ERYTHEMA NODOSUM IN CHILDREN FOLLOWING ADMINISTRATION OF SULPHATHIAZOLE

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The occurrence after the administration of sulphathiazole of a rash similar to erythema nodosum (sulphathiazole erythema nodosum) has been reported frequently since the introduction of this sulphonamide compound. In the first reports (Carey, 1940; Long et al., 1940; Havilland and Long, 1940; Berglund and Frisk, 1941) this rash did not receive any special attention, being regarded with many other rashes as evidence of sensitivity to sulphonamides. Gsell (1940) was the first to suspect that this eruption did not depend on the toxic effect of the drug only, but that changes in the body due to the infection for which sulphathiazole was given were also responsible.

Wissler (1942) reported briefly on nineteen children with sulphathiazole erythema nodosum and drew attention to its varying incidence during the treatment of different infections; fifteen of these children had a positive Pirquet test.

Jersild and Iversen (1942) presented nine cases, none of which had an active tuberculous infection, and reported on the histological changes in an excised lesion which they found similar to those previously described in erythema nodosum.

Miescher (1943) was the first to attempt a thorough clinical and histological study of this manifestation. He rejected the possibility of sulphathiazole erythema nodosum being a common drug rash, and he put forward the hypothesis that this eruption is the result of action of bacterial substances of an allergenic or toxic nature.

Rollof (1945), giving sulphathiazole to children with a primary tuberculous infection during the active stage and later, found that the sooner after the infection the sulphathiazole was given, the more likely was sulphathiazole erythema nodosum to be provoked. All five children who received sulphathiazole during their initial fever developed erythema nodosum. Marie et al. (1945) reported on twelve children with sulphathiazole erythema nodosum, five of whom were tuberculin-negative, and they discussed various possible theories to explain this phenomenon. Amongst these was the theory that

erythema nodosum might be due to a virus and that sulphathiazole might act by activation of this virus.

Loefgren (1944a, 1944b, 1945a, and 1945b) was responsible for the most carefully studied series of sulphathiazole erythema nodosum in adults so far reported, and he concluded that this eruption is not an ordinary drug rash, but is similar in nature to the usual erythema nodosum, the sulphathiazole being a provocative factor only.

The present investigation confirms Loefgren's general conclusions but is presented because the material consists of children only, and because in some respects a different method of approach has been used and some further points have been made clear.

Material

The material for this investigation consists of (a) seventeen children in whom a course of sulphathiazole preceded the first appearance of a skin rash similar to erythema nodosum (Group A, table 1), (b) thirty-two children in whom sulphathiazole was given for therapeutic or experimental purposes at varying intervals after an eruption of erythema nodosum. Twelve responded with an eruption of lesions similar to erythema nodosum (Group B, table 2) and twenty did not (Group C, table 3). In addition the case histories of other eighteen children with erythema nodosum and of all children who were treated with one or more courses of sulphathiazole for various infections in this department were studied.

Possibility of Coincidence

Before an attempt is made to explain the nature of this eruption, the question arises whether the occurrence of erythema nodosum following the administration of sulphathiazole is not a simple coincidence.

Were the occurrence of erythema nodosum after the administration of sulphathiazole a simple coincidence, the eruption should appear in a similar proportion of patients receiving other sulphonamide drugs; yet the numerous published reports of erythema nodosum following sulphonamide therapy include only three cases in which the drug was not

TABLE I
SULPHATHIAZOLE ADMINISTRATION BEFORE THE FIRST ERUPTION OF ERYTHEMA NODOSUM

Case	Age	Sex	Reason for sulphathiazole administration*	Amount taken until eruption (g.)	Days until eruption†	Mantoux	X-ray findings	Duration of skin lesions (days)	Remarks
W.McK.	10	M.	Abd. pain thought to be peritonitis	10	3	0.01 mg. O.T. positive	Enlarged L. hilum + extension to L. middle zone	4	
R.B.	10	M.	Abscess of calf and inguinal adenitis	17	2½	0.01 mg. O.T. positive	Nil	4	
J.M.	4	F.	Abscess of neck	12 and 14 (2 courses)	13 4	0.01 mg. O.T. positive	Nil	6	Biopsy from gland of neck after incision showed T.B. granulation tissue.
J.L.	2	F.	Symptoms from respiratory system	4.5	9	0.1 mg. O.T. positive	Enlarged L. hilum	Not accurately known	Died 3 months later from Tb. meningitis.
P.S.	5	M.	Tb. meningitis. Sulphathiazole given to study possible renal lesions	44	11	0.01 mg. O.T. positive	Some peribronchial thickening	2	Died 2 days after eruption. Lesions faded during few hours before death. Mantoux after eruption negative to 0.01, positive to 0.1 mg. O.T.
A.L.	6	F.	Ruptured appendicitis and local peritonitis	9	2	0.1 mg. O.T. positive	Enlarged R. hilum. Pleurisy R. horizontal fissure	3	Developed parenchymatous lesion R. upper lobe, which resolved after one year.
S.S.	8	F.	Sore throat	10 (in 2 days)	9 (last 7 days no sulphathiazole)	0.005 mg. O.T. positive	Enlarged R. hilum and probable thickening interlobar fissure	15	The small amount of sulphathiazole the long incubation period, and the long duration of the rash make possible that in this case genuine E.N. would have appeared without provocation by the drug.
E.H.	15	F.	Symptoms of acute respiratory illness diagnosed as pneumonia	18	1½	1 mg. O.T. positive	Many ill-defined patches in upper and middle zones	8	No changes in x-ray findings after a year.
N.H.	11	F.	Febrile illness	6-12	1-2	0.1 mg. O.T. positive	Parahilar parenchymatous changes	2	
R.McF.	11	M.	Febrile illness	6	2	0.1 mg. O.T. positive	Suspicion of basal infiltration, miliary type	2	
D.C.	1½	F.	Abscess of buttock	1-2	2	0.01 mg. O.T. positive	Nil	8	
A.H.	13½	M.	Febrile illness with pain in chest	9	6	0.01 mg. O.T. positive	R. pleural effusion	Less than 9	
D.H.	2½	F.	Abscess of neck	12.5	5	0.01 mg. O.T. positive	Nil	3	
W.McQ.	11	M.	Acute respiratory illness	7	4	0.1 mg. O.T. positive	No evidence of primary T.B. infection	3	
J.W.	1½	M.	Cervical adenitis	3	2	10 mg. O.T. negative	Nil	5	
E.M.	9	F.	Sore throat	6	2	1 mg. O.T. negative	Nil	3	
M.G.	4	F.	Cellulitis of foot	3	1	1 mg. O.T. negative	Nil	5	

* The initial diagnosis is given, although it might not have been the correct one. In twelve cases the sulphathiazole was given by the family doctor and in five while the children were treated as in-patients.

† From the first day of the administration of sulphathiazole.

TABLE 2

SULPHATHIAZOLE ADMINISTRATION AFTER A SPONTANEOUS ERUPTION OF ERYTHEMA NODOSUM: PROVOCATION OF NEW CROP

Case	Age	Sex	Interval between spontaneous E.N. and beginning of sulphathiazole administration (days)*	Amount given till eruption (g.)	Days till eruption†	Duration of skin lesions (days)	Remarks.
J.R.	6	M.	120 8‡ 5‡ 2‡ 4‡ 200‡	14 6 1 18 3 24	3 1 One dose 3 6	3 3 No effect 2 No effect	Sulphathiazole was originally given for symptoms from the chest, due to a pleural effusion. Subsequent administrations made for experimental purposes.
S.R.	10	F.	90	9	3	2	Tuberculin negative. Etiology of genuine eruption not clear. Family history of E.N. and erythema multiforme.
W.P.	12	M.	4	9	3	2	
E.B.	13	F.	9	11	2	8-16	
E.T.	12	F.	5	18	4	3	
D.J.	10	F.	6	3	‡	15	
E.W.	15	F.	10	16	4	1	
F.B.	9	M.	4	6	2	6	
N.J.	13	M.	12 7‡	4 4	1 1	5 4	Phlyctenular conjunctivitis appeared during second provocation.
S.W.	8	F.	22	10	2	6	
B.R.	3	M.	330	6	3	6	More details about this case given in text.
E.D.	13	F.	13	12	2	10	

* From the day of the eruption of the last lesion.

† From onset of administration of sulphathiazole.

‡ After the preceding eruption.

sulphathiazole (one after sulphanilamide: Loveman and Simon (1940) and two after sulphapyridine: Loeffgren (1945a)). Similarly, while five out of five hundred children treated with sulphathiazole in the wards of this department since 1943 developed erythema nodosum, this manifestation was not once seen in one thousand and forty children who received other sulphonamides. This difference is statistically significant (Difference = 1 per cent., Standard error = 0.436).

If no causal relationship existed between the ingestion of sulphathiazole and erythema nodosum, provocation by this drug of new crops after the original eruption would be unlikely. As can be seen from tables 2 and 3, out of twelve cases of erythema nodosum to whom sulphathiazole was given after the complete fading of the lesions but within thirteen days from the eruption of the last lesion, a new crop appeared in eight. In thirty-seven similar cases in which there was no provocation within thirteen days from the appearance of the last lesion no new crop was noticed after the fading of the original eruption. The difference between the two groups is statistically significant (Difference = 61 per cent., Standard error = 13.53).

A slight difference in the clinical course between provoked and spontaneous erythema nodosum is mentioned below. Such a difference would not be

expected if the eruption were entirely independent of preceding sulphathiazole administration. Another possible explanation of this difference is offered later.

The weight of evidence is therefore that the occurrence of erythema nodosum following administration of sulphathiazole is not a coincidence.

Comparison with Typical Drug Rash

The next question which arises is whether sulphathiazole erythema nodosum is a common 'drug rash' due to allergic hypersensitivity to sulphathiazole. Miescher (1943) described as typical of drug rash the following five points which are here compared with the corresponding characteristics of the sulphathiazole erythema nodosum cases in this series.

Drug rashes are morbilliform, scarlatiniform, or urticarial, and are diffusely distributed over the trunk and extremities. Sulphathiazole erythema nodosum is nodular and localized to the anterior surface of the legs and occasionally the thighs and extensor surfaces of arms.

Group specificity is usually present in drug rash, while it is absent with sulphathiazole erythema nodosum. As already pointed out the occurrence of erythema nodosum following the administration

TABLE 3
SULPHATHIAZOLE ADMINISTRATION AFTER A
SPONTANEOUS ERUPTION OF ERYTHEMA NODOSUM:
FAILURE TO PROVOKE NEW CROP

Case	Age	Sex	Interval between E.N. and beginning of sulphathiazole administration (days)*
A.Y. . .	7	M.	300
M.S. . .	10	F.	270
M.R. . .	5	F.	28
M.H.† . .	9	F.	40
W.J. . .	12	M.	35 155
B.H. . .	11	F.	26
J.S. . .	8	F.	33
V.C. . .	11	F.	26
B.B. . .	9	F.	50
J.L. . .	9	M.	13
G.D. . .	4	M.	15
M.A. . .	12	F.	40
M.L. . .	5	F.	14
C.J. . .	14	F.	40
S.T. . .	9	F.	7
P.C. . .	8	F.	More than 20
B.S. . .	11	F.	10
E.S. . .	12	F.	More than 14
F.M. . .	10	M.	More than 6
J. Ry. . .	13	M.	90

* From the day of the eruption of the last lesion.

† Seven days after onset of sulphathiazole administration; patient had a rise of temperature and developed a generalized morbilliform drug rash.

of a sulphonamide compound other than sulphathiazole is extremely rare. In this respect it is of interest that in case J.R., sulphamezathine was given without any effect between two successful provocations of erythema nodosum by sulphathiazole.

Continuation of the medication after the eruption of a drug rash intensifies the rash and often causes stormy constitutional symptoms. In sulphathiazole erythema nodosum this does not happen. Sulphathiazole administration, continued from twelve hours to five days after the eruption in six cases of Group A and in nine of Group B, caused no difference either in the severity of constitutional symptoms, which were generally mild, or in the intensity and duration of the rash between these children and the children in whom sulphathiazole was discontinued immediately after the eruption. The lesions often began to fade while the child was still receiving sulphathiazole.

In cases of drug rash, repetition of the medication with the offending drug causes a recurrence of the rash. In seven cases of sulphathiazole erythema nodosum this sulphonamide was given again six days to several months after the first eruption. In

only three cases was a new crop provoked, and as will be seen later the success of the provocation depends on some other factor or factors.

Finally drug rashes are independent of the underlying condition, that is, of the illness under treatment or of the state of allergy of the patient. The occurrence of erythema nodosum following treatment with sulphathiazole is not independent of these factors.

Of 191 tuberculin-negative and fifty-six tuberculin-positive children who received sulphathiazole for various infections and who were watched for twelve days or more after the onset of the treatment, five developed erythema nodosum unexpectedly, and all five were among the tuberculin-positive, a percentage of 8.9 (standard deviation = 3.806). Roloff (1945) had already observed this predilection of sulphathiazole erythema nodosum to develop in tuberculin-positive children. Of thirty-five children with recent primary tuberculosis who received sulphathiazole, twenty-four, or 68.6 per cent., developed erythema nodosum, while of 788 tuberculin-negative children who were treated with the same compound, only eight, or 1 per cent., developed erythema nodosum.

Another argument against sulphathiazole erythema nodosum being a drug rash is the short interval between the course of sulphathiazole and the appearance of the nodules. In fourteen children of this series the interval was six days or less, while it is usually longer in true hypersensitivity. Treatment by sulphonamides in the past and therefore possibility of previous sensitization could be excluded in nine of these fourteen children with certainty.

The findings in the present series therefore confirm Miescher's opinion that sulphathiazole erythema nodosum is not a drug rash due to the development of allergic hypersensitivity to sulphathiazole. However, as all the above-mentioned differences between drug rash and sulphathiazole erythema nodosum are based on clinical data, a more direct approach was attempted by use of skin tests to detect hypersensitivity to sulphathiazole. The use as a testing substance of solutions of the free drug usually fails to elicit positive reactions both in typical hypersensitivity reactions to sulphonamides (references in Leftwich, 1944) and in sulphathiazole erythema nodosum (Miescher, 1943; Loeffgren, 1945a). As a testing substance, therefore, serum from persons who had received sulphathiazole was used, as suggested by Leftwich (1944), with the only difference that 0.1 ml. and not 0.05 ml. of both the control and sulphathiazole-containing serum was injected intradermally; serum removed from the same person before administration of the drug was in each case used as a control. Twenty-two tests were performed on fifteen children of the present series, three of Group A, four of Group B, and eight of Group C. In addition to these, another twenty-two tests were performed on twenty-two children, seven tuberculin-negative, and

TABLE 4
SKIN TESTS FOR SENSITIVITY TO SULPHATHIAZOLE
(LEFTWICH'S METHOD)

	Control cases		Cases of present series.		
	Tuber- culin nega- tive	Tuber- culin posi- tive	Group A	Group B	Group C
No difference between test-serum wheal and control ..	4	11	3	3	7
Test-serum wheal 1-3 mm. bigger than control ..	1	2	1	1	1
Control wheal 1-3 mm. bigger than test wheal ..	1	2	1	3	1
Test wheal 4 mm. bigger than control (considered as significant) ..	1				1
Total ..	7	15	5	7	10

fifteen tuberculin-positive controls. The results are presented in table 4.

Leftwich considered the test positive when the difference in diameter between the test and control wheal was 4 mm. or more. As can be seen from table 4, such a difference was noticed in two children only, and neither child had developed a sulphathiazole erythema nodosum. As there was no opportunity in the present investigation to try the effectiveness of the test sera on cases of typical drug rash, and the only other published work with Leftwich's method (Fink et al., 1946) throws doubts on its reliability, the results of these tests are not conclusive; but at least they do not disprove the conclusion, based on clinical data, that erythema nodosum following sulphathiazole administration is not a simple drug rash.

Nature of Sulphathiazole Erythema Nodosum

What, then, is the nature of sulphathiazole erythema nodosum? As it is not a drug rash it is natural to try to correlate it with spontaneous erythema nodosum, and a comparison between the two eruptions becomes necessary.

Clinical picture and course. On first sight sulphathiazole erythema nodosum can in no way be distinguished from true erythema nodosum. It is only by following the further development of the eruption that a slight difference becomes evident. As can be seen from table 1, in only one case was the interval between the eruption of the rash and its fading more than nine days, while among fifty cases of spontaneous erythema nodosum the rash only rarely lasted less than nine days. As appearance and evolution of lesions are otherwise the same, this difference could be considered as quantitative only, sulphathiazole erythema nodosum running a shorter course. This difference in duration has already been commented on by Miescher (1943). As the impression has been gained that the lesions of erythema nodosum fade

more rapidly when the patient is at rest in bed, it is likely that this shorter duration is due, at least in part, to the fact that most of the children have been confined to bed on account of the illness for which the sulphathiazole was being administered.

Histological changes. A nodule was excised from four children with sulphathiazole erythema nodosum under general anaesthesia and in one (P.S.) after death. In three of these (R.McF., P.S., J.W.) the lesions were similar to those of erythema nodosum, and in one (A.L.) there were very mild changes; while in the last (S.S.), whose nodule was excised two weeks after fading of the lesions, the changes were compatible with the appearances in an erythema nodosum lesion of the same age. No significant difference in the histological appearances could, therefore, be detected between sulphathiazole erythema nodosum and erythema nodosum. More details about the histology of erythema nodosum and sulphathiazole erythema nodosum will be given elsewhere (Hart-Mercer and Doxiadis). Miescher reached the same conclusion although he found some quantitative differences, the lesions of sulphathiazole erythema nodosum exhibiting milder changes.

Etiology and underlying infection. Although the pathogenesis of erythema nodosum remains the subject of discussion, there is general agreement on its etiology. It is widely accepted that the eruption occurs in the course of an infective illness at a stage when allergy to the infecting agent is being established. The most common infection responsible is, in European children, primary tuberculosis, and Wallgren (1930) has shown that the appearance of the eruption usually coincides with the establishment of tuberculin sensitivity. Streptococcal infection ranks second to tuberculous as a causal agent. A survey of fifty children with erythema nodosum in the past three years confirms this view. Forty-six reacted strongly to tuberculin (0.01 mg. O.T.) and thirty-five of these had radiological evidence of primary tuberculous infection. The four who were tuberculin-negative even with large doses of tuberculin (1 to 10 mg. O.T.) had signs of other preceeding infection. Two were suffering from a pyogenic cervical adenitis following scarlet fever and tonsillitis respectively, one had acute tonsillitis, and in the fourth (S.R.) the underlying infection was unknown as the child was not seen during the original eruption. As can be seen from table 1, the seventeen children who developed sulphathiazole erythema nodosum formed a very similar group from the point of view of the underlying infection. Fourteen reacted strongly to tuberculin (0.01 to 0.1 mg. O.T.); of these, eight had radiological evidence of active tuberculous infection, one had tuberculous meningitis, and one had suppurative cervical adenitis, biopsy of which revealed tuberculous granulation tissue. Of the remaining four tuberculin-positive children in whom other evidence of active tuberculous infection was lacking, one was less than two and another less than three years old,

so it is likely that they were still in an active stage of their infection. Of the three tuberculin-negative cases (up to 1-10 mg. O.T.) one had pyogenic cervical adenitis, another acute tonsillitis, and the third cellulitis of the foot. It seems, therefore, that sulphathiazole evokes the appearance of erythema nodosum in the same phases of the same infections as in children in whom the eruption appears spontaneously. It is noteworthy that although sulphathiazole has been used extensively in the treatment of children suffering from pneumonia or meningococcal meningitis, never in this series did sulphathiazole erythema nodosum develop in such a case.

The similarity in clinical appearance, histological changes, and underlying infection between erythema nodosum and sulphathiazole erythema nodosum justifies the assumption that these two manifestations are fundamentally the same. As pointed out above, administration of sulphathiazole before the appearance of the eruption of sulphathiazole erythema nodosum is more than a simple coincidence.

In order to obtain further evidence on the relationship between erythema nodosum and sulphathiazole, observations were made on thirty-two children suffering from spontaneous erythema nodosum who were treated with the drug at varying intervals after the appearance of the initial eruption. Twelve children responded with a new crop of skin lesions. These lesions were neither as large or as indurated as the initial lesions. They tended to be localized to sites not previously affected, for example the lateral surfaces of the legs and the lower halves of anterior and lateral surfaces of the thighs, but localization on sites previously affected was also not uncommon. These lesions often faded without first turning purple.

These provoked lesions were therefore similar to those lesions of a spontaneous erythema nodosum which appear a few days after the start of the eruption and sometimes after a flare-up following a tuberculin test, and which have the characteristics mentioned above. It is only when the interval between original eruption and provocation is long that the provoked lesions have the character of the typical lesions occurring in the first few days of the spontaneous eruption, that is, the lesions are larger, more tender, and more indurated (cases J.R. and B.R.). The histology of these provoked lesions was studied in three nodules excised under general anaesthesia from two children (J.R. and W.P.). No significant difference from the histological changes in erythema nodosum could be detected in these three biopsies (see Hart-Mercer and Doxiadis).

As can be seen from tables 2 and 3, the shorter the interval between the initial eruption and the course of sulphathiazole, the more likely is provocation successful. In all but four cases with successful provocation (Group B) the sulphathiazole course began thirteen days or less after the eruption of the last skin lesion of the initial attack. In all but

three cases in which provocation was unsuccessful (Group C) this interval was thirteen days or more. Of the four exceptions in Group B, the two (J.R. and B.R.) with successful provocations four and eleven months respectively after the original lesion had had at the time of provocation a reactivation or extension of their infection. J.R. developed a pleural effusion, at the first signs of which, and before the diagnosis had been established, sulphathiazole was given. B.R.'s history has some points of particular interest and it is given in more detail.

B.R. In April, 1946, at age of 2½ years, this child developed erythema nodosum. Two months later a tuberculin test was positive and radiograph of his chest showed a right hilar flare. It is fair to assume, therefore, that the erythema nodosum was a manifestation of his primary tuberculous infection. Apart from an attack of measles, and occasional attacks of bronchitis for which he was treated at home with one of the sulphonamides, probably sulphathiazole, he remained well until the beginning of December, 1946, when his cough became worse and he lost his appetite and some weight. He was admitted to hospital on Dec. 12, 1946, and at that time the chest radiograph showed extension of the opacity to the right lower lobe. Because of febrile episodes he had two courses of sulphathiazole, from Dec. 22 to 27, 1946, and from Feb. 10 to 13, 1947; he responded well on each occasion and had no skin manifestation. On March 11, 1947, his temperature rose again, but this time it was accompanied by phlyctenular conjunctivitis. He was given sulphathiazole, and three days later typical erythema nodosum appeared on both legs. A radiograph taken at that time showed a small pleural effusion which was localized anteriorly.

In this child sulphathiazole taken at various intervals after his original eruption was ineffective in provoking a new eruption. As soon as there was a reactivation of his tuberculous infection as manifested by the pleural effusion, administration of sulphathiazole provoked a new eruption of erythema nodosum.

It can very well be argued that both children were in any case going to develop a second attack of erythema nodosum, since other signs of activity of their tuberculous infection were present; but, if this were so, this spontaneous second eruption would be more likely to appear simultaneously with the other signs of reactivation, and therefore before the commencement of the administration of the drug. It is unlikely that sulphathiazole played no role, since the provocative nature of sulphathiazole has been established beyond doubt in other cases.

In all three cases of Group C in which sulphathiazole was given within thirteen days from the onset of the last lesion, the original eruption was mild and of short duration (eleven, four, and seven days respectively). It can, therefore, be assumed that in these cases the period during which sulphathiazole could still elicit a reaction ended earlier

TABLE 5
RESULT OF BIOPSY AND OF SULPHATHIAZOLE
PROVOCATION ON CASES OF ERYTHEMA NODOSUM

Case	Interval between eruption and biopsy (days)	Histological changes	Result of provocation by sulphathiazole immediately after biopsy
B.H.	18	Changes of E.N.	Unsuccessful
S.W.	18	Slight changes compatible with but not specific of E.N.	Successful
S.S.	24	Slight changes compatible with but not specific of E.N.	Successful
J.W.	32	Slight changes compatible with but not specific of E.N.	Unsuccessful
M.H.	52	Negative	Unsuccessful
S.R.	90	Negative	Successful
J. Ry.	90	Negative	Unsuccessful

than in other cases with an original rash which was more marked and of longer duration.

Miescher (1943) was struck by the extent of the histological changes in nodules which were only a few hours old. He thought it likely that a flare-up was provoked by sulphathiazole in pre-existing but clinically undetected granulomatous processes. An attempt was made to clarify this point by excising under general anaesthesia a piece of skin from the exactly recorded site of a nodule at varying intervals for each case after the fading of the rash, and then giving sulphathiazole to see whether a new crop of lesions was provoked. This was done in seven cases, and the results are given in table 5. The number of observations is admittedly small, but it seems that the provocation of a new crop by sulphathiazole does not depend on the presence of persisting though clinically invisible lesions. The successful provocation in the absence of histological changes (S.R.) could perhaps be explained by assuming that the excised piece of skin did not happen to contain any of the latent lesions. But the opposite, that is, the failure to provoke a new crop although histological changes were present (B.H.), is against Miescher's hypothesis.

Conclusions

From these observations it seems that, to provoke erythema nodosum, sulphathiazole must act in the presence of infection and bacterial allergy. A first eruption following administration of sulphathiazole has always developed during the active stage of infections which are known to be present in cases of erythema nodosum even without sulphathiazole. Provocation of new lesions after an original eruption

was successful only when the great degree of hypersensitivity to bacterial allergens known to exist during the appearance of erythema nodosum had not subsided below a certain level, or when sensitivity had been enhanced again by reactivation of the infection. It seems, therefore, certain that in sulphathiazole erythema nodosum the drug acts as a provocative factor only, the indispensable etiological factors being the same as in erythema nodosum.

Three possibilities may thus exist in certain infections, notably tuberculous and streptococcal, in relation to the appearance of erythema nodosum. The first in which the eruption of erythema nodosum is in any case impossible, the second in which infection alone cannot cause an erythema nodosum but in which the stimulus of a course of sulphathiazole may provoke an eruption, and the third during which infection alone can cause an erythema nodosum eruption. To which of these groups each infected organism belongs depends on many factors, the definition and investigation of which would lead into the still unsolved question of the pathogenesis of erythema nodosum in general.

The circumstances and conditions under which sulphathiazole may cause the eruption of erythema nodosum have so far been described, but the mechanism of provocation is still a matter of speculation. The first possible explanation would be that sulphathiazole by its deleterious action on bacteria liberates more bacterial antigenic substances. Against this conception is that sulphathiazole has bacteriostatic and not bactericidal properties on *M. tuberculosis* and other bacteria (Ballou and Guernon, 1942) and that other compounds, for example sulphadiazine, exert a stronger chemotherapeutic activity on tubercle bacilli in vivo (Smith et al., 1942), and should therefore cause erythema nodosum to a similar or greater extent. It should be borne in mind that any theory attempting to explain this mechanism of erythema nodosum provocation by sulphathiazole should also explain the peculiar position of this compound in relation to the other sulphonamides. The only property in which sulphathiazole differs from all the other commonly used sulphonamide compounds is its capacity for being bound to serum proteins much more than the others (Davis, 1943). Chemical substances acquire antigenic properties after being bound to body protein (haptens), and it is suggested that this capacity of sulphathiazole may have some connexion with its provocative power. No further explanation can be offered at the moment for the mode of action, but it is likely that further research in this direction may be fruitful.

Summary

1. Observations are recorded on seventeen children developing erythema nodosum after receiving sulphathiazole.

2. On the basis of clinical, biological, and histological data the conclusion is reached that this manifestation is not a 'drug rash' due to allergic sensitivity to sulphonamides, but is fundamentally the same as erythema nodosum.

3. In order to elicit an eruption of erythema nodosum, sulphathiazole must be given to subjects who are in the active stage of one of the infections commonly associated with spontaneous erythema nodosum. It is therefore a provocative and not an etiological factor.

4. The mechanism of this provocation is unknown.

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