PAPERS AND ORIGINALS

Malformations of Central Nervous System and Softness of Local Water Supplies

C. R. LOWE, C. J. ROBERTS, S. LLOYD

British Medical Journal, 1971, 2, 357-361

Summary

The mean annual prevalence at birth of congenital malformations of the central nervous system for the three years 1964-6 in 48 local authority areas in South Wales was negatively correlated ($r = -0.402$, $P < 0.01$) with estimates of the mean total hardness of the related water supplies.

The mean annual perinatal mortality rate from anencephalus for the five years 1963-7 in 58 county boroughs in England and Wales was also negatively correlated with estimates of the mean total hardness ($r = -0.220$, $P > 0.05$) and calcium content ($r = -0.289$, $P < 0.05$) of the related water supplies.

It is concluded that the relationship between these associations may well be secondary. Analytical epidemiological studies of the association are called for.

Introduction

There is good evidence that environmental influences must play some part, possibly a major part, in the aetiology of neural tube malformations in the human embryo. Almost all that evidence, however, relates to non-specific and uncertain markers of as yet unidentified specific teratogens. For example, the frequency of malformations of the central nervous system varies greatly from country to country (Penrose, 1957; Stevenson, Johnston, Stewart, and Golding, 1966). It also varies from area to area within countries: in the United States for the period 1950-9 mortality from spina bifida was two to three times greater on the Atlantic coast than on the Pacific coast (Hewitt, 1963); in South Wales the frequency of central nervous system malformations in the coal-mining valleys is almost twice as high as in the coastal plain (Laurence, Carter, and David, 1967); in England and Wales as a whole the

frequency is highest in the north, the north-west, and Wales and lowest in the east, south-east, and south (Rogers, 1969; Stocks, 1970). It is higher in first-born than in later born infants and in infants born to young and old mothers than to mothers in mid-reproductive life (Record and McKeown, 1949; Record, 1961; Rogers, 1969). It is higher among infants born in the poorer than in the well-to-do strata of society (Anderson, Baird, and Thomson, 1958; Edwards, 1958; Laurence, Carter, and David, 1968). It tends to be higher among winter than among summer births (McKeown and Record, 1951; Edwards, 1961; Record, 1961; Slater, Watson, and McDonald, 1964; Leck and Record, 1966; Rogers, 1969). Striking secular swings in frequency have been reported in Birmingham, Scotland, Dublin, and Boston (Leck, 1966; Leck and Rogers, 1967; MacMahon and Yen, 1971).

Penrose (1957) seems to have been the first to speculate that "the geographical variations observed in the incidence [of anencephalus] might suggest a...causal agent, such as the presence or absence of trace elements in the water supply." This suggestion has been taken up by Fedrick (1970). She related data on anencephalus for 10 different areas in the United Kingdom (from 10 different studies and relating to 10 different time-periods) to information about the water supplies of those areas obtained from various sources. Despite such manifestly unsatisfactory data she found that the frequency of anencephalus was significantly related to measurements of the total hardness, calcium content, and pH of the local water supplies.

Stocks (1970) examined the mean annual death rates (stillbirths plus infant deaths) for congenital malformations in the 15 hospital regions of England and Wales. Mortality rates were highest in the north and the west and lowest in the south-east. Having observed that mortality from cardiovascular disease followed much the same regional pattern, he proceeded to correlate death rates from congenital malformations in the 15 regions with death rates of women aged 25-54 from certain causes in the corresponding regions. He found that mortality from malformations of the neural tube correlated very closely with mortality from the cardiovascular diseases (the correlation coefficients all exceeded 0.8), whereas other malformations produced insignificant negative correlations. He concluded that because mortality from cardiovascular disease in the county boroughs of England and Wales has been shown to be strongly associated with softness of their water supplies (Crawford,

Department of Social and Occupational Medicine, Welsh National School of Medicine, Cardiff

C. R. LOWE, M.D., M.R.C.P., Professor
C. J. ROBERTS, M.D., PH.D., Lecturer
S. LLOYD, B.SC., Scientific Officer

Gardner, and Morris, 1968a, 1968b), a water factor might possibly be responsible for the regional variations of mortality from central nervous system malformations.

In this paper, and against this background, we relate area differences in mortality from malformations of the central nervous system in South Wales to estimates of the hardness of the water supplies in these areas. We also present new data on perinatal mortality from anencephalus in the county boroughs of England and Wales and relate them to estimates of the hardness of their water supplies.

Sources of Data

SOUTH WALES

For the three years beginning 1 January 1964 we have collected information about all the infants born to women resident in a defined area in South Wales and about all the congenital defects identified in that birth population. The scope of this investigation and the methods used have been described in detail elsewhere (Richards and Lowe, 1971). The area surveyed was defined by the boundaries of Glamorganshire and Monmouthshire and included four county boroughs—Cardiff, Merthyr Tydfil, Newport, and Swansea. For administrative purposes this part of South Wales is divided into 51 local authority areas. During the three years of the investigation 92,982 infants (live births and stillbirths) were born to women resident in these areas. Of these infants 90,921 were the outcome of singleton pregnancies and 743 of these were ascertained to have neural tube defects.

Hart (1970) examined the distribution of mortality from coronary artery disease in exactly the same geographical area. His concern was with the high mortality from coronary heart disease in the South Wales coal-mining valleys, and one hypothesis he explored was that this high mortality might be attributable to the softness of the water supplies. To this end he estimated the mean total hardness of the water supplied to each local authority area in South Wales from data supplied by the engineers and chemists of the water undertakings, supplemented by data from the *Water Engineers Handbook* (1968). In Appendix A we have tabulated our data on mean annual central nervous system malformation rates in the local authority areas of South Wales against Hart's estimates of the hardness of the water supplies. Four of the 51 areas had three-year birth populations of fewer than 250. These have been combined with their appropriate neighbours so that there are in all 48 local authority areas.

ENGLAND AND WALES

The Medical Statistics Division of the Office of Population Censuses and Surveys kindly supplied us with data about all reported perinatal deaths from anencephalus for each county borough in England and Wales, 1963-7. Gardner, Crawford, and Morris (1969) have already published data about the water supplies of county boroughs in England and Wales with total populations in 1961 of over 80,000. Three of those county boroughs had changed their boundaries between 1963 and 1967, the period for which we have the data on perinatal deaths from anencephalus. In Appendix B we have tabulated annual perinatal deaths from anencephalus (1963-7) and the mean annual death rate per thousand births for the 58 county boroughs with populations of over 80,000 who had not changed their boundaries during these years.

Results

The data in Appendix A are presented in Fig. 1 as a scatter diagram of central nervous system malformation rates in the 48 local authority areas of South Wales in relation to the estimated total hardness (p.p.m.) of their water supplies. There

is an obvious tendency for malformation rates to decrease as the hardness of the related water supplies increases and the correlation coefficient ($r = -0.402$) is significant at the 1% level.

FIG. 1—C.N.S. malformation rates in 48 local authority areas in South Wales and water hardness (1964-6).

Though malformations of the neural tube are among the commonest of the major congenital defects, they are still not common enough to permit a more detailed analysis of their frequency in relation to the hardness of local water supplies without some grouping together of the small local authority areas. This we have done, largely on a geographical basis, to give eight areas with substantial birth populations (see Appendix A). Estimates of mean water hardness have been made for the grouped county areas (three in Glamorgan and two in Monmouthshire) from the hardness indices given by Hart (1970) for each of the constituent small local authority areas, making allowances for the varying proportions of births in those areas. Table I gives the weighted correlation coefficients (Appendix

TABLE I—C.N.S. Malformation Rates in Eight Areas in South Wales (1964-6) Related to Estimates of Mean Hardness of Local Water Supplies

Area	No. of Singleton Births	Mean Annual Malformation Rates per 1,000 Total Births			Estimated Mean Total Hardness (p.p.m.) of Water Supplies
		All C.N.S. Malformations	Anencephalus	Spina Bifida without Anencephalus	
Cardiff	14,451	7.54	2.91	3.18	110
Newport	6,540	5.20	0.76	3.36	100
Swansea	8,419	8.08	3.33	4.16	95
Glamorgan East Valleys	17,738	10.03	3.72	4.96	42
Glamorgan West Valleys	11,278	9.40	3.28	5.05	39
Rest of Glamorgan Monmouthshire Valleys	13,823	6.87	2.82	2.97	161
Rest of Monmouthshire	13,309	8.87	3.83	3.61	83
Rest of Monmouthshire	5,361	6.53	2.42	3.54	122
Weighted correlation coefficient between malformation rates and water hardness..		—0.805*	—0.446	—0.918†	

*Significant at 5% level.

†Significant at 1% level.

C) of water hardness in the eight large birth populations with all C.N.S. malformations, anencephalus with or without spina bifida, and spina bifida without anencephalus (Fig. 2). Again there is a negative correlation of malformation rates with water hardness, significant for all C.N.S. malformations ($P < 0.05$) and for spina bifida ($P < 0.01$) but not for anencephalus. (The anencephalus rate for Newport is very much out of line.)

But the coal-mining valleys, with their high malformation rates and soft water supplies, differ from the rest of South

FIG. 2—Spina bifida and water supply in South Wales 1964-6.

Wales in other important respects. As Hart (1970) pointed out, "they have been in a state of economic decline since 1921, and have suffered drastic depletion by migration for several generations . . . [and] the villages are almost single-class communities." The frequency of neural tube malformations is known to be related to social class (it is higher in the lower social classes); so the association of high malformation rates with softness of water in South Wales may be in part, perhaps wholly, no more than a reflection of this. In Table II we

TABLE II—C.N.S. Malformation Rates in South Wales (1964-6) Related to Social Class

Social Class	Number of Singleton Births	Mean Annual Malformation Rates per 1,000 Total Births		
		All C.N.S. Malformations	Anencephalus	Spina Bifida without Anencephalus
I and II	11,275	5.76	1.77	3.55
III non-manual	10,806	6.48	2.68	2.87
III manual	34,212	9.03	3.36	4.27
IV and V	28,262	8.85	3.26	4.42

examine the relation between central nervous system malformations and social class for the whole of South Wales. There is, indeed, evidence of a social class difference, but the difference is more a dichotomy than a gradient. The incidence of all C.N.S. malformations, anencephalus, and spina bifida is consistently lower among non-manual workers (social classes I, II, and III non-manual) than among manual workers (social classes III manual, IV, and V). In Table III we have correlated the frequency of all C.N.S. malformations, of anencephalus, and of spina bifida with water hardness in our eight large birth populations, subdivided into non-manual and manual classes. Once again the correlation coefficients are consistently negative.

TABLE III—C.N.S. Malformation Rates in Eight Areas in South Wales (1964-6) Related to Social Class and to Hardness of Local Water Supplies

Area	All C.N.S. Malformations		Anencephalus		Spina Bifida without Anencephalus		Water Hardness (p.p.m.)
	I, II, and III Non-manual	III Manual IV and V	I, II, and III Non-manual	III Manual IV and V	I, II, and III Non-manual	III Manual IV and V	
Cardiff	4.62 (4,110)	8.21 (9,502)	1.22	3.26	2.19	3.47	110
Newport	5.25 (1,523)	5.18 (4,634)	0.66	0.65	4.60	3.24	100
Swansea	5.81 (2,408)	9.50 (5,579)	3.74	3.41	2.08	5.38	95
Glamorgan East Valleys	8.15 (3,189)	10.85 (13,362)	2.82	4.12	4.39	5.31	42
Glamorgan West Valleys	8.02 (1,995)	10.15 (8,279)	2.51	3.62	5.01	5.31	39
Rest of Glamorgan	5.14 (4,863)	8.26 (7,868)	2.26	3.18	2.47	3.56	161
Monmouthshire Valleys	7.56 (2,380)	8.56 (10,048)	2.52	3.58	3.36	3.68	83
Rest of Monmouthshire	5.58 (1,613)	7.50 (3,201)	1.86	2.50	3.72	4.06	122
Weighted correlation coefficient between malformation rates and water hardness	—0.841*	—0.569	—0.302	—0.365	—0.639	—0.674	

*Significant at 1% level.

It should be noted that the association between all C.N.S. malformations and water supplies is at its most significant level for the non-manual social classes among whom the frequency of neural tube malformations is lower and whose standard of living and general way of life probably varies less from area to area than that of the manual social classes.

Finally we have calculated the correlation coefficient of anencephalus perinatal mortality rates in 58 county boroughs of England and Wales (provided for us by the Registrar General) with estimates of total hardness and of calcium content of the local water supply taken from data published by Gardner *et al.* (1969). Here again there is some indication of a trend in the scatter diagram (Fig. 3), confirmed by negative

FIG. 3—Perinatal mortality from anencephalus and calcium content of water supply in 58 county boroughs in England and Wales 1963-7.

correlation coefficients. With total hardness as the index the correlation coefficient is -0.220 ; with calcium content it is -0.289 ($P < 0.05$).

Discussion

We have found some evidence of an inverse relation between the frequency of malformations of the central nervous system and the hardness of the local water supplies, in the sense that hard water areas tend to have lower malformation rates than soft water areas. In South Wales reliable data on malformations and less reliable data on hardness of water supplies gave a correlation coefficient of -0.402 ($P < 0.01$). But in South Wales the poorer areas (notably the coal-mining valleys) tend to have

softer water supplies than the more prosperous areas of the coastal plain, and the frequency of C.N.S. malformations is known to be higher among infants born to manual workers than to non-manual workers. We have found, however, that the association persists when the families of manual and non-manual workers are considered separately. At the national level perinatal mortality rates from anencephalus in 58 county boroughs in England and Wales (which can be assumed to be reliable since anencephalic infants are either stillborn or die very shortly after birth and the malformation is so gross that reporting of it is likely to be reasonably complete) were also negatively correlated with estimates of the mean hardness of their water supplies. Here, however, the correlation coefficients were lower and reached significance at the 5% level only for calcium content.

This negative association of C.N.S. malformation frequency in South Wales and of anencephalus perinatal mortality in the county boroughs of England and Wales with water hardness is less pronounced than the now widely reported and also negative association of mortality from cardiovascular disease with water hardness for which in general $r > 0.5$ (Crawford *et al.*, 1968a). However, in view of the difficulty of obtaining reliable estimates of the hardness of the water supplies in the county boroughs and even more in the local authority areas of South Wales, it is perhaps surprising to find a significant correlation at any level. "For most county boroughs the water-supply [is] extremely heterogeneous . . . the relative contributions of the various sources often change throughout the year. Also from year to year water undertakings, like businesses, are merged for greater efficiency" (Loutit, 1968). While Hart (1970), whose data on water hardness we have used, admits that "water supplies in South Wales are of great complexity. Many communities draw mixed water from different sources, in varying proportions at different seasons and different states of water reserve." In addition, it is not always clear when published figures of water hardness relate to water at source, at supply point before distribution, or at the tap of the householder; information about the extent to which naturally hard waters are artificially softened for domestic purposes is not available; there seems to be little information about how hard water is modified when ingested as tea, coffee, or beer; and there are no reliable estimates of the proportion of our daily intake of water which may have been modified in this way.

If there is, in fact, a negative association between the frequency of central nervous system malformations and hardness of the local water supplies, the problem is to determine whether there is a "water factor" in the aetiology of those malformations (causal) or whether the association is no more than a reflection of a third factor to which both the frequency of malformations and water hardness are independently related (secondary). The same problem arises in respect of the negative correlation of mortality from cardiovascular disease with water hardness. It seems unlikely, however, that some unknown local factor could be producing a secondary association between cardiovascular mortality and water hardness in countries as diverse as Japan, U.S.A., Sweden, and U.K. For this and other reasons Crawford *et al.* (1968a) consider that a causal water factor is probably involved. It is curious, however, that Crawford *et al.* found that infant mortality, death rate from bronchitis, and death rate from all causes less cardiovascular disease and bronchitis also had significant negative correlations with water hardness, though to a lesser degree. Some at least of these associations must be secondary.

At this stage we think it likely that the association we have found, if confirmed, may also be a secondary one. Certainly in South Wales the less prosperous areas tend to have the softest water supplies, and the correction we have been able to make for this is inadequate. It is possible, therefore, that in our investigation hardness of water supplies is no more than an uncertain pointer to some as yet undetermined specific teratogen in the non-specific poverty complex.

The relation between mortality from cardiovascular disease

and water softness is now believed to be causal, but so far there is no acceptable explanation of the mechanism. If there should eventually prove to be a water factor causally involved in the aetiology of malformations of the neural tube, a satisfactory explanation of the mechanism is likely to be even more elusive. Among the questions that would need to be answered are: does the water factor operate immediately, possibly by inducing a teratogenic metallic contaminant or trace element, or is a long exposure required to effect some change in the maternal chemistry? and is there a protective factor in hard water rather than a teratogenic factor in soft water? There is also the difficulty that the prevalence at birth of central nervous system malformations may bear little relation to the incidence—that is, the attack rate—early in pregnancy. These malformations are triggered off soon after conception (normally the neural tube is closed at four weeks) and there is almost certainly a high early embryonic mortality. It would therefore need to be borne in mind that a hardness factor might possibly be augmenting that early mortality, thereby decreasing the point-prevalence at birth.

There is little point in pursuing these speculations any further. What is needed is confirmation or refutation of the negative association between neural tube malformations and hardness of local water supplies by an analytical type of epidemiological study—that is, by a comparison of tap-water from the houses of women who give birth to malformed infants with tap-water from the houses of controls who give birth to normal infants.

Appendix A

Mean Annual C.N.S. Malformation Rates in 48 Local Authority Areas in South Wales, with Estimates of Total Hardness of Their Water Supplies

Local Authority	No. of Singleton Births 1964-6	Mean Annual C.N.S. Malformation Rates	Total Hardness (p.p.m.) of Water Supply (Hart, 1970)
1. Cardiff C.B.	14,451	7.54	110
2. Newport C.B.	6,540	5.20	100
3. Swansea C.B.	8,419	8.08	95
4. East Glamorgan mining valleys:			
Aberdare U.D.	1,885	10.08	36
Caerphilly U.D.	2,394	8.35	42
Gelligaer U.D.	1,993	8.53	42
Merthyr C.B.	3,157	9.19	33
Mountain Ash U.D.	1,504	5.98	65
Pontypridd U.D.	1,750	12.00	46
Rhondda M.B.	4,589	13.29	44
Rhymney U.D.	466	4.29	35
5. West Glamorgan mining valleys:			
Glyncorwg U.D.	593	15.18	22
Llwchwr U.D.	1,242	9.66	20
Maesteg U.D.	1,136	7.04	50
Neath M.B.	1,409	8.52	35
Neath R.D.	1,972	11.16	26
Ogmore and Garw U.D.	971	17.51	50
Pontardawe R.D.	1,285	4.67	25
Port Talbot M.B.	2,670	7.49	61
6. Rest of Glamorgan:			
Barry M.B.	2,243	10.25	110
Bridgend U.D.	717	5.58	265
Cardiff R.D.	2,504	4.39	110
Cowbridge M.B. and R.D.	1,174	7.67	265
Gower R.D.	722	4.16	95
Llantrisant and Llantwit Fadre R.D.	1,756	9.68	42
Penarth U.D.	1,237	8.89	110
Penybont R.D.	2,729	5.50	265
Porthcawl U.D.	743	2.69	265
7. Monmouthshire mining valleys:			
Abercarn U.D.	886	15.80	45
Abertillery U.D.	1,039	5.77	42
Bedwas and Machen U.D.	697	7.17	42
Bedwellty U.D.	1,494	8.03	53
Blaenavon U.D.	371	10.78	47
Cwmbran U.D.	1,966	7.12	100
Ebbw Vale U.D.	1,482	11.47	50
Mynyddislwyn U.D.	830	3.61	114
Nantyglo and Blaina U.D.	695	10.07	42
Pontypool U.D.	1,959	9.19	160
Risca U.D.	867	5.77	110
Tredeggar U.D.	1,025	12.68	95
8. Rest of Monmouthshire:			
Abergavenny M.B.	563	3.55	100
Abergavenny R.D.	426	7.04	100
Caerleon U.D.	478	6.28	100
Chepstow R.D.	977	8.19	100
Chepstow U.D.	603	8.29	100
Magor and St. Mellons R.D.	1,232	4.06	110
Monmouth M.B. and R.D.	447	4.47	210
Pontypool R.D. and Usk U.D.	635	11.02	185

Appendix B

Annual Perinatal Deaths from Anencephalus, 1963-7, and Mean Annual Death Rate per 1,000 Births during this Period, in 58 County Boroughs in England and Wales

County Borough	No. of Deaths					Mean Annual Perinatal Death Rate
	1963	1964	1965	1966	1967	
England:						
Bath	4	3	2	3	3	2.32
Birkenhead	10	10	11	6	7	3.08
Birmingham	39	28	36	41	35	1.61
Blackburn	2	4	6	2	4	1.97
Blackpool	8	6	5	10	7	3.54
Bolton	9	7	5	6	3	2.14
Bootle	7	5	3	1	9	2.93
Bournemouth	4	3	4	4	2	1.77
Bradford	4	10	4	13	8	1.35
Brighton	5	6	4	4	3	1.80
Bristol	14	13	20	15	11	1.95
Burnley	1	2	2	1	3	1.67
Coventry	12	12	13	8	12	1.71
Darlington	1	4	2	1	3	1.51
Derby	11	4	3	3	5	2.49
Doncaster	3	2	2	1	2	1.88
Exeter	1	2	2	1	1	1.01
Gateshead	7	13	3	7	3	3.44
Grimsby	7	2	6	2	1	1.89
Halifax	4	3	5	5	2	2.21
Huddersfield	4	8	5	6	4	2.16
Ipswich	4	0	5	3	0	1.07
Kingston-upon-Hull	15	6	9	9	10	1.67
Leeds	16	13	18	14	18	1.69
Leicester	8	10	9	7	10	1.69
Liverpool	45	45	41	44	47	3.03
Manchester	51	37	30	35	31	2.87
Middlesbrough	6	8	6	4	9	2.04
Newcastle upon Tyne	8	0	10	6	9	1.85
Northampton	3	0	12	2	2	1.74
Norwich	2	4	5	1	3	1.59
Nottingham	10	13	15	17	5	1.94
Oldham	3	2	10	5	5	2.39
Oxford	1	6	2	0	3	1.33
Plymouth	7	7	4	1	8	1.38
Portsmouth	10	9	4	4	9	1.91
Preston	7	2	6	1	7	2.24
Reading	4	7	2	6	4	1.85
Rochdale	5	8	5	4	0	2.67
Rotherham	5	0	4	4	4	2.04
St. Helens	4	7	9	9	5	3.66
Salford	11	11	14	6	10	3.44
Sheffield	10	15	9	22	9	1.51
Southampton	9	12	5	6	6	1.97
Southend-on-Sea	6	5	4	1	4	1.64
Southport	3	5	5	3	2	3.18
South Shields	6	5	4	6	2	2.41
Stockport	7	8	7	10	10	3.17
Stoke-on-Trent	10	18	14	12	9	2.79
Sunderland	5	9	6	6	8	1.81
Walsley	3	1	6	2	5	1.81
Walsall	3	6	5	4	6	1.70
West Bromwich	2	3	4	5	1	1.28
Wolverhampton	7	7	6	8	9	1.86
York	4	4	2	3	2	1.71
Wales:						
Cardiff	13	14	14	12	6	2.37
Newport	7	3	1	2	7	1.85
Swansea	7	12	5	9	7	2.78

Appendix C

The weighted correlation coefficient is calculated by the formula:

$$r = \frac{\sum W_i(X_i - \bar{x})(Y_i - \bar{y})}{\sqrt{(\sum W_i(X_i - \bar{x})^2)(\sum W_i(Y_i - \bar{y})^2)}}$$

where X_i is the weighted mean hardness of water, Y_i is the C.N.S. malformation rate, and W_i is the number of singleton births in 1964-6 in the i th area.

$\bar{x}$ here is the weighted mean of X s—that is $\bar{x} = (\sum W_i X_i) / \sum W_i$, and similarly for $\bar{y}$.

We acknowledge with gratitude the generous grant from the Association for the Aid of Crippled Children, New York, which made this investigation possible. It is with pleasure that we also acknowledge our indebtedness to the Medical Officers of Health of Cardiff, Merthyr Tydfil, Newport, Swansea, Glamorgan, and Monmouthshire for their interest and co-operation and to the many consultant obstetricians, paediatricians, pathologists, dermatologists, and orthopaedic, plastic, and ophthalmic surgeons who have notified and continue to notify to us the names of infants in our birth population who have come to their attention with congenital defects. We are also grateful to Dr. J. Howlett and Mrs. J. Lay, of the Atlas Computer Laboratory, Chilton, Berks, for the help they and their staff have always given us; to the Registrar General for providing us with the county borough data on anencephalus perinatal mortality; and to Dr. J. T. Hart and Dr. M. D. Crawford for their advice about hardness of water supplies in South Wales and in the county boroughs of England and Wales.

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