Pandy.	Lange.					Physical.	Mental.	
20	M.	11	Imb.	7	Before	+30+	++++	—	—	++	5555443210	27·5	13·3	3·0	Drowsy	Moderate	*Nil*	..
					After	+30	+++	+6	±	±	4433211000	24·5	12·3					
21	,,	11	,,	6	Before	+30+	++++	+30+	++	++	5555543210	22·3	11·6	7·0	Herpes	Good	Moderate	A case of juvenile G.P.
					After	+30+	++++	+30	—	+	5554321000	17·2	12·8					
22	,,	12	,,	7	Before	+30+	++++	+15	+	+	5544321000	24·8	11·8	2·7	..	Very good	Good	..
					After	+30+	++++	+6	—	—	—	30·8	13·0					
23	,,	13	,,	6	Before	+30+	++++	+3+	+	+	4443321000	42·1	12·8	4·0	..	,,	,,	..
					After	—	—	—	—	—	—	42·2	12·8					
24	,,	26	,,	7	Before	—	+	—	—	+	3322110000	47·0	12·3	16·0	..	Moderate	*Nil*	A case of juvenile G.P.
					After	—	—	—	±	±	4433210000	50·0	14·4					
25	,,	16	,,	6	Before	+30+	++++	+6	++	++	3344553210	28·4	12·3	4·0	..	Good	Moderate	..
					After	+30+	++++	—	—	—	—	35·4	12·8					
26	F.	12	,,	7	Before	+30+	++++	+30+	+	++	5555554321	25·5	10·9	8·0	Dermal	Very good	,,	Minimal dosage.
					After	+30+	++++	+3	—	±	3222110000	39·4	12·3					
27	,,	34	F.-m.	7	Before	+30+	++++	+30	++	++	5555432100	56·3	12·8	3·7	..	Good	,,	..
					After	+30+	++++	+15	+	++	5555432100	58·5	13·5					
28	,,	14	,,	3	Before	+30+	++++	+15	±	±	2221110000	36·7	..	..	..	,,	,,	A case of juvenile G.P.
					After	+30+	++++	+15	—	±	—	44·5	..					
29	,,	51	Imb.	7	Before	+30+	++++	—	+	+	—	69·5	13·4	1·8	..	*Nil*	*Nil*	..
					After	+30+	++++	—	—	—	—	59·8	13·9					

Cerebro-spinal fluid.—Cells negative (—) = under 6 per c.mm. Cells ± = 7 to 8 per c.mm. Cells + = 9 to 20 per c.mm. Cells ++ = 20 to 30 per c.mm. Cells +++ = 30 to 40 per c.mm. Cells ++++ = Over 40 per c.mm.

TABLE III.—*Group C: Untreated Control Cases; Observations made at Times Roughly Corresponding to those of Group A.*

Case No.	Sex.	Age.	Grade.	1934. Blood.		1936. Blood.		Weight in kgrm.		Clinical results. (Improvement.)		Remarks.
				W.R.	M.K.R.	W.R.	M.K.R.	1934.	1936.	Physical.	Mental.	
C. 1	F.	20	F.-m.	±	+++	+30+	+++	63·5	67·5	*Nil*	*Nil*	..
C. 2	,,	48	Imb.	+30	++++	+30+	+++	50·8	51·3	Moderate	,,	..
C. 3	,,	44	,,	+30	++++	+30	++++	58·9	62·1	*Nil*	,,	..
C. 4	,,	20	,,	—	+++	+15	+++	46·3	51·7	,,	,,	Epileptic. Fits increased.
C. 5	,,	22	,,	+30+	++++	+30+	++++	44·5	43·6	,,	Moderate	..
C. 6	M.	10	,,	+30	+++	—	—	25·8	29·7	Good	Good	..
C. 7	,,	24	,,	+30+	++++	+30+	++++	47·7	47·2	*Nil*	*Nil*	Epileptic. Fits increased.
C. 8	,,	21	,,	—	++++	+10	+++	43·6	42·2	,,	,,	..
C. 9	,,	25	,,	+30	++++	+30	++++	51·2	53·5	Moderate	,,	Epileptic. Fits increased.
C. 10	,,	27	,,	+30	++++	+30+	++++	44·0	43·6	*Nil*	,,	..
C. 11	,,	27	,,	—	—	+10+	++	46·3	47·6	,,	,,	..
C. 12	,,	20	,,	—	—	+15	++++	49·5	50·8	Moderate	,,	..

Group B.

This comprised those with abnormal cerebro-spinal fluid. There were 10 cases, 6 males and 4 females. Included are 3 cases of juvenile general paralysis (Nos. 21, 24 and 28), the last of whom is still undergoing treatment; the others were considered to be examples of meningo-vascular syphilis.

Blood sera.—Of 9 with positive Wassermann reactions, only 1 became negative and 1 slightly decreased in strength. Two out of 10 positive M.K.R.'s became negative (one was only slightly positive before treatment), and 1 slightly reduced in strength. These results are in marked contrast with those of Group A.

The cerebro-spinal fluid: Wassermann reaction.—Of 7 positive before treatment, 2 became negative and 4 reduced in strength. One (No. 20), originally negative, became slightly positive after treatment.

Cells.—Of 7 showing abnormal increase of cells before treatment, 6 were back to within normal limits and 1 showed reduction after treatment. The cells were of the lymphocytic type.

Pandy's test.—Of 9 originally positive, 4 became negative, 3 almost negative, and 1 reduced in strength after treatment.

Lange's colloidal gold test.—Before treatment 9 gave positive curves of varying strength, mainly of the paretic type. At the end of treatment, 4 of these were completely negative, 3 weaker, 1 unchanged, and 1 slightly stronger.

Of the total 10 cases with abnormal cerebro-spinal fluids, 3 such fluids became completely normal and 7 improved after treatment.

No controls were available in this group.

TABLE IV.—*Number of Cases showing Serological Changes during Treatment.*

Total number of cases 29.	Blood.		Cerebro-spinal fluid.			
	W.R.	M.K.R.	W.R.	Cells.	Pandy.	Lange.
Number of cases negative before treatment . .	3	1	22	22	20	20
,, ,, ,, after 1st course . .	8	3	21	24	26	21
,, ,, ,, ,, 2nd ,, . .	7	2	22	26	24	22
,, ,, ,, ,, 3rd ,, . .	6	4	23	25	24	24
,, ,, ,, ,, 4th ,, . .	10	4	24	26	26	25
,, ,, ,, ,, 5th ,, . .	12	6	23	26	26	24
,, ,, ,, ,, 6th ,, . .	10	8	23	29	25	25
,, ,, ,, ,, 7th ,, . .	12	9	23	28	27	24

Pandy ± reactions and ± cells (slight increase) have been taken as negative.

RELAPSES.

As will be seen from the above table, serological relapse during treatment was fairly common in those whose blood Wassermann reaction or M.K.R. had become negative. The best results were obtained in the 10 cases showing abnormal increase of cells in the cerebro-spinal fluid—after the 6th course cells were in every case within normal limits. At the end of the 7th course, however, one case had relapsed.

The following are brief details of those cases showing serological relapse during treatment:

CASE NO. 1.—S. M—. After 1st course both W.R. and M.K.R. became negative. Four months later they were still negative. Seven months later blood W.R. + 30, M.K.R. +. He then had a 2nd course, at the end of which his blood W.R. was negative, M.K.R. +++. After 3rd course both W.R. and M.K.R. were negative and remained so after subsequent courses.

This case is an example of the uselessness of giving a single course.

CASE NO. 2.—H. M—. Blood M.K.R. negative at end of 4th course. At end of 5th course M.K.R. ++. At end of 6th course M.K.R. negative.

CASE NO. 4.—W. F—. Blood W.R. negative at end of 4th and 5th courses. At end of 6th course W.R. + 6. At end of 7th course W.R. negative again.

CASE NO. 5.—S. J—. At end of 1st course blood W.R. negative. After 2nd course W.R. + 6. 3rd course W.R. negative, 4th course W.R. + 6, and finally after 5th course W.R. negative.

CASE NO. 7.—M. C—. At end of 5th course blood W.R. negative. At end of 6th course W.R. + 30. At end of 7th course W.R. negative.

CASE NO. 11.—M. C—. At end of 4th course blood W.R. negative. At end of 5th course W.R. + 6. At end of 6th course W.R. negative again.

CASE NO. 16.—A. B—. At end of 2nd course blood W.R. negative. At end of 3rd W.R. + 6. At end of 4th and 5th courses W.R. negative. At end of 6th W.R. + 6, and finally at the end of the 7th course W.R. negative.

CASE NO. 17.—A. T—. At end of 1st course blood W.R. negative. At end of 2nd W.R. + 30. At end of 3rd and 4th W.R. + 15, and at the end of the 5th course W.R. + 6. She died of aplastic anæmia soon after.

CASE NO. 18.—R. G—. At end of 2nd course W.R. negative. At end of 3rd course W.R. + 6. At the end of 4th course W.R. + 30+, and at the end of the 5th course W.R. negative. M.K.R. also negative for the first time.

In contrast with the above the following two cases showed no signs of relapse after having become negative :

CASE No. 6.—J. C—. Blood became Wassermann negative at the end of the 4th course and showed no tendency to relapse subsequently.

CASE No. 14.—K. V—. From being Wassermann and Meinicke strongly positive before treatment, she became both Wassermann and Meinicke negative after the 1st course, and remained so throughout treatment, 4 further courses being given.

HÆMATOLOGY.

In 25 cases blood-counts were made before treatment and after the 1st and 3rd courses. Hæmoglobin content was estimated, using the Klett biocolorimeter with the Newcomer Standard. As a result of treatment, hæmoglobin was increased in 13 cases by 1 grm. or more per 100 c.c. blood, in 4 cases 2 grm. or more. Five cases showed loss of 1 grm. or less.

Red blood-cells.—21 cases showed gains of between 50,000 and 950,000; 6 of these gained over 500,000 per c.mm. Four cases showed losses of 20,000 to 210,000 per c.mm. There were increases in the colour index in 13 cases. Abnormal red cells were absent.

Leucocytes.—Counts varied from 6,000 to 12,000 per c.mm. In 8 cases the lymphocytic percentage was over 45. Treatment resulted in an increase in eosinophil cells in all 25 cases. Only 15 of these cases, however, showed an eosinophilia of 3% or over.

Urine.

Urinary examinations were made at least once a week throughout treatment. Abnormal constituents were uncommon.

CASE No. 13.—One of chronic nephritis, with albuminuria varying from 0·1 to 0·2% (Esbach), and moderate number of granular casts, showed no change during or after treatment.

CASE No. 17.—Developed mild glycosuria during the 2nd course, persisting throughout treatment.

CASE No. 27.—Showed transient albuminuria (1% Esbach) during the 2nd course.

CASE No. 29.—Showed slight albuminuria during the 2nd course.

CASES No. 12 AND 16.—Showed traces of reducing substance at irregular intervals during treatment.

Bile-salts or pigment were absent from all samples tested during treatment.

Weight.

Records of weight before and after each course were made. At the end of treatment 22 cases had gained, and 7 lost weight. In those of 20 years or under the average gain of weight per case was 4·2 kgrm. (14 cases), and the

average loss 4·3 kgrm. (4 cases). Of those over 20 years old the corresponding figures were 2·7 kgrm. (8 cases) and 5·7 kgrm. (3 cases). With the exception of Case No. 29 all those showing loss of weight had at one time or another shown idiosyncrasy to the drug.

Two of the 3 cases of juvenile general paralysis gained weight.

Control group.—In those of 20 years or under the average gain was 3·6 kgrm. (4 cases). None lost weight. Of those over 20 the average gain per case was 1·8 kgrm. (4 cases), and the average loss 0·8 kgrm. (4 cases).

Epilepsy.

There were 8 epileptics in the treated and 3 in the control group. Fits were of the major type, non-Jacksonian in character, and, when numerous, bromides or luminal had been administered continuously. This has unfortunately introduced a factor whose influence has to be taken into account in the assessment of the value of acetarsol in epilepsy associated with congenital syphilis. Two further unselected small groups of non-syphilitic epileptics are therefore given for comparison, one treated by bromides, and the other by luminal.

Treated Group.

Case No. 5 had his first fit during 1934, prior to treatment with acetarsol. He had 1 fit in 1935 and none in 1936. No sedatives given.

Case No. 9 had 7 fits in 1934, 2 in 1935 and 2 in 1936 (up to June).

Case No. 12 had fits for the first time in February, 1935. She had 8 during that year and 4 up to July, 1936.

The 5 remaining cases had sufficiently numerous fits to allow comparison with the untreated and other groups.

The influence of acetarsol is best seen in cases Nos. 4 and 20, where a progressive reduction of fits occurred.

Case No. 14 did not show any real reduction of fits until 1936, when there was a sudden drop.

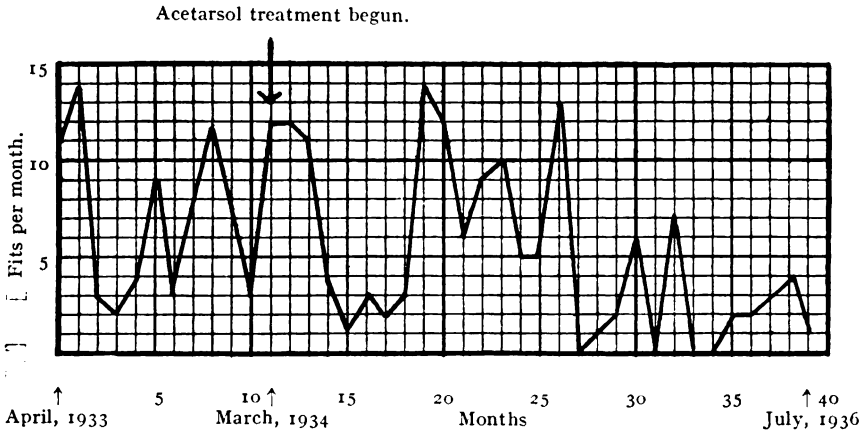
Case No. 17 showed a reduction of fits up to two months before death.

Case No. 10 was the only one to show an increase in fits, but the increase was small. It will be noted, however, that she was the only one in this group taking luminal.

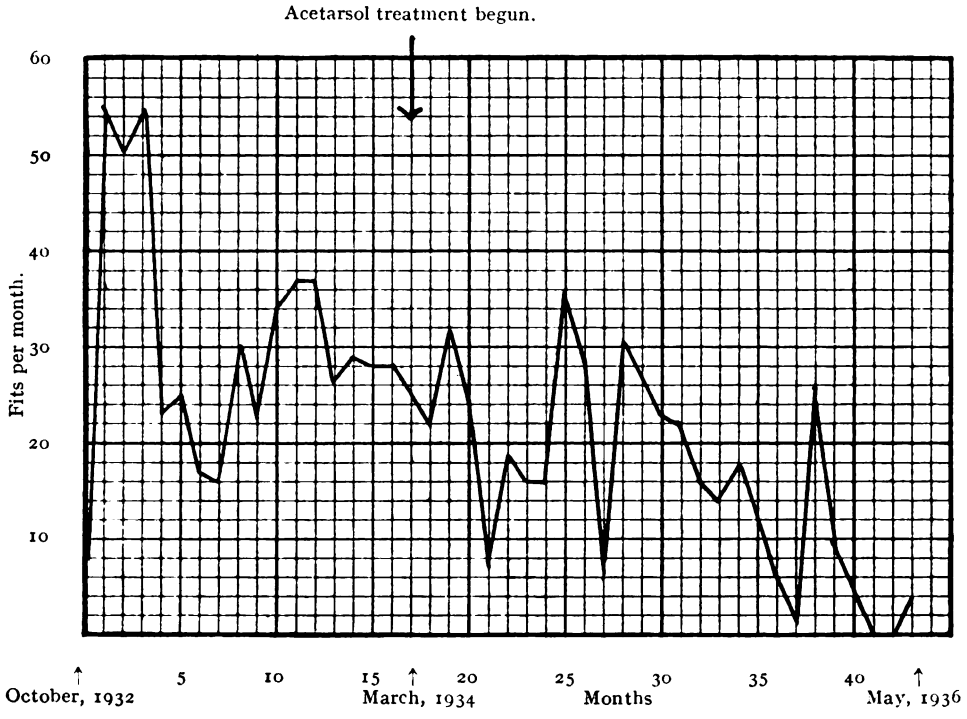
Control group.—(Untreated congenital syphilitics with epilepsy). In this group the fits tended to increase in number, the administration of luminal appearing to have only a temporary sedative influence.

Is the reduction of fits in the acetarsol-treated group mainly due to the influence of bromides, and the increase in the control group to luminal? The answer is not easy, but I would suggest that the reduction of fits in the

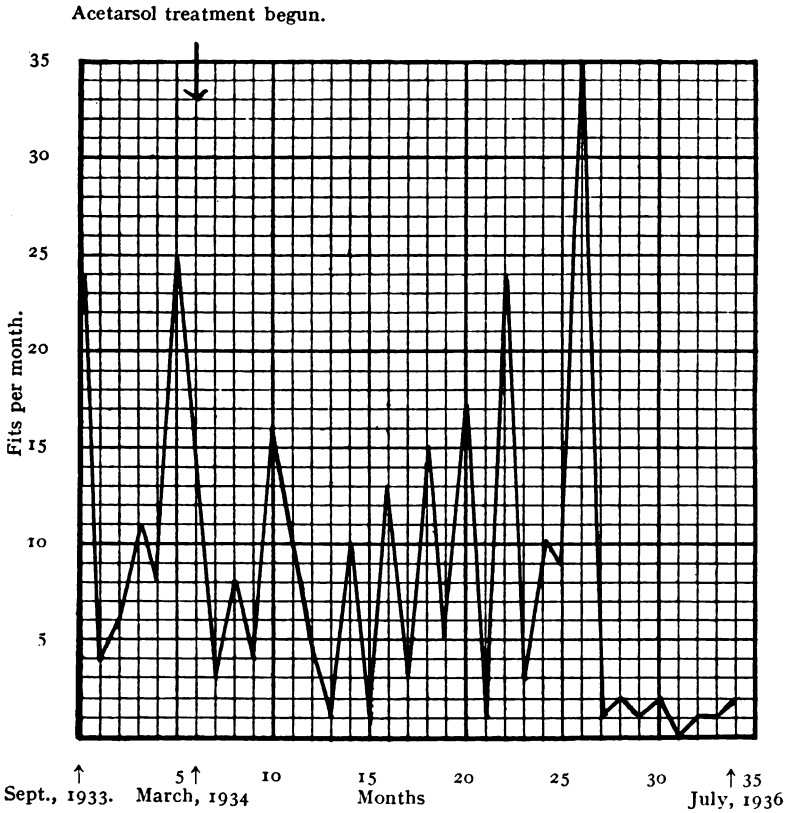
CASE No. 20. Sod. brom. gr. xv twice daily.



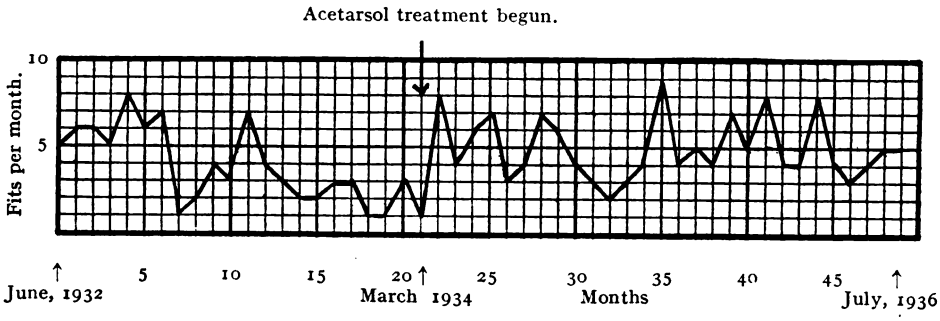
CASE No. 4. Pot. brom. gr. xv *t.d.s.*



CASE NO. 14. Pot. brom. gr. xv *t.d.s.*



CASE NO. 10. Luminal gr. i daily.



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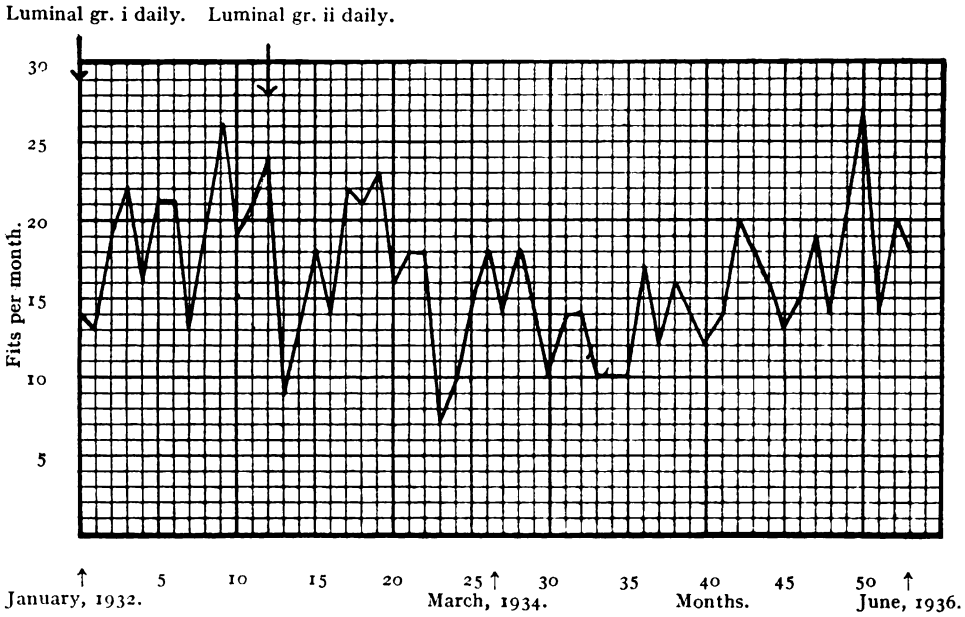
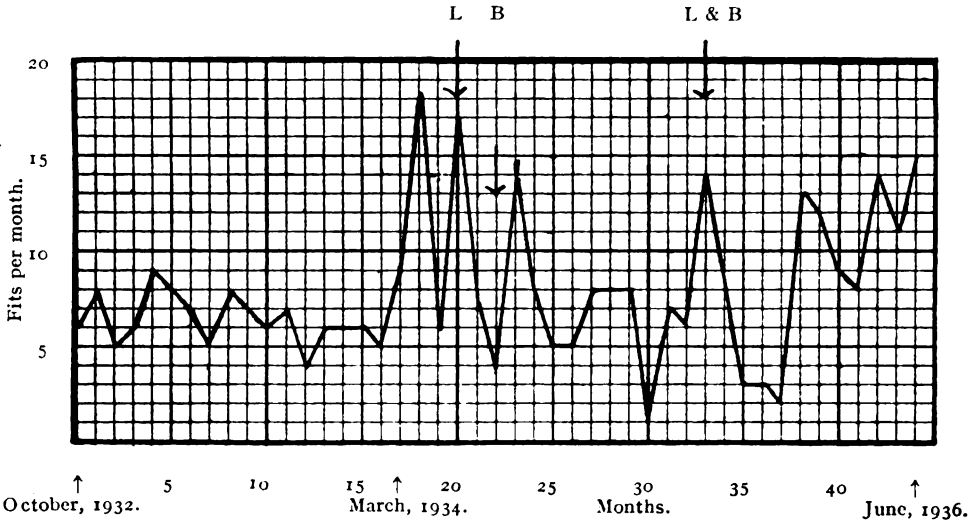
CASE. CONTROL NO. C4.



CONTROL NO. C7.

Treatment: At L, luminal gr. ½; at B, pot. brom. gr. x; at L & B, luminal and bromide in same doses.



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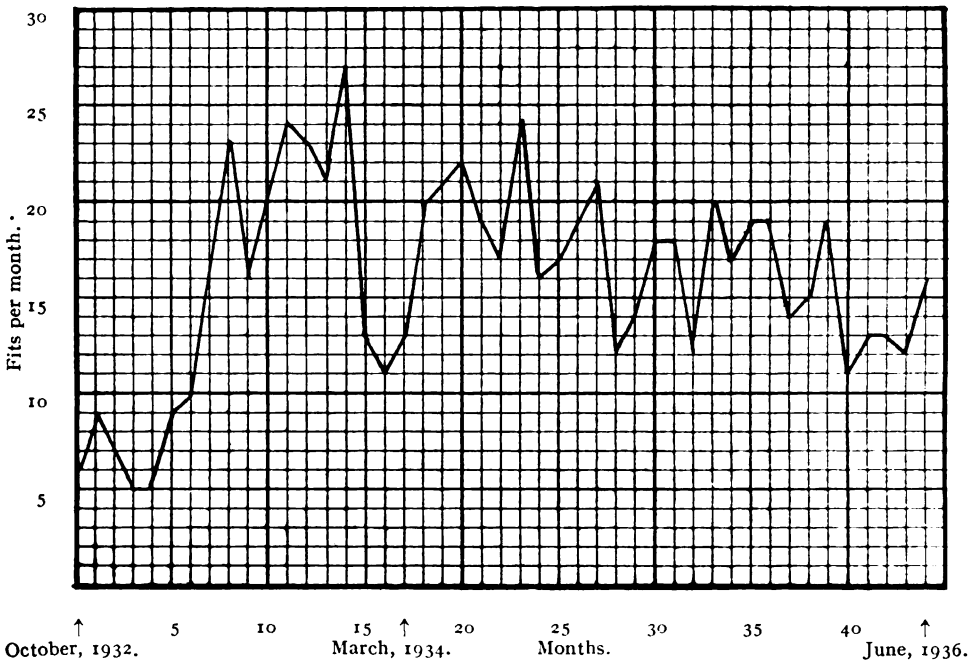
CONTROL No. C9. Luminal gr. i daily.



acetarsol-treated group is mostly, if not entirely due to specific treatment, for the following reasons :

1. In the treatment of epileptics at Caterham (where there are over 650 in residence) the sedative most suitable for the individual case is always chosen. It is pure coincidence that the acetarsol-treated group should have had 4 out of 5 epileptics on bromides continuously, and all 3 of the control group on luminal.

2. On the whole, defective epileptic children appear to do better on luminal than bromides. The latter have often been noticed to produce mental confusion and fits are not always reduced. For example, the following are brief details of two non-syphilitic epileptic boys selected at random :

M. G—, æt. 6 in 1932. Average number of fits per month during 1932 (5), 1933 (3), 1934 (3), 1935 (5), 1936 (7 months' average) (7).

He received pot. brom. gr. xv (grm. 1) twice daily throughout. No mental improvement.

R. D—, æt. 8 in 1931. Had an average of 9 fits per month from March to August, 1931, when he was put on luminal gr. ½ (grm. 0·032) daily. Fits then numbered 14 in September, 20 in October, 8 in November and 3 in December. Dose then doubled. In January, 1932, 2 fits, in February 1, then none until

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November, 1933, when 1 fit was recorded. None during 1934. One in March, 1935, and none in 1936 (7 months). He was much brighter mentally.

In the acetarsol-treated group there were two epileptic children (Cases No. 14 and 20), both on bromides. They have nevertheless done quite well. Fits were reduced in number.

3. Figures are given of average number of fits per case per month in (*a*) acetarsol-treated group, (*b*) control group, (*c*) non-syphilitic epileptic group on bromide, (*d*) similar to (*c*), but on luminal. The acetarsol-treated group is the only one to show any significant reduction of fits.

The non-syphilitic epileptic group was unselected, the only criteria for inclusion being suitability of age and continuous treatment by bromide or luminal over $3\frac{1}{2}$ years.

TABLE V.—*Epileptics.*

AVERAGE NUMBER OF FITS PER CASE PER MONTH.

Groups.	Number of cases.	1933.	1934.	1935.	1936.*
Syphilitic :					
Treated group	5	11	10	9	3†
Control ,,	3	14	13	13	14
Non-syphilitic :					
Bromide ,,	4	7	9	9	7
Luminal ,,	4	7	9	11	9

* 7 months' average.
† Average of 4 cases.

ACETARSOL-TREATED GROUP EPILEPTICS.

Case No.	Age.	Average number of fits per month. 1933.	1934.	1935.	1936.*	Treatment for epilepsy.
4	20	29	23	17	6	Pot. brom. gr. xv, *t.d.s.* throughout.
10	32	3	5	5	5	Luminal gr. i daily throughout.
14	13	11	9	12	1	Pot. brom. gr. xv *t.d.s.* throughout.
17	59	6	3	4 (9 mos.)	Died	Pot. brom. gr. xv *t.d.s.* during August, 1935.
20	11	7	8	5	1	Sod. brom. gr. xv *b.d.*
	Total	56	48	43	13	

* 7 months' average.

CONTROL GROUP EPILEPTICS WITH CONGENITAL SYPHILIS.

Case No.	Age.	Average number of fits per month. 1933.	1934.	1935.	1936.*	Treatment for epilepsy.
C. 4	20	17	13	16	19	Luminal gr. i daily until Jan., 1933; gr. ii after.
C. 7	23	7	9	7	10	Luminal gr. $\frac{1}{2}$ c̄ pot. brom. gr. x varied (*see* graph).
C. 9	24	17	18	17	14	Luminal gr. i daily throughout.
	Total	41	40	40	43	

* 7 months' average.

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NON-SYPHILITIC EPILEPTIC GROUP TREATED WITH BROMIDE.

Case.	Age.	Average number of fits per month. 1933.	1934.	1935.	1936.*	Treatment.
D. H—	24	9	14	13	10	Pot. brom. gr. xv, *t.d.s.* throughout.
E. C—	22	9	11	16	12	Sod. brom. gr. xv *t.d.s.* throughout.
M. G—	19	5	4	3	3	Tri. brom. gr. xv *t.d.s.* throughout.
A. B—	26	6	5	3	3	Sod. brom. gr. xv *t.d.s.* throughout.
	Total	29	34	35	28	

* 7 months' average.

NON-SYPHILITIC EPILEPTIC GROUP TREATED WITH LUMINAL.

Case.	Age.	Average number of fits per month. 1933.	1394.	1935.	1936.*	Treatment
E. L—	24	3	2	2	2	Luminal gr. i *b.d.* throughout.
R. D—	27	6	9	15	11	,, ,, ,,
K. H—	25	13	13	16	16	,, ,, ,,
E. S—	22	7	11	10	7	,, ,, ,,
	Total	29	35	43	36	

* 7 months' average.

SEIZURES.

Two of the 3 cases of juvenile general paralysis were subject to seizures.

CASE No. 24.—The average number of seizures per month was 22 in 1932, 29 in 1933, 26 in 1934, 22 in 1935 and 26 in 1936 (average 7 months). No sedatives given. Treatment by acetarsol appeared to have had little influence on the frequency of seizures in this case.

CASE No. 21.—This boy had convulsions when aged 1. He had a seizure in June, 1933, and another in November, 1933, then none until June, 1934. Thereafter he had from 1 to 7 seizures per month. For 7 months of 1936 he only had 4, with 3 clear months. No sedatives given. Treatment by acetarsol has been beneficial in this case. Physical and mental improvement coincided with reduction of seizures in 1936.

CLINICAL RESULTS.

The physical and mental condition of the patients were noted before and after treatment. Physical improvement was assessed in terms of general physical fitness, improved muscle tonus, and disappearance of active signs of disease.

Bodily Condition.

Group A : Improvement was marked in 5 cases, good in 11, and moderate in 2.

Group B : Improvement marked in 3 cases, good in 4, moderate in 2, and *nil* in 1.

There was no correspondence between physical and serological improvement.

Mental Condition.

Mental improvement was judged in terms of general " brightness ", increased interest, better response to training, retentivity and emotional stability.

Many of the treated cases were receiving specialized training by skilled occupational supervisors, and it is not here suggested that the administration of the drug was solely responsible for physical or mental improvement, but only that, in alleviating bodily disease, physical and mental education were thereby facilitated.

GROUP A.—Mental improvement was good in 6 cases, moderate in 10 and *nil* in 2.

GROUP B.—Mental improvement was good in 2, moderate in 5 and *nil* in 3.

GROUP C.—The results in this untreated control group compare unfavourably with the treated groups.

Bodily condition: There was good improvement in 1 case, moderate in 3 and *nil* in 8.

Mental condition: Good improvement in 1, moderate in 1 and *nil* in 10.

As an example of mental improvement in a case from Group A, I quote a report from the occupational supervisor: *

CASE NO. 25.—J. E—. Male. Imbecile. Æt. 16. " This boy has definitely improved in school work for some time. His rote memory has improved; he recognizes primary colours but cannot distinguish varying tones of these colours. Auditory powers better but still lacking in fine discrimination. His handwork shows good motor co-ordination as compared with former attempts. General bearing more purposeful, and though still stubborn can give a better account of himself in class work and games."

This boy had, prior to treatment, been attending the school for over 3 years, but little progress had been noted. His cerebro-spinal fluid was abnormal before treatment, became normal after the 2nd course, and remained so throughout (three further tests being done). His blood-serum remains Wassermann and Meinicke positive.

Cases with Active Lesions.

There were two cases of this type. One was an example of active disease with persistent negative Wassermann and Meinicke reactions. Treatment by acetarsol gave very satisfactory results in both cases.

CASE NO. 9.—J. S—, female, æt. 33. Family history, 7th of 13 by mother's 1st marriage. Five still-born, 4 died in early infancy, 3 alive, one of whom is stone deaf. By 2nd marriage: 1 miscarriage, 3 still-born, 1 died in early infancy, 1 alive but in poor health and only 1 healthy.

Signs: Peripheral opacities of lens.

* I am indebted to Miss MacAlister for this report.

On November 1, 1934, she developed a painless ulcer of the pharyngeal wall, about ¼ in. across, with well-defined edges, and dirty whitish base. Treated with gargles for 1 week but no response.

First course acetarsol begun on November 8, 1934. Ten days later, after having received gr. 58 (grm. 3·9), the ulcer was completely healed. This course and 5 others were undergone with benefit.

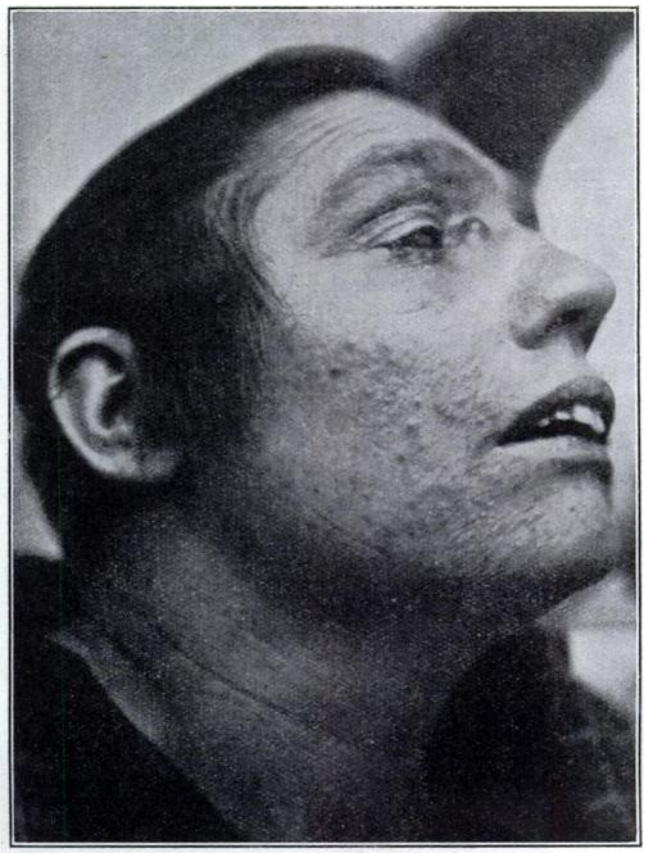

FIG. 1*a*.—Case No. 19: Before treatment.

CASE NO. 19.—E. G—, female, æt. 48. Family history, 1st of 12, 5 of whom died in early infancy.

Signs: Advanced double interstitial keratitis. Mitral stenosis.

This patient's blood was Wassermann positive up to 1928, but without treatment became persistently negative. Nevertheless in 1934 she developed a right dacryocystitis, with activation and extension of an old interstitial keratitis of the right cornea. Her hair became coarse, dry, and was falling off freely. Her face was covered by an "acne rosacea".

Treatment with acetarsol was instituted, and she received 4 full courses,

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at the end of which the facial rash had almost cleared up, her hair was growing profusely and had regained its normal lustre. The dacryocystitis and interstitial keratitis subsided in 2 months. Eyesight was practically *nil*, but it was found possible to perform a high iridectomy, giving a limited vision. Her general health is much improved; she is much brighter and takes much more interest in her surroundings (*see* Figs. 1*a*, 1*b*, before and after treatment).

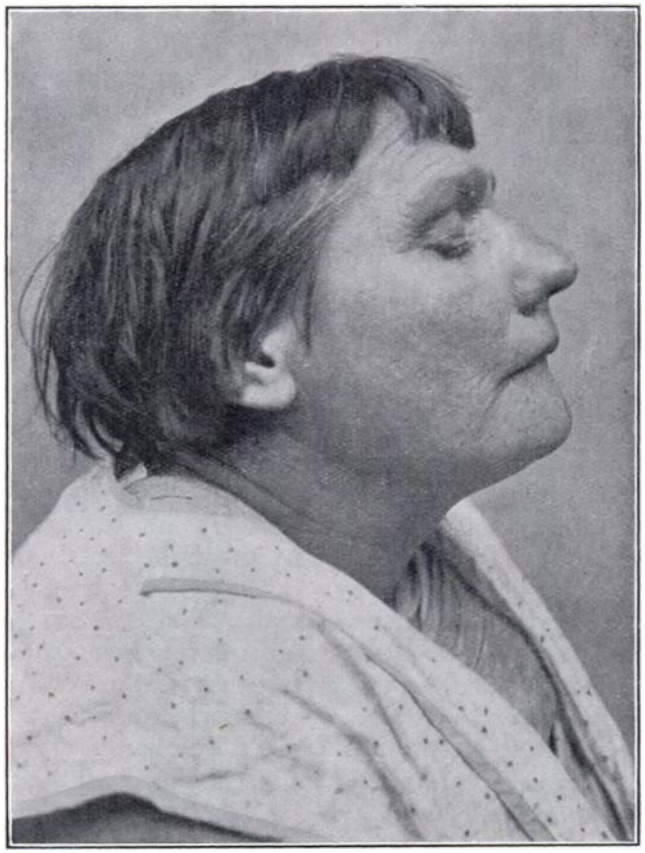

FIG. 1*b*.—Case No. 19: After treatment with acetarsol.

COMPLICATIONS.

As many as 13 of the 29 treated developed toxic symptoms at one time or another. Only 4 of these 13, however, were finally unable to follow the ordinary dosage according to weight. The chief complications were (1) erythematous skin rashes (6 cases), (2) herpes (3 cases), (3) pharyngitis (3 cases), (4) enlarged cervical glands (2 cases), (5) stomatitis (1 case), (6) aplastic anæmia (1 case, fatal), (7) congestion of lung (1 case), (8) headache (1 case), (9) vomiting (2 cases),

(10) dysphagia (1 case), (11) drowsiness (2 cases), (12) collapse (1 case). Erythematous eruptions formed the most troublesome of the complications—6 out of 18, or one-third of the females treated were affected. The males, on the other hand, showed singular freedom from skin reactions. Of the 6 females so affected, 3 later developed tolerance and were able to complete treatment on full dosage. The other 3, however, became increasingly intolerant until minimal doses were resorted to.

The type of skin reaction varied from a mild blush to an intense blotchy erythema, rather like that which occasionally follows serum injections. Scarlatiniform or morbilliform rashes were also seen. The usual sites were the arms and legs (outer aspects mostly), neck and trunk. Over the face œdema and diffuse erythema with circumoral pallor were common. Termination was by desquamation of the "branny" or "flaky" variety. Dermal reactions usually make their appearance in from 9 to 42 days from the 1st day of treatment. Once intolerance had appeared, however, this period was considerably reduced. Case No. 12, for example, developed erythema in 6 hours after taking only gr. 1 (grm. 0·06). It was usually sufficient to discontinue administration of the drug for fading to set in. In troublesome cases calcium thiosulphate gr. 9 (grm. 0·6) in 5 c.c. sterile water, intravenously was found effective.

Drowsiness occurred in 2 cases, both epileptics. As one of them had a similar attack a year before treatment, its relation to acetarsol must be doubtful.

Unlike the majority, Case No. 16 did not show any signs of intolerance until the end of the 4th full course; stomatitis with localized dermatitis of the face then appeared. After this the patient could not tolerate more than gr. $\frac{1}{50}$ (grm. 0·0012) three times daily.

Case No. 17 developed an aplastic anæmia at the end of the 5th course. Discontinuance of the drug and the administration of iron with liver extracts had no influence on the course of the disease which went to a fatal termination.

Dermal reactions and eosinophilia.—As previously mentioned all cases showed increase in eosinophil leucocytes after treatment. There was, however, no correspondence between degree of intolerance and eosinophilia. In 4 of the most intolerant cases the highest eosinophil count recorded was as follows:

Case No. 26, 8%.	Case No. 6, 2%.
,, 12, 3·1%.	,, 16, 0·6%.

On the other hand the following cases showed no toxic reactions, and the highest eosinophil count recorded was as follows:

Case No. 1, 23·4%.	Case No. 3, 6·3%.
,, 24, 16·0%.	,, 7, 3·0%.

The development of an eosinophilia cannot therefore be relied upon as an indication of intolerance.

Details of cases developing complications are given below:

Cases Showing Marked Idiosyncrasy to Acetarsol.

CASE No. 6.—J. C—, female, æt. 19. Family history, little known except that she was the 4th of 5. Had been under supervision from an early age.

Signs: Frontal bossing.

Thirty-seven days from the 1st day of treatment, when she had received a total of acetarsol gr. 501 (grm. 33) and was receiving gr. 6 (grm. 0·39) 3 times daily, she developed a bright patchy erythematous rash of the extremities. Over the palms of the hands it took the form of pale pink spots, slightly raised,

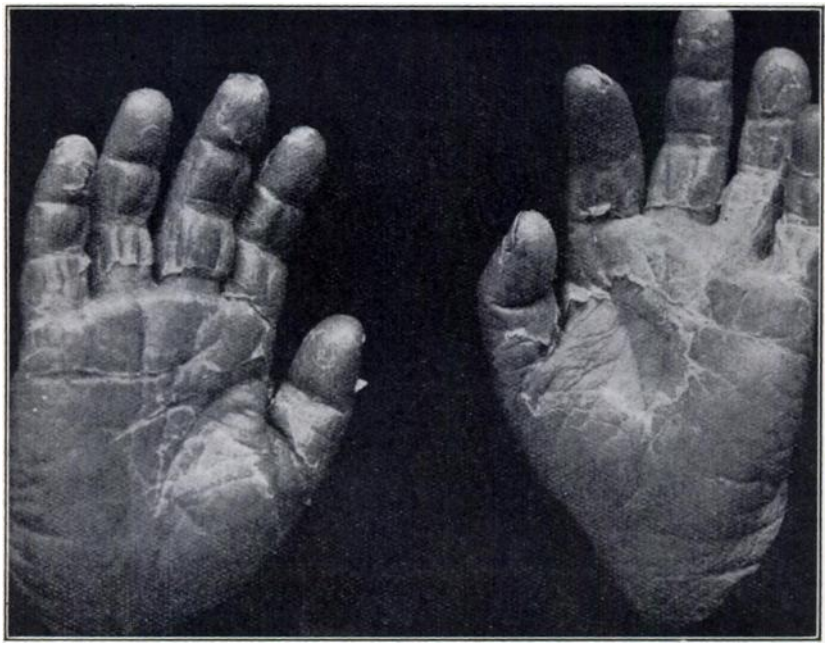

FIG. 2.—Case No. 6: Flaky desquamation of the palms of the hands following treatment with acetarsol.

set in an erythematous background. Face swollen, cervical glands enlarged, tongue dry and coated, pharynx dry and inflamed. No pyrexia. The drug was stopped. Three days later the rash had spread to the neck. An intravenous dose of calcium thiosulphate grm. 0·6 was given in 5 c.c. sterile water. Fading followed soon after. Œdema of the face subsided in two days, and desquamation occurred in five.

Two months later the 2nd course was begun. On the 1st day she received gr. 1½ (grm. 0·096) half an hour before breakfast, the same dose before dinner, and gr. 1¼ (grm. 0·08) half an hour before tea. This was repeated the next day and the day after. One hour after receiving the last dose before tea, she collapsed. Was pale with cyanosed lips and fingers. A few hours later she developed pyrexia up to 102·4° F. Pulse 130. Respirations 40. The next morning an intense scarlatiniform rash appeared over the whole body. Face

swollen, eyelids puffy, tongue dry and furred, pharynx dry and red, cervical glands enlarged. The drug was discontinued promptly and all symptoms had disappeared in 3 days. Branny desquamation present.

Three days later, acetarsol gr. $\frac{1}{50}$ (grm. 0·0012) *t.d.s.* for 1 week was tried. No toxic symptoms.

The following week the dose was doubled, and then trebled. Finally gr. $\frac{1}{6}$ (grm. 0·01) was given *t.d.s.* for a period of 6 weeks without ill effect.

In the 3rd course the dose was increased up to gr. $\frac{1}{4}$ (grm. 0·15) *t.d.s.* at which level it remained for 6 weeks. Towards the end of the course, however, her face became swollen and eyelids puffy, skin dry. Succeeding courses were, therefore, limited to a maximum dose of gr. $\frac{1}{6}$ (grm. 0·01) *t.d.s.* without any signs of intolerance.

CASE NO. 12.—J. T—, female, æt. 14. Family history, not very reliable. Said to be 4th of 6.

Signs: Frontal bossing, saddle nose, rhagades, Hutchinson's teeth, 8th nerve deafness, alopecia, old osteochondritis of wrist, spastic quadriplegia.

Nine days from the commencement of treatment, when she had received a total of acetarsol gr. $22\frac{1}{4}$ (grm. 1·5), she developed a morbilliform rash mostly over the outer aspects of the arms, and over the trunk and buttocks. Pyrexia up to 99° F. Next day temperature normal, rash over buttocks confluent, fading over arms. Four days later rash persisting but not so intense. Calcium thiosulphate grm. 0·6 intravenously in 5 c.c. sterile water, repeated next day and the day after with little effect on the rash. Acetarsol then discontinued. Seven days later the rash had gone, desquamation present.

Two weeks later drug resumed. After receiving gr. $10\frac{1}{4}$ (grm. 0·7) in 1 day she developed an intense erythematous rash over the whole body, accompanied by vomiting and headache. Tongue furred, pharynx dry and inflamed. The drug was discontinued and 2 days later the rash was fading, but gums bled easily, cracks about lips. Five days later rash gone, desquamation present.

One month later acetarsol gr. $\frac{1}{2}$ (grm. 0·32) *t.d.s.* was tried but had to be discontinued 8 hours after the first dose on account of erythema of limbs and trunk. Two months later a similar dose resulted in similar symptoms. After an interval of a week acetarsol gr. $\frac{1}{50}$ (grm. 0·0012) *t.d.s.* was tried, but even this small dose produced an erythematous rash on the 7th day. She was, however, found to tolerate gr. $\frac{1}{50}$ once daily. By giving this dose twice daily at the end of a week and then 3 times daily after another week, it was found possible to treat this patient successfully without further complications.

CASE NO. 26.—H. R. C—, female, æt. 12. Family history, 10th of 11. 1st two born dead, next 7 apparently healthy, 11th "backward". Mother's blood W.R. and M.K.R. strongly positive. Father's negative. Patient had "snuffles" after birth.

Signs: No signs of congenital syphilis.

Fifty-five days after the beginning of treatment, when she had received a total of acetarsol gr. 230 (grm. 15·4), she developed a dry, scaly rash about the lips and chin (Fig. 3). Raised erythematous spots over the dorsum of the hands. No constitutional disturbance. Treatment was persisted in, and she received a further gr. 68 (grm. 4·5) in 8 days without aggravation of symptoms, but there was no tendency for the rash to fade. Drug discontinued. One week later rash disappeared, flaky desquamation taking place. Two months later the 2nd course was started, 30 hours after the 1st dose and after receiving only gr. 3 (grm. 0·18) she developed a blotchy erythema over the arms and

thighs, also over the buttocks. Herpes of lips. No constitutional disturbance. Drug discontinued, rash disappeared in one week. Three weeks later gr. $\frac{1}{4}$ (grm. 0·15) *t.d.s.* was tried, 6 days later similar signs and symptoms developed, disappearing on withdrawal of the drug. One month later gr. $\frac{1}{50}$ (grm. 0·0012) *t.d.s.* was tried, but a week later had to be discontinued on account of early signs of dryness of skin about the lips and chin.

A month later similar symptoms appeared after a week on acetarsol gr. $\frac{1}{25}$ (grm. 0·0024) *t.d.s.* She was then given gr. $\frac{1}{50}$ (grm. 0·0012) once daily for 2 weeks, then the same dose twice daily for the next week, and 3 times daily

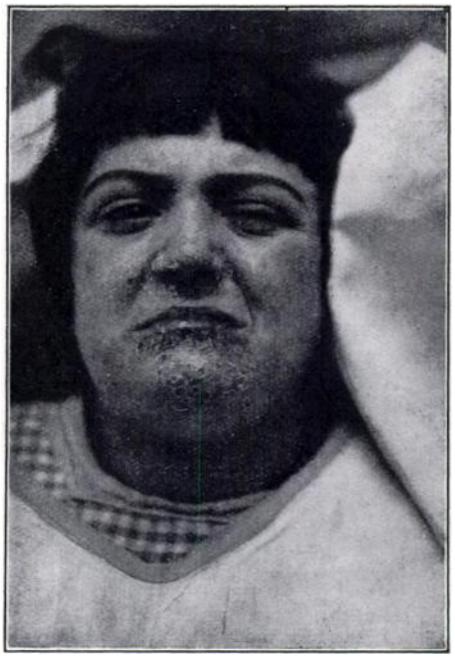

FIG. 3.—Case No. 26: Dry scaly rash of face following treatment with acetarsol.

for the succeeding 6 weeks, without any signs of intolerance. All further courses were confined to a dose of gr. $\frac{1}{50}$ (grm. 0·0012) *t.d.s.* throughout, without complications.

Case Showing Late Idiosyncrasy to Acetarsol.

CASE NO. 16.—A. B—, female, æt. 17. Family history, 3rd of 4. 4th said to be dull. Mother deserted family in 1927. Father last heard of in 1928, when he was selling matches.

Signs: Irregular thickening of tibiæ. Irregular scar $\frac{1}{2}$ in. across at lower end of sternum.

Past history: Developed iritis in 1933 and received one course of N.A.B. (8 intravenous injections at weekly intervals, grm. 0·3 to grm. 0·75). After

the second injection developed pyrexia up to 99° F. with headache and dizziness. Subsequent injections symptomless.

This patient underwent 3 full courses of acetarsol without signs of intolerance. During the 1st course the maximum dose was gr. 6 (grm. 0·39), in the 2nd, 3rd and 4th courses it was gr. 5 (grm. 0·33). At the beginning of the 8th week of the 4th course she developed linear ulceration of the mucous membrane of the mouth corresponding to the cutting margin of the teeth. It started on the left side and spread to the right involving the lower lip. A patch of dry scaly dermatitis also appeared below the right eye. The drug was discontinued.

Total amount of acetarsol received :

1st course	gr. 945	(grm. 63).
2nd ,,	gr. 842	(grm. 56).
3rd ,,	gr. 829	(grm. 54).
4th ,,	gr. 598	(grm. 40).

Two months later the 5th course was begun. At the beginning of the 3rd week, after having received acetarsol gr. 73 (grm. 4·9) she developed ulceration of the mouth and tongue. Drug discontinued for 3 weeks. On resumption, a daily dose of gr. 4½ (grm. 0·3) was given for 5 days at the end of which stomatitis reappeared, with scaly dermatitis below the right eye. Drug discontinued. Two weeks later acetarsol gr. 1 (grm. 0·064) *t.d.s.* was tried, but 3 days later similar symptoms appeared. Drug discontinued. The 6th and 7th courses had to be confined to minimal doses of acetarsol gr. $\frac{1}{50}$ (grm. 0·0012) *t.d.s.* throughout. Any attempt to increase this dose invariably led to the appearance of scaly dermatitis below the right eye.

Withdrawal of the drug always gave relief in from 3 to 5 days.

Cases Showing Moderate Idiosyncrasy to Acetarsol.

CASE NO. 7.—M. C—, female, æt. 30. Family history, only child by 1st husband, 4 by second (1st died of tubercle), 3 by third, all apparently healthy.

Signs : Right eye atrophied, left interstitial keratitis with old iridectomy. Scars of old ulcers over body. Absent xiphoid appendix.

Forty-two days from the 1st day of treatment, after having received acetarsol gr. 400 (grm. 26·6) she developed an erythematous rash over the feet and ankles. Treatment was persisted in to the end of the course. Though the rash did not fade until the end of the course there was no tendency to spread.

Six weeks later, the second course was begun. She completed this, as well as 4 others on full dosage, without any signs of intolerance whatever.

CASE NO. 13.—D. S—, female, æt. 17. Family history, last of 4. 3rd died 4 months old. Father has been treated for syphilis.

Signs : Frontal bossing, hypoplastic teeth. Choroiditis.

Past history : Patient is reported to have undergone 3 courses of weekly injections during infancy. Suffers from chronic nephritis. On the 34th day of treatment when she was receiving a daily dose of acetarsol gr. 18 (grm. 1·2) and had received a total of gr. 423 (grm. 28·2), she developed an erythematous rash over the arms and trunk. No constitutional disturbance. No increase in albumin-content of urine (0·12%). Drug was discontinued and one intravenous injection of calcium thiosulphate grm. 0·6 in 5 c.c. sterile water given. The rash had completely gone in 8 days' time. In the second

and subsequent courses no intolerance developed. The maximum daily dose did not, however, exceed gr. 14 (grm. 0·94). The drug appeared to have no ill effects on the already damaged kidneys. Albumin was not increased and few casts only observed. This patient who was often puffy about the face before treatment was much improved physically at the end.

CASE No. 15.—R. D—, female, æt. 31. Family history, 5th of 7. Nos. 1, 2 and 6 died in early infancy. No. 4, female, æt. 30, married—2 of her 4 children were born dead. Two abortions between Nos. 6 and 7. Father died of a stroke, æt. 40.

Signs: Frontal bossing. Left interstitial keratitis. Pupils unequal, irregular, inactive to light.

Thirty-one days after the beginning of treatment, when she had received a total of acetarsol, gr. 410 (20·3), she developed an erythema of the face, neck and limbs with dry skin. No constitutional disturbance. Next day after taking gr. 12 (grm. 0·8), she vomited. Drug discontinued. Rash gone in 3 days. After 6 weeks' rest she was given a second course in the usual way, but the maximum dose did not exceed gr. 5 (grm. 0·33) *t.d.s.* No further complications developed in this or subsequent courses.

Herpes.

CASE No. 10.—E. N—, female, æt. 31. Family history, 3rd of 9. 1st born dead, 2nd died, æt. 26. 4th died 7 weeks old. Abortion between 5th and 6th.

Signs: Frontal bossing, scars of old ulcers over trunk. Moderate hydrocephalus.

Nine days after commencement of treatment, when she had received a total of acetarsol gr. 35 (grm. 2·3), she developed a herpetiform rash over the upper lip with pyrexia up to 101° F. Drug not suspended. Temperature normal in 2 days. Herpes away in 5 days. She completed the full course without further incident, as much as gr. 20 (grm. 1·3), being taken daily after the 3rd week. During the 3rd and subsequent courses, however, the maximum dose did not exceed gr. 5 (grm. 0·33) *t.d.s.*, on account of a tendency to "itchy" skin.

CASE No. 21.—A. E. M—, male, æt. 11. Family history, 1st of 2. Mother has recently been admitted to a mental hospital suffering from advanced general paralysis of the insane.

Signs and symptoms: Parietal regions of skull much thickened.

Rhagades: Central notching of upper central incisors. Eighth nerve deafness. Pupils inactive to light, but react to accommodation, irregular, unequal. Tremors at corners of mouth. Spastic quadriplegia. Persistent grinding of teeth. Seizures. This case is considered one of juvenile general paralysis.

Halfway between the 3rd and 4th courses of acetarsol he developed a herpetiform rash over the left side of the abdomen and extending to the umbilical region, lasting 10 days (Fig. 4). No constitutional disturbance. He underwent 2 further full courses without incident, at the end of which he showed good physical improvement and was much brighter mentally.

Lethargy.

CASE No. 14.—K. V—, female, æt. 13. Family history, last of 6. 3rd had meningitis in infancy.

Signs: Hypoplastic teeth. Multiple small scars over back. Nodal thickening of tibiæ. Quadriplegia.

Thirty-seven days after the beginning of treatment, having received a total of acetarsol gr. 391 (grm. 26·1), she developed an acute naso-pharyngitis with enlarged cervical glands. Dysphagia present. No pyrexia, no rash. She was very drowsy at the time. The drug was discontinued and all signs and symptoms had cleared up in 4 days. Ten days later the course was resumed on full dosage without any signs of intolerance. Later four further full courses were taken without incident.

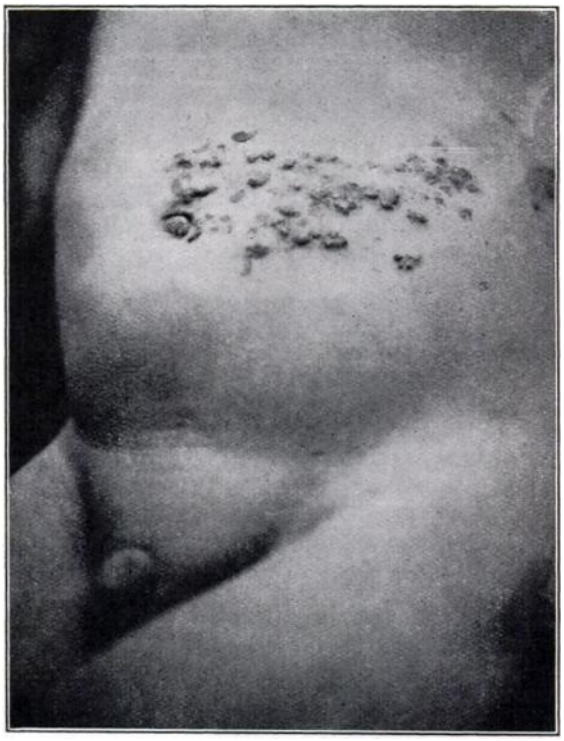

FIG. 4.—Case No. 21 : Herpes of abdomen following treatment with acetarsol.

This patient had suffered from a similar drowsy attack with naso-pharyngitis 6 months before treatment by acetarsol, so that its relation to the drug in the second attack is doubtful.

CASE No. 20.—R. F. S—, male, æt. 11. Family history, 1st of 4, 2nd is being treated for congenital syphilis elsewhere. 3rd still-born. Mother's blood-serum : W.R. + 30^{+}, M.K.R. ++++.

Signs : Rhagades, hypoplastic teeth.

On the third day of the 1st course, after having received acetarsol gr. $7\frac{1}{2}$ (grm. 0·5), he became drowsy and slowly lost all interest in his surroundings. He was put to bed where he lay apparently asleep for days, though able to be roused to take food. Limbs were semi-flaccid but deep reflexes were present.

Treatment was continued and he completed the 1st course without showing any mental change. An epiphysitis of the lower end of the left femur developed during this course but had cleared up towards the end. During the interval he brightened up again. In the 6th week of the 2nd course, when he had received acetarsol gr. 238 (grm. 15·9), he again developed similar symptoms of drowsiness. Treatment was this time discontinued and a month later he was sufficiently recovered to complete the course. He received five further full courses without symptoms of drowsiness, but the 5th course was temporarily interrupted on account of the sudden onset of hyperpyrexia of unknown origin.

Pulmonary Complication.

CASE NO. 11.—M. C—, female, æt. 30. Family history, 7th of 13. 6th premature, died. Four others died in infancy. Mother underwent inadequate course of " injections ".

Past history : Patient was a 7½ months' child.

Signs : Rhagades, hypoplastic teeth, right internal strabismus.

During the 5th week of the 1st course, when she had received a total of acetarsol, gr. 462 (grm. 30·8), and was taking gr. 7 (grm. 0·45) *t.d.s.*, she developed signs of pulmonary congestion of the lower lobe of the right lung. The drug was stopped, and 10 days later she was quite well again. The course was then resumed and completed without incident. Six further courses were symptomless, but after the 3rd course the maximum dose did not exceed gr. 5 (grm. 0·33) *t.d.s.* There is some doubt in this case whether treatment was responsible for the onset of pulmonary congestion.

Aplastic Anæmia. A Fatal Termination.

CASE NO. 17.—A. T—, female, æt. 61. Family history, little known. Was one of 16, many of whom had died in infancy.

Past history : Had been in mental hospitals continuously from an early age.

Signs : Scars over palate, osteo-periostitis of tibiæ, dactylitis, onychia, thickening of lower end of radius.

She received 4 full courses without symptoms.

Total amount of acetarsol during 1st course gr. 959 (grm. 64).
,, ,, ,, ,, 2nd ,, gr. 955 (grm. 63·7).
,, ,, ,, ,, 3rd ,, gr. 779 (grm. 52).
,, ,, ,, ,, 4th ,, gr. 812 (grm. 54·2).
,, ,, ,, ,, 5th ,, gr. 797 (grm. 53·2).

The interval between courses was 6 to 8 weeks except between the 3rd and 4th courses, when it was 3 months. During the 9th week of the 5th course it was noticed that the patient was becoming breathless on slight exertion and had a dusky colour. Mucous membranes were pale. The drug was discontinued. Blood examination showed the following : Red blood-cells 3,520,000, colour index 0·8, hæmoglobin 62%. She was given 3 Blaud's pills 4 times daily, together with ½ lb. raw liver daily. Ten days later, on October 19, 1935, red blood-cells 3,300,000, hæmoglobin 8·5 grm. per 100 c.c. (55%), colour index 0·6, white blood-cells 4,800 ; polymorphonuclears 49%, leucocytes 51%. Red cells irregular in size and shape. No nucleated forms. Van den Bergh reaction negative for both direct and indirect tests. At this time

she developed a crop of herpes about the nose, and had hæmorrhages from the nose and petechiæ over the palate.

October 10, 1935: Petechial hæmorrhages over chest and forehead. Bruised areas over arms and legs.

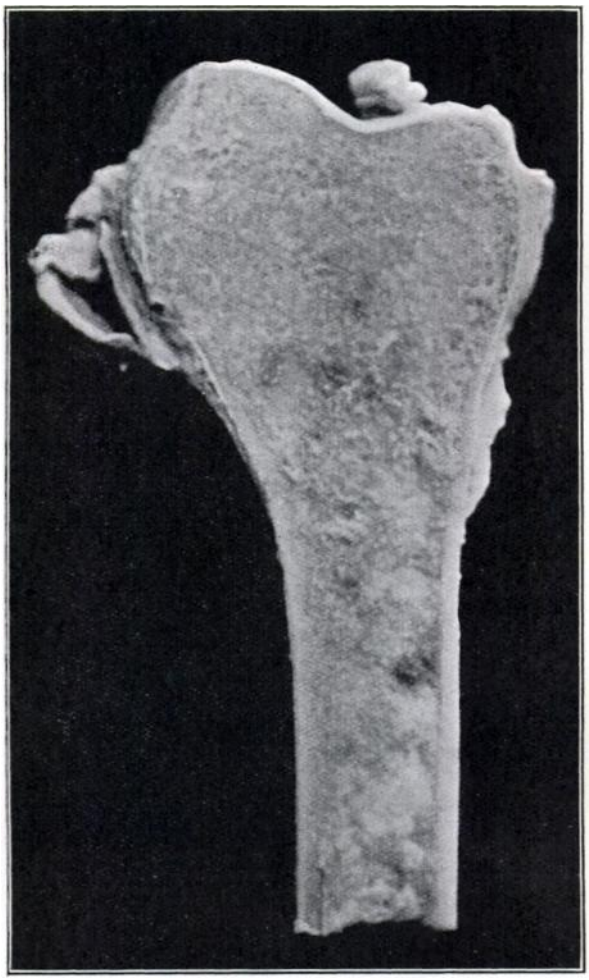

FIG. 5.—Case No. 17: Aplastic anæmia following acetarsol. Right femur showing aplasia of bone-marrow with a few hæmorrhagic spots.

October 31, 1935: Becoming worse. Red blood-cells showed marked microcytosis and poikilocytosis. Platelets diminished.

November 2, 1935: 8 c.c. "Hepastab" given intramuscularly. Repeated next day. Half the dose given on successive days.

November 5, 1935: Blood-film stained by brilliant cresyl blue showed reticulocytes and nucleated red cells in fair numbers.

November 6, 1935 : She became suddenly dyspnœic in the afternoon and died soon after.

Post-mortem.—Bones examined, right femur and right ulna. There was almost complete aplasia of the bone-marrow, which was pale yellow with a few scattered hæmorrhagic spots (Fig. 5). All mucosa and internal organs pale. There was a large wedge-shaped hæmorrhagic infarct of the lower lobe of the right lung. The heart was pale, right ventricle dilated, mitral valve thickened. Atheroma of aorta present.

Histological examination of pieces of liver, heart, spleen and kidneys showed no fatty or other degenerative changes.

Cause of death : Pulmonary infarction following aplastic anæmia.

Discussion.

This investigation deals with a mixed group of late congenital syphilitics complicated by mental deficiency, who must be regarded as the least promising for purposes of treatment. None of those treated, however, can in any way be considered " cured ". It will take many years of careful observation before a final decision can be given.

Possibly a combination of acetarsol and some other anti-luetic drug, such as bismuth, would have given better results than acetarsol alone, but it would have then been impossible to judge the true value of the drug.

Acetarsol has many advantages over the other arsenobenzene derivatives, the chief of which is ease of administration. Disadvantages such as uncertainty of intake when given to out-patients do not, of course, apply to hospital inmates, especially those of large mental hospitals and mental defective colonies. Dermal reactions are certainly troublesome ; many, however, develop subsequent tolerance and can undergo full dosage. A few prove quite intolerant, and can only take small doses. In support of minute dosage in such cases, I will quote no less an authority than Hutchinson, when mercury was the drug of choice : " In the employment of specifics in the treatment of syphilis, everything may be said to depend on dose. The statement so often made respecting patients, that they ' cannot bear the smallest quantity of mercury or iodide ', may always be set down as a mistake. Reduce the dose sufficiently and the drug will be borne, and when it is borne it will cure. It is not quantity of the drug which is needed, but its effect on the organism, and if the specific effect is gained by a minute quantity it is not only not needful, but bad practice to attempt to increase it. I have never yet met with a patient who could not take either iodide of potassium or mercury, if only the dose was sufficiently reduced. The chief difficulties in treatment occur in those who are insusceptible, not in those who respond easily. I have repeatedly reduced the iodide of potassium and grey powder, respectively, to one-sixth of a grain for a dose, and found them to agree well and to manifest specific influence."

The 3 cases showing most intolerance to acetarsol and who were treated with small doses improved both physically and mentally. In one case the

blood Wassermann reaction was changed from positive to negative and the M.K.R. reduced in strength. In the second the Wassermann reaction was reduced in strength and the M.K.R. unchanged. In the third case the Wassermann reaction of the cerebro-spinal fluid was changed from strong positive to weak positive and the increased cells and protein fell to within normal limits. Lange's colloidal gold curve, originally strongly paretic, became weakly paretic, the blood Wassermann reaction and M.K.R. remained positive —this case only received gr. $\frac{1}{50}$ of acetarsol three times daily throughout. On the other hand another patient on full dosage showed no serological change after treatment—does he belong to the "insusceptible" class of Hutchinson?

As a result of experience the following scheme of dosage is recommended:

1. Those showing no idiosyncrasy, dosage and duration of course according to that advised by Bratusch-Marrain. Maximum daily dose not to exceed gr. 15 (1 grm.).

2. Those showing moderate idiosyncrasy, drug discontinued promptly on appearance of first symptoms. Two weeks' rest after the disappearance of symptoms, drug then resumed, gr. $\frac{1}{120}$ (grm. 0·005) three times daily for 1st week, gr. $\frac{1}{8}$ (grm. 0·01) three times daily for the second, and so on, doubling the dose at the end of each week until either the normal dosage according to weight is attained or symptoms of intolerance develop. In the latter event the case is placed in the category of extreme idiosyncrasy and is treated accordingly.

3. Those showing extreme idiosyncrasy, drug discontinued promptly on appearance of first symptoms. If reaction severe and of dermal type, calcium thiosulphate grm. 0·6 in 5 c.c. sterile water given intravenously. Two weeks rest after disappearance of all symptoms. Drug then resumed, gr. $\frac{1}{500}$ (grm. 0·0012) daily, as a single dose before principal meal, for one week. Increased to twice daily during second week, and then three times daily for the third week. The dose may then be doubled in the fourth and, failing symptoms of intolerance, trebled in the fifth week. Usually mild signs of intolerance will appear before this, in which case the drug is stopped for one week, and is then resumed at a dose just below that which produced intolerance, and maintained at this level throughout. Each complete course lasts 9 weeks, with similar intervals to those taking full dosage.

For all three classes the minimum number of courses should be six, irrespective of any change in serological reaction.

Results of Treatment.

In the group of cases with normal cerebro-spinal fluids, of 17 with positive Wassermann reactions 8 became negative at the end of just over two years. In Davidson and Birt's series 14 out of 23—with presumably normal cerebro-spinal fluids—became negative in 2 years. The better results obtained by

these authors are probably due to the average age of their group being much lower. Even in the Caterham series there is a tendency for the younger members to become serologically negative more easily than the older ones.

The serological reactions of the blood sera of cases with abnormal cerebro-spinal fluid appear to be extremely resistant to treatment, only one of nine becoming negative. The treatment of congenital neuro-syphilis in older children is unfortunately very disappointing. Nabarro is of opinion that there are only two forms of neuro-syphilis worth treating: (1) that which occurs in early infancy and (2) latent neuro-syphilis of older children. "Clinical neuro-syphilis, although it may be considerably benefited by treatment, does not, in my experience, result in the production of cure or of an individual who is going to be an asset to the community." Again, "and nowadays I regard the treatment of congenital neuro-syphilis with symptoms as practically hopeless."*

Although acetarsol has been shown not to penetrate into the cerebro-spinal fluid, it nevertheless appears to exert a specific effect on the majority of abnormal fluids. Pleocytosis is the first abnormality to disappear, next increase in protein, and then Lange's colloidal gold curve; lastly the Wassermann reaction, though reduction in strength is fairly common. Even in cases with definite juvenile general paralysis the cerebro-spinal fluid has tended to improve. A reduction in the frequency of fits in congenital syphilitic epileptics is perhaps to be expected with any form of effective treatment, so it is not surprising to find a reduction of fits in 7 of 8 such cases. Diminution in the number of seizures in one case of juvenile general paralysis was, however, unexpected; it coincided with mental and bodily improvement and was considered a "remission". The majority of those treated improved both physically and mentally to some degree, weight was gained and hæmoglobin and red-blood corpuscles increased in a number of cases. Such all round improvement is fairly common in congenital syphilitics treated with other forms of arsenic and is not confined to acetarsol.

Two cases of congenital syphilis with active signs responded to treatment with acetarsol as well as might have been expected with N.A.B. or other similar preparation.

Complications.

Bratusch-Marrain states that where an overdose of spirocid is given diarrhœa may occur. Semon, in 1923, was of opinion that stovarsol's relative toxicity as compared with the trivalent N.A.B. was great, as a single 4 gr. (grm. 0·27) tablet was said to contain more arsenic than an ampoule of 0·3 grm. of neo-salvarsan. He described a lady, æt. 42, who developed a rash resembling German measles on the 9th day of treatment. On the 14th day

* Communication from Dr. Nabarro to Dr. Lindsay, quoted by their kind permission.

there was swelling of hands and feet, œdema of lids and lips and conjunctivitis. Petechiæ on fingers and feet, thighs and buttocks. Cervical glands enlarged. Nausea complained of, but no vomiting or diarrhœa. As only 40 gr. (grm. 2·67) had been administered in 13 days he suggested an inherent susceptibility to the drug.

In 1925 Izar mentioned 4 cases in which moderate doses of stovarsol were followed by severe symptoms of vertigo, collapse, cyanosis, abdominal pain, pyrexia and tachycardia. He attributed the results in these cases to individual idiosyncrasy. In 1926 O'Brien reported a case of a man, æt. 46, who, after the ingestion of a single 4 gr. (grm. 0·27) tablet of stovarsol one hour after breakfast developed within two hours severe cramp-like pains over the abdomen and lower limbs. There was much vomiting for two hours and also diarrhœa, prostration and collapse. He suggested that stovarsol may produce these symptoms after food.

In 1927 Bender reported 6 cases of poisoning by stovarsol. He stated that " mention of undesirable effects is present in nearly every report of its use in a series of 10 or more cases, including one or several of the following manifestations—coryza, bronchitis, sore throat, malaise, aching, chill, skin eruptions, jaundice, adenitis, diarrhœa, abdominal pain, eosinophilia and albuminuria ".

In 1929 Michael reported a case of exfoliative dermatitis in a woman. Two tablets of acetarsone each 0·25 grm. were given at 10 a.m. and 2 p.m. Eight hours after the second dose she experienced burning and itching of the face and arms ; these parts became congested and exudative, eyelids were swollen, and there was moderate abdominal cramping and diarrhœa.

Recently Davidson and Birt stated that only 3 patients out of 51 treated developed mild toxic symptoms, 2 had headache relieved by stopping the drug, and not reappearing when resumed, the third had coryza, gastro-intestinal distress and diarrhœa. They state " there have been fewer toxic effects in this series than is usually found with arsphenamine or neoarsphenamine. Those that have been produced were readily controlled by dosage ".

In the Caterham series, 13 out of 29 cases developed toxic symptoms of one kind or other, dermal reactions being the most common ; other manifestations were fever, herpes, pharyngitis, adenitis, stomatitis, congestion of the lungs, headache, vomiting, dysphagia, drowsiness and collapse. Aplastic anæmia occurred in one case. Contrary to most observers' findings, diarrhœa did not occur. Drowsiness for long periods appears rather unusual, and has not been previously reported. I have not been able to trace any report of the development of aplastic anæmia following stovarsol. Findlay states that " just as benzene poisoning is known to cause an aplastic anæmia so the arsphenamines may also, in rare cases, produce an aplastic anæmia with degeneration of the bone-marrow ". It will be noted that this fatal case of aplastic anæmia occurred in a woman whose age was 61. She was originally included in the series so as to make the group as representative as possible of all ages. It is,

however, doubtful whether much good can result from the treatment of a latent congenital syphilitic of her age merely because she had a positive Wassermann reaction and M.K.R. of the blood. It is suggested that similar cases should, if necessary, be treated by less drastic methods.

Summary.

1. Twenty-nine mental defectives, the subjects of congenital syphilis, were treated with acetarsol. The majority underwent 6 to 7 courses of 9 weeks each, over a period of just over 2 years.

2. In one case it was shown by direct experiment that after ingestion the concentration of the drug in the systemic blood-stream was still rising after 24 hours. The drug failed to penetrate into the cerebro-spinal fluid.

3. The scheme of dosage was based on that of Dr. Alois Bratusch-Marrain with modifications, details of which are given.

4. For analytical purposes the 29 cases were divided into two main groups: (*a*) those with normal cerebro-spinal fluids, and (*b*) those with abnormal cerebro-spinal fluids.

Group (*a*).—19 cases, 17 of whom had positive blood Wassermann reactions before treatment. After treatment 8 became negative, 7 reduced in strength, and 2 unchanged.

Group (*b*).—10 cases, 9 of whom had positive blood Wassermann reactions before treatment. After treatment, one became negative, one slightly reduced in strength, and 7 unchanged.

The M.K.R. blood reactions of both groups, though more resistant, showed similar trends.

5. Of 10 abnormal cerebro-spinal fluids before treatment, 3 became completely normal and 7 were improved after treatment.

6. A control group of 12 untreated congenital syphilitics with normal cerebro-spinal fluids was observed over approximately the same time as the treated group. The following serological changes took place. Of 7 positive Wassermann reactions 1 became negative, 4 were unchanged, and 2 increased in strength. One doubtful and 4 negative Wassermann reactions became positive.

7. Blood analyses were done in 25 cases. Thirteen showed increase in hæmoglobin, 21 increase in red blood-corpuscles. All showed increase in eosinophil leucocytes.

8. Twenty-seven cases improved bodily and 23 mentally. Twenty-two gained weight.

9. Of 8 epileptics 7 showed reduction of fits.

One of 2 cases of juvenile general paralysis showed reduction in number of seizures.

10. Two cases had active lesions before treatment. One with a pharyngeal

ulcer, healing took place in 10 days. The other, with dacryocystitis and interstitial keratitis was well in 2 months.

11. Toxic manifestations occurred in 13 cases; only 4 of these, however, were unable to follow the usual dosage according to weight and were treated with modified courses. Dermal reactions were the most frequent and troublesome of the complications. One case, æt. 61, died of aplastic anæmia, with sudden onset at the end of the 5th course.

Conclusion.

Acetarsol is a drug with a powerful salvarsan-like action on cases of congenital syphilis. It has the added advantage of oral administration, rendering possible the treatment of large numbers of cases with the minimum of apparatus and great saving in time. It will be found very useful in those large mental hospitals and mental defective colonies where patients are under constant care and supervision. If the scheme of dosage as given in this paper is adhered to there will be little likelihood of serious toxic reactions resulting. The close relationship of acetarsol to tryparsamide, and the fact that many abnormal cerebro-spinal fluids were improved and 2 cases of juvenile general paralysis benefited, suggests the desirability of further research along these lines.

Perhaps treatment aided by other antisyphilitic drugs may be found more effective, but there is little doubt that acetarsol is entitled to a place in the modern treatment of congenital syphilis.

I am indebted to Dr. T. Lindsay, Medical Superintendet, Caterham Hospital (L.C.C.), for his help and advice in this work and for permission to publish details of these cases.

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References.—Abt, A. F., and Traisman, A. S., "Stovarsol in the Peroral Treatment of Congenital Syphilis", *Journ. Pediat.*, 1932, i, p. 172.—Bender, W. L., "Stovarsol Poisoning", *Amer. Journ. Med. Sci.*, 1927, clxxiv, p. 819.—Bratusch-Marrain, Alois, "Wert und Durchführung der Spirocidbehandlung der Syphilis im Kindesalter", *Arch. f. Kinderheilkunde*, 1930, xcii, i, pp. 26–39.—Davidson, A. M., and Birt, A. R., "The Treatment of Congenital Syphilis with Stovarsol", *Canadian Med. Assoc. Journ.*, 1936, xxxiv, p. 33.—Ehrlich, P., and Hata, S., *Die Experimentelle Chemotherapie der Spirillosen*, 1911, Berlin.—Findlay, G. M., *Recent Advances in Chemotherapy*, 1930, London, p. 344.—Fourneau, E., "Sur l'emploi de l'acide oxyaminophenyl-arsinique et des acides arylarsiniques en général dans le traitement des spirilloses et des trypanosomiases", *Ann. de l'Inst. Pasteur*, 1921, xxxv, p. 571.—Hutchinson, Sir J., *Syphilis*, second edition, p. 511.—Izar, G., *Paris Méd.*, 1925, p. 139.—King, Ambrose, "Discussion on the Treatment of Congenital Syphilis", *Brit. Journ. of Ven. Dis.*, 1934, x, p. 25.—Levaditi, C., and Nabarro-Martin, A., "Recherches sur l'action curative et préventive de l'acide acetyloxyamino-phenylarsinique (190 ou Stovarsol) administré par voie digestive dans la syphilis", *Ann. de l'Inst. Pasteur*, 1922, xxxv, p. 729.—MacQueen, J., "Syphilis Insontium in Palestine", *Brit. Journ. of Ven. Dis.*, 1934, x, p. 47.—Mann, S. A,

and Partner, F., *Memorandum on the Wassermann Reaction in Mental Hospitals' Practice*, 1931 (King & Son, Ltd.).—Maxwell, C. H., and Glaser, J. " Treatment of Congenital Syphilis with Acetarsone given by Mouth ", *Amer. Journ. Dis. Child.*, 1932, xliii, p. 1461.—Michael, J. C., " Exfoliative Dermatitis from Acetarsone ", *Journ. Amer. Med. Assoc.*, 1929, xcii, p. 645.—Nabarro, D., " Discussion on the Treatment of Congenital Syphilis ", *Brit. Journ. of Ven. Dis.* 1934, x, pp. 8 and 7; *Proc. Roy. Soc. Med.*, 1934, xxviii, p. 170.—O'Brien, J. R., *Lancet*, 1926, i, p. 313.—Paddle, K. C. L., " Congenital Syphilis in Low-Grade Mentally Defective Children ", *Brit. Journ. of Child. Dis.*, 1933, xxx, pp. 249–261; " Hydrocephalus and Endocarditis in a Congenital Syphilitic Mental Defective ", *Brit. Journ. of Ven. Dis.*, 1933, ix, p. 145.—Semon, Henry C., " Acute Stovarsol Dermatitis ", *Lancet*, 1932, ii, p. 340.—Sézary, A., and Barbé, A., " Résultats cliniques et biologiques de la stovarsol-thérapie dans 125 cas de paralysie générale ", *Paris Méd.*, 1929, xxxvii, p. 1.—Veeder, Borden S., " Hereditary Syphilis in the Light of Recent Clinical Studies ", *Amer. Journ. of Med. Sci.*, 1916, clii, p. 522.