A case of chronic lymphoid leukaemia with much temporary benefit from benzol treatment / by H.D. Rolleston and J.D. Rolleston.

THE BRITISH JOURNAL
OF
CHILDREN'S
DISEASES.

REPRINT

PRINTED AND PUBLISHED BY ADLARD & SON,
BARTHOLOMEW CLOSE, LONDON, E.C.

A CASE OF CHRONIC LYMPHOID LEUKÆMIA WITH MUCH TEMPORARY BENEFIT FROM BENZOL TREATMENT.

By H. D. ROLLESTON, M.D., F.R.C.P., and J. D. ROLLESTON, M.D.

Reprinted from 'The British Journal of Children's Diseases,' February, 1915, Vol. XII, pp. 33–39.

A CASE OF CHRONIC LYMPHOID LEUKÆMIA WITH MUCH TEMPORARY BENEFIT FROM BENZOL TREATMENT.*

By H. D. Rolleston, M.D., F.R.C.P., and J. D. Rolleston, M.D.

A boy, aged 6½ years, was admitted on December the 11th, 1913, to the Victoria Hospital for Children, suffering from general debility and swelling in the neck of eight months' duration.

Previous health.—He had had measles twice, the second attack eight months before admission and followed by pneumonia. Otherwise he had been exceedingly healthy.

The *family history* did not contain anything of importance.

History of present illness.—Eight months ago, during his recovery from the second attack of measles, his mother noticed several lumps in his neck, these got progressively larger, but were never painful.

On admission the patient was pale, anæmic, constipated, listless, and was obviously very ill. There were numerous hard enlarged painless glands in the cervical, parotid, submaxillary and occipital regions, axillæ and groins. There was some dyspnœa, but *x*-ray examination of the mediastinum did not reveal any enlarged glands. The heart was slightly enlarged and a systolic apical murmur was present. The spleen was distinctly palpable on deep inspiration. The eyes were swollen and puffy, the forehead somewhat œdematous, and the superficial veins in that region dilated.

Examination of the blood pointed to lymphoid leukæmia—large lymphocytes being in great excess. The total leukocyte count was then 60,000.

On December the 29th, benzol treatment was commenced with an initial dose of ♏vi *per diem*. On January the 10th it was increased to ♏xii *per diem*, and on January the 25th to ♏xiv. This dose was continued until February the 12th, when the benzol was stopped altogether. The accompanying chart shows the progressive dimi-

* The case was shown on two occasions at the Royal Society of Medicine, 1914, vii, (Children's Section), pp. 71, 129.

nution in the total leucocyte count during the treatment. The patient's general condition appeared to be greatly improved; lassitude and weakness disappeared, his appetite improved, and the œdema of the head passed away. On the other hand the spleen remained practically unchanged in size, the glandular enlargement did not become less, and the patient did not put on weight satisfactorily. After the benzol was omitted from the treatment the leucocyte count was still taken weekly and at one time was as low as 2900. About a week after the benzol had been stopped, a purpuric rash appeared on the forehead. As benzol poisoning causes purpura hæmorrhagica, this rash was regarded as a manifestation of mild benzol poisoning. On March the 4th, as the patient appeared to be extremely well and was running about the ward all day, he was transferred to the Convalescent Home at Broadstairs. On April the 2nd he was re-admitted to hospital. The lymphatic glands were found to be distinctly harder and a trifle larger. The patient's general condition was decidedly worse. He was exceedingly languid and very dyspnœic.

The total leucocyte count was 123,000, the small lymphocytes being the predominant cells present. Benzol ɱix *per diem* was again given, and in ten days' time the count had fallen to 15,000. This marked decrease was also accompanied by an improvement in his general condition. On April the 16th, the benzol was again omitted, and on April the 20th, the leucocyte was found to be 20,000, and on April the 30th, 29,400.

On May the 11th the child was put on benzol ɱxij *per diem*, but later in the day the temperature rose to 101·2° F.; the whole face became œdematous, with a purpuric rash on the right cheek and an offensive nasal discharge. A culture from the throat showed the presence of numerous diphtheria bacilli, and the child was therefore transferred on May the 13th to the Grove Hospital, Tooting, where 15,000 units of anti-diphtheritic serum were given. A smear from the mouth showed a very various flora, chiefly cocci, only a few fusiform bacilli and spirilla, not more than would be found in any infective condition of the mouth. No diphtheria bacilli were found in smears or cultures from the mouth or nose. The condition of the face suggested cancrum oris, and, though the stomatitis improved considerably under the local application of salvarsan, the child passed into a septicæmic state and died on May the 20th. Blood-examination by Dr. E. B. Gunson showed a well-marked leucopenia —1400 leucocytes on May the 14th and 1600 on May the 15th.

At the autopsy on May the 21st there was no obvious enlargement of the submaxillary, cervical, tracheo-bronchial, or mesenteric

lymphatic glands. The epiglottis was much thickened and so were the ary-epiglottidean folds. The lungs were normal. The heart was normal except for some thickening of the mitral valve. The liver (29¼ oz.) and spleen (2 oz.) did not show any obvious change. Kidneys (3 oz. each) were pale, with numerous small hæmorrhages on the surface.

A microscopical examination of the organs was made by Dr. Stanley Wyard, who reported as follows :

" The submaxillary gland, the liver, and the mitral valve were all normal. Nowhere throughout any of the specimens is there any leucocytic infiltration such as is found in lymphoid leukæmia. The kidneys show cloudy swelling, the change being most marked in the cells lining the tubules as far as and including the descending limb of the loop of Henle. The glomeruli and the blood-vessels appear quite normal. The spleen presents no abnormality except that the perivascular spaces are very densely packed with lymphocytes. The epiglottis is thickened by an increase in the fibrous tissue and a small round-celled infiltration of its anterior surface. The bone-marrow contains very few cells and their place seems to be taken by a fibrillar substance showing affinity for acid stains. The origin of this fibrillar substance is apparently from a few multipolar cells which send out branches in all directions. A few leucocytes are present, but the majority of the cells are large and round, with a small nucleus—the ordinary marrow-cell. No myeloplaxes can be found."

It should be added that the lymphatic glands showed considerable endothelial proliferation which did not appear to one of us (H. D. R.) to point to lymphadenoma. Some writers would probably regard the change as " myeloid transformation," but it is probable that this proliferation of the endothelium lining the sinuses and covering the trabeculæ may lead to the production of large lymphocytes.

Remarks.

The treatment of leukæmia by benzol was originated by von Korányi (5), who based it on Selling's (9) clinical and experimental observations that benzol poisoning produces leucopenia which persists after the cause is removed. Clinically, benzol poisoning produces purpura hæmorrhagica, aplastic anæmia, almost complete absence of blood platelets, and progressive leucopenia. In Selling's two fatal cases the total leucocytic count fell to 480 and 140 per cubic centimetre. Benzol appears to inhibit the leucoblastic tissues.

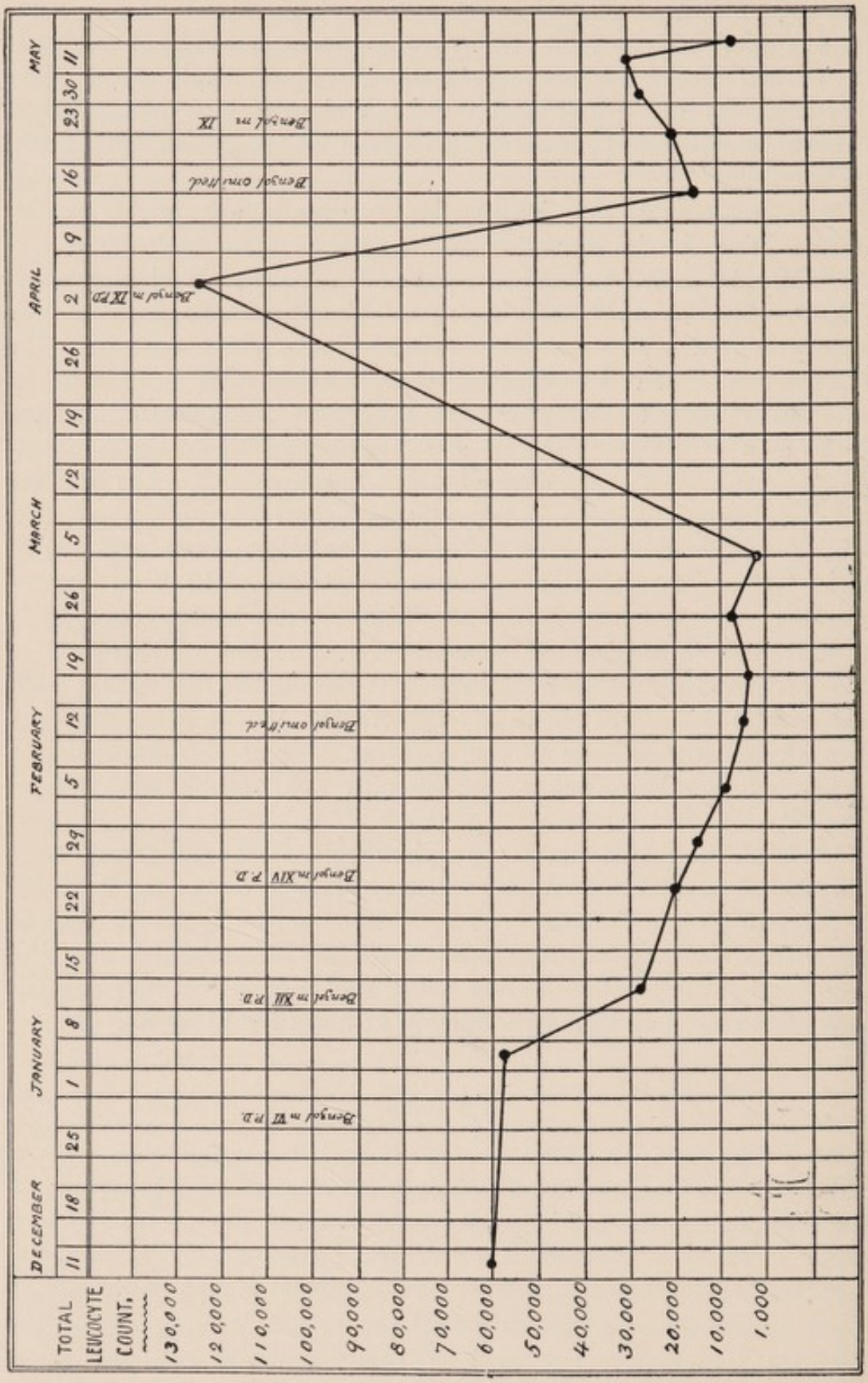

Chart showing the total leucocyte count in a case of chronic lymphoid leukæmia treated by benzol.

Table showing the Blood Counts at Intervals during the Treatment.

	Total leucocytes.	Lymphocytes.		Polymorphonuclears.		Hyaline.	Transitional.	Myelocytes.	Hæmoglobin.	Total reds.
		Large.	Small.	Neutrophils.	Eosinophils.					
1913.		Per cent.	Per cent.	Per cent.	Per cent.	Per cent.	Per cent.		Per cent.	
December the 11th	60,000	54	16·5	25	0·5	3	1	1 seen	—	—
1914.										
January the 5th	57,000	53	30	13	0	3·5	0·5	0	—	—
„ „ 12th	26,000	41·5	46	10	0	1·5	1	Large number	40	4,300,000
„ „ 23rd	20,000	26	24	39	1	7	3	1 seen	50	3,560,000
„ „ 29th	15,000	18	44·5	29	1	4	3·5	3 seen	45	3,368,000
February the 5th	9,000	39	29	27	1	3	1	1 seen	50	3,462,000
„ „ 12th	4,500	28·5	34	32	0·5	2	2·5	1 seen	60	3,300,000
„ „ 18th	3,400	41	12·5	39·5	2	3·5	1	2 seen	55	5,000,000
„ „ 25th	7,000	51	14	34	0	1	0	0	—	4,500,000
March the 4th	2,900	32	29·0	35	0·5	1	2·5	4 seen	60	3,856,000
April the 4th	123,000	19	38	43	0	0	0	7 seen	62	5,000,000
„ „ 15th	15,000	19	41	35	0	4	1	2 seen	58	4,384,000
„ „ 20th	20,000	25	39·5	32	1·5	1	1	0	70	5,024,000
„ „ 30th	29,400	39	35	22	2	2	0	7	55	4,804,000
May the 11th	30,000	35	50	14	1	0	0	0	50	4,000,000
„ „ 14th	1,400	—	—	—	—	—	—	—	—	—
„ „ 15th	1,600	—	—	—	—	—	—	—	—	—

Barker and Gibbes (1) have recently collected fourteen cases of myeloid and three cases of lymphocytic leukæmia treated with benzol, and since then Parkes Weber (11) reported the failure of benzol in a man with myeloid leukæmia, and Calvert (3) a case of chronic lymphoid leukæmia successfully treated with benzol; in his patient, a man, the total leucocytic count gradually fell from 128,000 to 6000. Korányi, at the International Congress in London, 1913, referred to eighty known cases of leukæmia treated by benzol and to twenty-three papers on the subject. The effect of benzol appears to be less rapid than that of *x*-rays exposures. Milne's (6) experiments on dogs showed that in small doses benzol stimulates both erythroblastic and leucoblastic tissues. If these doses are persisted in for some time the leucoblastic tissue is worn out and the leucocytes decrease. Clinically he tried the treatment in seven cases though in only three did he continue it long enough to justify any conclusions. He found that it acted equally well both in the lymphoid and myelogenous types. In moderate doses it not only destroyed circulating leucocytes and prevented the formation of new cells in the leucoblastic tissues, but also stimulated erythrocyte formation and so tended to increase the red cell and hæmoglobin counts. It was not, however, definitely curative, as a relapse soon occurred when the drug was stopped. He thought the treatment should be avoided when the case was very acute with fever and a very high count, also in nervous subjects and particularly in cases with a high degree of leukæmic retinitis.

The terminal leucopenia in the present case, though remarkable, is not unparalleled. Spiegler (10) has recently reported a case and quoted others from the literature in which the leucocytes in myelogenous leukæmia dropped almost to zero before death. In Spiegler's own case they numbered 1400 and then 400, and in two others they fell from 998,000 to 1720 and from 56,000 to 5300 and then to 200.

The occurrence of bucco-pharyngeal lesions in leukæmia which formed the terminal episode of the present case has received special attention from Continental writers. Gilbert and Weil (4) describe pseudo-scorbutic and anginal forms of leukæmia; Wechselmann and Hirschfeld (12) state that noma may be a prodromal symptom, the blood changes occurring later. A case of Vincent's angina with destruction of the uvula (7) recently reported by one of us (J. D. R.) which died four months later of lymphoid leukæmia was probably an instance of this kind. Boudet (2) has found from a study of the literature that stomatitis or angina exists in 66 per cent. of the cases. In sixty-one cases there was stomatitis only, and in thirty-six angina only, and in twenty-one both affections coincided.

The presence of diphtheria bacilli in gangrenous conditions of the mouth and throat which clinically cannot be regarded as diphtheria has been noted by one of us (J. D. R.) in a previous paper (7). It is not probable that they played any considerable part in the morbid process in the present case and, as already stated, were soon outgrown by the other organisms, as they were no longer present when the child had been transferred to the fever hospital.

Though several cases of cancrum oris have been attributed to the symbiosis of Vincent's fusiform bacilli and spirilla, these organisms were by no means predominant in the present case. This may in some measure account for the fact that the local condition though improved did not yield so rapidly to the action of salvarsan as when the process is entirely due to Vincent's organisms (8).

We are much indebted to Dr. Ross, lately house-physician at the Victoria Hospital for Children, for the notes and charts of the case.

References.

(1) Barker and Gibbs.—'Bull. Johns Hopkins Hosp.,' Balt., xxiv, 1913, p. 365.
(2) Boudet.—'Thèses de Paris,' 1909–10, No. 251.
(3) Calvert.—'Proc. Roy. Soc. Med.,' 1914, vii (Clin. Sect.), p. 39.
(4) Gilbert and Weil.—'Arch. de méd. expériment.,' 1899, p. 157; *ibid.*, 1904, xvi, p. 163.
(5) Korányi.—'Berl. klin. Woch.,' 1912, xlix, p. 1357.
(6) Milne.—'Journ. Kansas Med. Soc.,' 1913, xiii, p. 1467.
(7) Rolleston, J. D.—British Journal of Children's Diseases, 1912, ix, p. 311.
(8) *Idem.*, 'Proc. Roy. Soc. Med.,' 1914, vii (Clin. Sect.), p. 1.
(9) Selling.—'Bull. Johns Hopkins Hosp.,' 1910, xxi, p. 33.
(10) Spiegler.—'Wien. klin. Woch.,' 1914, xxvi, p. 458.
(11) Weber, Parkes.—'Proc. Roy. Soc. Med.,' 1914, vii (Clin. Sect.), p. 39.
(12) Wechselmann and Hirschfeld.—'Zeitsch. f. klin. Med.,' 1908, lxvi, p. 349.

ADLARD AND SON, IMPR., LONDON AND DORKING.