REFERENCES

- Beatson, G. T. (1896). *Lancet*, 2, 104, 162.
 Huggins, C., and Bergenstal, D. M. (1951). *J. Amer. med. Ass.*, 147, 101.
 — (1952). *Cancer Res.*, 12, 134.
 — and Dao, T. L.-Y. (1953). *J. Amer. med. Ass.*, 151, 1388.
 Lett, H. (1905). *Med.-chir. Trans.*, 88, 147.
 Pyrah, L. N., and Smiddy, F. G. (1954). *Lancet*, 1, 1041.
 Taylor, S. G., Li, M. C., Eckles, N., Slaughter, D. P., and McWonald, J. H. (1953). *Cancer, N.Y.*, 6, 997.
 West, C. D., Hollander, V. P., Whitmore, W. F., jun., Randall, H. T., and Pearson, O. H. (1952). *Ibid.*, 5, 1009.

PROBLEMS INVOLVED IN PREVENTION OF BACTERIAL COMPLICATIONS OF MEASLES

WITH SPECIAL REFERENCE TO PROPHYLACTIC SULPHADIAZINE*

BY

G. I. WATSON, M.D.
General Practitioner

There is general agreement that sulphonamides and penicillin have contributed greatly to the fall in the mortality of measles in recent years (*British Medical Journal*, 1952), but the need for further study of the prevention of morbidity arising as a result of measles is also recognized (*British Medical Journal*, 1953). Since this essay was submitted, the *Lancet* (1954), in discussing the prophylaxis of measles complications, makes the following statement: "In this country quite satisfactory prevention of bacterial complications can still be obtained by the simpler and cheaper method of sulphonamide prophylaxis. This is one of the few forms—if not the only form—of routine sulphonamide prophylaxis that can be generally recommended." Two questions, however, have not yet been satisfactorily answered. The first is whether sulphonamides are, in fact, effective in the prophylactic as opposed to the curative treatment of the bacterial complications of measles. The second is whether the preventive dose, if effective, is sufficiently lower than the curative to warrant the expense involved by putting every case of measles on a prophylactic, even when no evidence of bacterial infection is present at the onset of the virus illness.

Historical

Haerem (1943) attempted to evaluate the effect of sulphonamides as antiviral rather than antibacterial agents in patients, probably mainly adults, admitted to a military hospital with measles. The dosage was 1 g. four times daily for four days. He found no significant differences in the duration of fever or the stay in hospital between treated and control cases, and he could find no previous mention of the use of sulphonamides in measles.

Begg *et al.* (1947) attempted to assess the total bacterial and haemolytic streptococcal counts in measles cases nursed in an L.C.C. hospital, and made a subsidiary study of the value of sulphadiazine in such cases. They concluded that sulphadiazine in a dose of 0.25 to 1 g. daily according to age was "of very doubtful prophylactic value," but were dissatisfied with their controls. The ages of the children are not given.

Badr El-Din (1951) attempted to assess the possible value of chlortetracycline ("aureomycin") "as an anti-viral agent" in measles by attention to three things:

(a) the increase or decrease of "catarrhal signs"; (b) the development and fading of the rash; and (c) the presence or absence of complications. The ages of only some, possibly the youngest, of the children are given. They were treated in hospital. Two out of 10 controls developed bronchopneumonia. No case of acute otitis media was reported, and no complications occurred in cases treated prophylactically, either with chlortetracycline or with combined penicillin and sulphadiazine. He found that chlortetracycline, given in the phase before the rash, diminished the catarrhal signs and also the intensity of the rash, if given early enough. He interpreted these as actions of chlortetracycline on measles virus, but other possible interpretations are discussed below.

No report has been traced of the use of sulphonamides or antibiotics in measles treated at home, nor of any attempt to assess the prophylactic value of these drugs in relation to the age of the child, to its past medical history, or to the presence or absence of bacterial infection at the onset of its measles. The present paper is an attempt to do this, as well as to define more clearly the limits of the problem, and to suggest what still remains to be done in any future, more extensive investigations.

Present Investigation

From December, 1950, to May, 1951, I attended 142 cases of measles in a rural partnership practice in the south-east of England, and the notes made at the time of seeing these patients, many of whom were treated prophylactically, mainly with sulphadiazine, have provided the material for this paper. As my notes were not then made with this particular research in mind, desirable details have sometimes not been recorded. Details of late complications after the children were out of the house from their attack of measles have not been analysed, as I was not then the only doctor seeing them. Particular care, however, was being taken during the epidemic to determine what signs of bacterial infection were present in each child at the onset of measles, and what evidence arose later in the illness to show that bacterial invasion had occurred. The details in this respect are therefore as accurate as circumstances allowed, and were all observed and recorded by me.

In defining the virus illness for myself, I took as its onset the first day of fever or typical symptoms, such as coughing or sneezing; and the end as the day when the rash had faded from the abdomen. At this stage a child was allowed up in the house, and outside on the next suitable occasion; but it was not returned to school or other crowds until three weeks after the onset of the rash, so as to minimize the risk of bacterial infection for that time. The episode which appeared to throw open the air passages of the head and chest to bacterial infection was the rash, first in the form of Koplik's spots. As the rash faded, so the mouth and eyes visibly healed, and one pictured the whole epithelium of the head and chest gradually recovering its resistance. Each of these stages in the virus illness might be defined more exactly in terms of changes in the leucocyte count, as is suggested below.

Information about the drugs used is incomplete in respect of dosage. The system I used for prophylaxis as a rule was a dose of tablets daily that totalled one more than the child's age in years, up to a total of six, in divided doses—that is, a child of 2 would have three tablets (each 0.5 g.) daily, in halves, while a child of 5 or over would have six tablets daily, one at a time. The duration of prophylactic treatment was from the day the child was first seen until at least the day the rash began to fade from the legs, sometimes until the rash had completely faded from the abdomen. I usually gave out the tablets at the time of my visit, working on this basis.

*Based on the Sir Charles Hastings Clinical Prize Essay, 1954.

Results

The first case was seen on December 3, 1950, and the last on May 25, 1951. Table I shows that the peak of the epidemic came in February and that the proportion of children on prophylactic drugs rose to a peak then and fell away again.

TABLE I

	Dec.	Jan.	Feb.	Mar.	Apr.	May	Total
On antibacterial prophylaxis ..	7	15*	38	25*	3	2	90
Not on drugs ..	13*	11	5	6*	2	4	41
On treatment for complications ..	1	1	2	2	1	0	7
On gamma-globulin ..	1	1	0	2	0	0	4*
Record of drugs missing	0	0	1	3	0	0	4
Total cases ..	21	27	46	36	6	6	142

* The four cases on gamma-globulin are shown in two places.

In later tables two cases on gamma-globulin alone are excluded from those receiving antibacterial prophylaxis, being shown as among those "not on drugs." Aspirin in some form was used for most children at the height of the fever. Details of the drugs used in the 90 cases receiving antibacterial prophylaxis are as follows: sulphadiazine alone, 74 cases; sulphadimidine alone, 10; "sulphatriad" suspension alone, 2; injection of penicillin alone, 1; sulphadiazine + sulphapyridine, 1; sulphadiazine + gamma-globulin, 1; sulphadimidine + sulphatriad suspension + gamma-globulin, 1.

Ages of Children Affected.—The epidemic began among the older schoolchildren of one village towards the end of term. From these it spread to their families and to other villages. Table II shows how, by February, it was the youngest schoolchildren and the older pre-school children

TABLE II.—Monthly Distribution of Cases by Age Groups (The Number on Prophylactic Drugs is Shown in Parentheses)

Age	Dec.	Jan.	Feb.	Mar.	Apr.	May	Total
1- ..	1	1 (1)	0	5 (3)	2 (1)	0	9 (5)
2- ..	3 (2)	2 (2)	1 (1)	8 (4)	1 (1)	0	15 (10)
3- ..	1	4 (4)	6 (4)	7 (4)	2 (1)	1	21 (13)
4- ..	1	3 (3)	4 (4)	3 (2)	0	1 (1)	12 (10)
5- ..	1 (1)	4	9 (8)	1 (1)	0	2	17 (10)
6- ..	2	3 (2)	10 (8)	1 (1)	0	1 (1)	17 (12)
7- ..	3 (3)	5 (2)	3 (2)	2 (2)	0	0	15 (9)
8- ..	3 (1)	1 (1)	6 (6)	3 (3)	0	0	13 (11)
9- ..	0	1	0	4 (3)	1	0	6 (3)
10- ..	2	1	2 (1)	2 (2)	0	0	7 (3)
11- ..	2	1	3 (3)	0	0	0	6 (3)
12-20 ..	0	0	1	0	0	0	1 (0)
Over 20 ..	0	1	1 (1)	0	0	1	3 (1)
		(age 29)	(age 26)			(age 21)	
Total	21 (7)	27 (15)	46 (38)	36 (25)	6 (3)	6 (2)	142 (90)

who were being most heavily attacked. Not until March was the brunt of the attack borne by the youngest children at home. During April and May, which included the Easter holidays, the epidemic spent its force on the non-immune population.

Selection of Cases for Drug Prophylaxis

During December, and especially during January, as will be seen from Table II, drug prophylaxis was given particularly to the youngest children on the basis of the teaching in textbooks, as it was among them I expected the worst complications. Price (1947) states: "Measles is most fatal to infants and young children, 70% of the mortality occurring in children under 3 years of age." Gunn (1951) confirms this view, as follows: "Case fatality is highest under 1 year of age, but the greatest number of patients die in the second year because morbidity is much higher at this period." The two youngest children infected in this epidemic were each 14 months.

Children under 3.—The number of cases in infants was too small to allow more than a tentative opinion to be formed; but the impression gained from this outbreak was

that if bacterial infection was absent, prevented, or adequately treated in children under 3 years of age, who had been breast-fed and whose mothers had had measles, the illness due to the virus infection was less severe than in older children of, for example, 10-12 years, some of whom were amongst the most prostrated, even in the absence of complications. The mildness of measles in a group of children between 8 months and 3 years, to whom Badr El-Din (1951) gave chlortetracycline in the stage before their rash, he attributed to an action of the drug on the virus itself; it may, however, have been due solely to the antibacterial effects of this drug. The duration of benefit derived from maternal immunity should be studied again among a larger number of the very young.

Other "Poor-Risk" Groups.—In addition to any which might occur in very young children, complications were also expected to be particularly prevalent among two other groups—namely, those who started their measles with evidence of bacterial infection already upon them, and those who, though evidently free of such infection, had a bad past history of naso-bronchial catarrh.

Evidence of Bacterial Infection Present at the Onset of Measles

The nature and severity of any signs of bacterial infection present in every child examined, whether for measles or not, was being recorded in detail at that time even though no symptoms referable to these signs were mentioned. From those records the Tables which follow have been prepared. The term "acute chest" has been used in the sense of Fry's (1953) paper, but limited to conditions that are usually febrile. "Subacute chest" includes the afebrile cases and others with minimal abnormal signs.

In Table III the incidence and severity of such preliminary bacterial infection is shown, followed by details of the actual conditions allotted to each degree of severity.

TABLE III.—Monthly Incidence and Severity of Bacterial Infection Present at Onset of Measles

	Dec.	Jan.	Feb.	Mar.	Apr.	May	Total
Total No. of cases ..	21	27	46	36	6	6	142
No. showing signs at onset ..	3	4	15	20	0	2	44
% showing signs at onset ..	14%	15%	33%	55%	—	30%	31%
Severe ..	1	1	4	5	0	0	11
Moderate ..	1	2	6	9	0	2	20
Mild or doubtful ..	1	1	5	6	0	0	13

In the 11 severe cases the following conditions were present: both drums very red, 4 cases; one drum very red and "subacute chest," 3; one drum very red, 2; bronchopneumonia, 1; "acute chest" and symptomless otitis media, 1.

In the 20 moderate cases were found: both drums injected, 4 cases; one drum reddened, 3; one drum opaque, healing, or old otitis media, 4; one drum with red malleolus, 2; both drums injected, one or both eyes sticky, 2; one drum reddened and "subacute chest," 1; one drum injected and mucopus in throat, 1; both drums injected and chronic tonsillitis, 1; tonsils exuding pus, 1; "subacute chest," 1.

The 13 mild or doubtful cases included: one drum slightly or partly injected, 7 cases; earache but drums not reddened, 2; both drums slightly injected but with good light reflex, 1; one meatus and drum reddened by heavy rash, 1; grossly enlarged tonsils but no exudate, 1; doubtful "moist sounds" in chest, 1.

In case the differences in severity of bacterial infection might merely be because the patients were seen early or late in the virus illness, the records have been analysed to show the stage reached by each case and the severity when the signs were first seen. This has been done in relation to "R" day—the day the rash appeared; "R minus" includes those seen before, and "R plus" those first seen after the rash appeared.

Table IV demonstrates that the severe infections were not necessarily seen late in the virus illness and confirms that these children were entering their measles already harbouring in varying degree the often symptomless seeds of possible bacterial complications.

TABLE IV.—*Severity of Bacterial Infection in Relation to Date of Rash*

	Time First Seen			Total
	R—	R	R+	
Severe	4	5	2	11
Moderate	7	7	6	20
Mild	3	7	3	13

Table III also reveals that the peak of preliminary bacterial infections was reached slightly later than the peak of the measles epidemic; but the relative incidence of severe, moderate, and mild bacterial infections did not materially alter with the change of season. The need, therefore, for an effective antibacterial prophylactic was greatest at the height of the bacterial rather than of the virus epidemic. This fact was not appreciated at the time, and Table V gives the monthly distribution of cases receiving antibacterial drugs in relation to the stage of their virus illness.

TABLE V.—*Cases Receiving Antibacterial Prophylaxis in Relation to "R" days, by Months*

	Dec.	Jan.	Feb.	Mar.	Apr.	May	Total
Total No. of cases ..	21	27	46	36	6	6	142
Prophylaxis:							
Starting on "R minus"	1	2	14	5	0	0	22
Starting on "R"	2	10	18	15	1	0	46
Starting on "R plus"	4	3	6	5	2	2	22
Total	7	15	38	25	3	2	90
% of monthly total ..	33	59	83	78	50	30	

It shows that the proportion of cases treated prophylactically more than doubled between December and February and that prophylactic doses of antibacterial drugs were being given earlier and to a slightly higher proportion of children at the peak of the measles epidemic in February than at the peak of the bacterial epidemic in March. The use of these drugs was evidently aimed more at preventing the complications of measles than at treating any bacterial infections which were found incidentally, though undoubtedly the latter factor was an influence.

"Catarrhal" Children

There were a number of children affected by measles in this epidemic who had suffered from recurrent previous attacks of respiratory infection often enough to merit being called "catarrhal" children. The number of such children seen is set out in Table VI, showing whether they presented with signs of bacterial infection as well as measles.

TABLE VI.—*Monthly Incidence of Bacterial Infection at Onset of Measles Among Normal and Catarrhal Children*

	Dec.	Jan.	Feb.	Mar.	Apr.	May	Total
Total cases	21	27	46	36	6	6	142
Normal children ..	17	22	32	22	6	5	104
With bacterial infection at onset } No.	2	2	8	7	1	0	20
% ..	12	9	25	32	20	—	19
Catarrhal children } No.	4	5	14	14	0	1	38
% ..	19	19	30	39	—	20	27
With bacterial infection at onset } No.	1	2	7	13	—	1	24
% ..	—*	—	50	93	—	—	63

Severity of These Infections

	Severe	Moderate	Mild	Total
Normal	4	6	10	20
Catarrhal	7	14	3	24

* No percentages were calculated for a total of fewer than six.

Table VI shows that in this epidemic the incidence of signs of bacterial infection at the onset of measles was three times as great in catarrhal children as in children with normal histories; and a higher proportion of those infections in the catarrhal children were severe or moderate, as opposed to mild.

As the catarrhal state should be considered in relation to age, Table VII gives the age distribution of these infected children.

The numbers involved in Table VII are too small for conclusions to be drawn, but there is a suggestion of two separate peaks in the incidence of the catarrhal state; one

TABLE VII.—*Ages of Catarrhal Children and Number Showing Signs of Bacterial Infection at Onset*

	1-	2-	3-	4-	5-	6-	7-	8-	9-	10-	11-	12-20	Over 20	Total
All children ..	9	15	21	12	17	17	15	13	6	7	6	1	3	142
Catarrhal:														
No.	1	2	4	5	3	4	6	6	3	2	2	—	—	38
%	10	13	19	42	18	24	40	46	50	30	30	—	—	27
No. infected ..	1	2	4	3	1	2	3	4	2	2	0	0	0	24
% infected*														63

* No percentages were calculated for a total of fewer than six.

comes in the 4-5 age group, at the end of home contact before school begins, and the other in the 7-9 age group after several years of school contact. If this were shown to be generally true, it might be that the catarrhal state is brought about, at least in part, by undue contact with carriers of bacterial infection, at first in the home and later at school. Mawson *et al.* (1953) noted a variation by age groups with a peak at 6 years, in the incidence of acute otitis media, among children treated at hospital, and suggested that, after going to school, "exposure of the child to an alteration in its usual bacterial environment plays a part in the causation of this disease." This is a subject that would repay further research.

Complications Resulting from this Epidemic

Table VIII sets out the number of children who were free of infection at onset, and the percentage of these who at a later visit showed signs of bacterial infection, complicating their measles.

TABLE VIII.—*Monthly Total of Children Free of Bacterial Infection at Onset of Measles, and Percentage of these Developing Complications Later*

	Dec.	Jan.	Feb.	Mar.	Apr.	May	Total
Total clear at onset	18	23	31	16	6	4	98
No. of these developing complications	5	6	8	4	2	0	25
% with complications ..	28	26	26	25	30	0	26

One should, however, differentiate between children with normal and catarrhal past histories in estimating the risk of complications arising in any particular child who is free of signs of bacterial infection when starting measles. This is done in Table IX.

Part A shows the high percentage of children with normal past histories who were clear of signs of bacterial infection at the onset of measles; more than three-quarters of these remained clear. On the other hand, it was found that the proportion of catarrhal children who started their measles clear diminished steeply from February onwards, and of all those who started clear one-half later developed signs of bacterial infection during their virus illness.

Badr El-Din (1951) reported that chlortetracycline, given in the phase before the rash, diminished the catarrhal signs of measles. He attributed this to an effect of the drug on the measles virus, but it is more probable that the effect was an antibacterial one. This raises the question of what abnormal signs in the chest in measles can be attributed wholly to the action of the virus and which are the results

TABLE IX.—*Number of Complications Arising During this Epidemic of Measles*A. *Among those who were clear of signs of bacterial infection when first visited for measles, but who showed signs later*

	Total Cases	Clear at Onset			
		No.	%	Showing Signs Later	
				No.	%
Normal histories	104	84	79	18	21
Catarrhal "	38	14	37	7	50

B. *Among those with signs of bacterial infection when first visited for measles, showing the number in whom these signs were changed*

	Total Showing Signs at Onset	Signs After Measles			
		Aggravated	I.S.Q.	Reduced	Not Noted
Normal histories	20	3	5	11	1
Catarrhal "	24	6	2	11	5

of any concomitant bacterial infection. Should any moist sounds, for example, be expected in the chest of a child with measles who is quite free from bacterial infection?

Part B of Table IX reveals at first sight a puzzling result—namely, that among 20 normal and 24 catarrhal children who started measles with signs of bacterial infection already present about half in each group showed a diminution or clearance of these signs during their virus illness. In discussing Table V, however, it was suggested that the presence of bacterial infection at onset had undoubtedly influenced the selection of cases for prophylactic treatment. This possibility is analysed in Table X, which shows separately, for both a pre-existing bacterial infection and a catarrhal history, how these factors influenced the selection of cases for prophylaxis.

It was shown in Table VI that signs of bacterial infection at onset were three times as common in catarrhal as in normal children during this epidemic. In Table X there is greatest

TABLE X.—*Distribution of Prophylactics Among those With and Without Preliminary Bacterial Infection or a Catarrhal Past History*

	Bacterial Infection at Onset		Past History	
	(1) Absent	(4) Present	(2) Normal	(3) Catarrhal
Total	98	44	104	38
No. on prophylactics	56 (57%)	34 (79%)	64 (62%)	26 (68%)

similarity between group 1 and group 2 with regard to the proportion on prophylactic drugs, while group 3 lies somewhere between those two and group 4, which had the largest proportion of children on prophylactics. In other words, the influence of selection for antibacterial prophylaxis was acting more strongly when I saw a case of measles in a catarrhal child with bacterial infection at the first visit, and was least active when I was dealing with normal children showing no early abnormalities.

The anomaly in Part B of Table IX now becomes understandable. Among those with signs at onset, whether with normal or catarrhal histories, such signs abated or disappeared in about half from each group because they were being given drugs in doses which were curative rather than prophylactic. The figures are too small for conclusions, but there is a further slight suggestion in part B of Table IX that, among catarrhal children, more often than among normal children, if the signs already present did not diminish, they were more likely to be aggravated than to remain *in statu quo* as a result of an attack of measles. In them the curative treatment had been insufficient.

What was the fate of those other children who were given drugs prophylactically, but who had shown no signs

of bacterial infection when first examined for their measles? This touches the crucial problem of prophylactic versus curative treatment. The results obtained in this epidemic are set out in Table XI. This Table shows an unexpected result: proportionately more fresh late bacterial infections were seen among those on prophylactic drugs than among those not taking any. In point of fact, 19 out of these 25 fresh late infections occurred during December to February, before the peak of the "bacterial infection at onset," shown in Table III.

TABLE XI.—*Number of Complications in those who had no Signs of Bacterial Infection at the Onset of Measles; With Reference to Prophylactic Drugs*

Part I

	On Drugs	Not on Drugs	Record Incomplete	Total
Total clear at onset	56	41	1	98
No. with complications	17 (30%)	8 (20%)		25 (26%)

Part II.—*Summary of Complications*

	On Drugs	Not on Drugs
Acute otitis media	2	—
Symptomatic otitis media	5	4
"Acute chest"	3	—
"Subacute chest"	3	—
"Acute" or "subacute chest" plus otitis media	1	1
Eyes abnormally affected	2	3
Nasal sores	1	—
Total	17	8

One possibility certainly is that by giving sulphadiazine or similar drugs to otherwise healthy children at the start of measles one was lowering their resistance to bacterial infection, should this reach them during the period of their rash. I have heard an eminent consultant paediatrician express the opinion that, since measles produces a leucopenia and since sulphonamides tend to depress the white-cell count, therefore sulphonamides should never be given to children during measles. While this may well be wise advice, it is possibly not the whole explanation of the anomalies revealed in Table XI, for one would then expect more evidence of infection in these treated children at the peak of the bacterial epidemic. Furthermore, it was shown in Table IX that in some children sulphonamides had exerted a beneficial action during measles.

Another possibility is that during the early months of the epidemic one was examining the children more closely. If this were true it could perhaps explain the larger proportion of cases noted during the first three months, but the overall difference in complications rate would still remain to be explained.

This difference between the complications rate of prophylactically treated and untreated children becomes even more striking if the children are divided into those with normal or catarrhal histories, in order also to test whether there had been any unconscious selection of bad-risk cases among those on prophylactics. This difference is shown in Table XII.

TABLE XII.—*Complications Rate in Prophylactically Treated and Untreated Children with Normal or Catarrhal Histories*

	Total	Clear at Onset							
		No.	No. Un-treated	On Drugs		Complications			
				No.	%	Untreated		On Drugs	
Normal histories	104	84	36	48	57	4	11	14	29
Catarrhal histories	38	14	5*	8	57	4	90	3	40

* One record of drugs incomplete.

Of those clear at onset, 57% were given prophylactic drugs, whether they were catarrhal or not; there was evidently no increased tendency for catarrhal children to be given these drugs, so long as they were free of signs of bacterial infection at the time measles began (see discussion of Table X). Table XII also reveals that, whereas sulphonamides given to those who showed no signs of bacterial infection when they first attended for measles may have prevented complications among catarrhal children, these same drugs appeared to increase considerably the risk of complications occurring in normal children.

The distribution of complications among the age groups was studied to see whether there was any difference in this respect between treated and untreated children.

Table XIII shows that in the untreated group the three severe or moderate complications all occurred in younger children than did the five mild complications; while in the

TABLE XIII.—*Number and Severity of Complications by Ages Among Prophylactically Treated and Untreated Children*

	1-	2-	3-	4-	5-	6-	7-	8-	9-	10-	11-	12-20	Over 20	Total
Untreated:														
Complication:														
Sev. + mod.	—	—	1	—	1	1	—	—	—	—	—	—	—	3
Mild	—	—	—	—	—	—	3	1	1	—	—	—	—	5
Nil	5	2	6	—	5	4	2	1	1	1	3	1	2	33
On drugs:														
Complication:														
Sev. + mod.	3	—	—	2	—	1	2	1	1	—	1	—	—	11
Mild	—	—	3	—	1	1	1	—	—	—	—	—	—	6
Nil	—	6	3	5	6	7	2	6	—	1	1	—	1	38
Record incomplete	—	1	—	—	—	—	—	—	—	—	—	—	—	1

treated group there were relatively more severe or moderate complications, and the 11 which occurred were at both younger and older ages than the six mild ones.

Discussion

In this epidemic the action of sulphadiazine appears to have been twofold. When given in near-curative doses to children, especially catarrhal children, who showed signs of active bacterial infection at the start of their measles, the drug acted beneficially by reducing the severity of the bacterial infection in about half the treated cases, while the remainder had probably received an insufficient dosage; but when sulphadiazine or another sulphonamide was given to normal children, apparently free of bacterial infection at the start of their measles, the drug appeared to confer no benefit, but rather to increase the rate and severity of complications as compared with similar untreated children.

If these findings were to be confirmed by other observers and in a larger series of cases, the whole question of the use of sulphonamides in any disease associated with leucopenia—for example, also influenza—would have to be re-examined. It might be possible to do serial white-cell counts throughout a sufficient number of cases of measles and influenza to determine the incidence and degree of leucopenia in relation to bacterial complications, both in prophylactically treated and in untreated cases. Penicillin and sulphonamides could be compared as antibacterial prophylactics in diseases associated either with leucopenia or with leucocytosis. It may be that when bacterial infection is already present at the onset of such a virus illness there is already a sufficient leucocytosis to offset any later drop in the white-cell count, due either to the superimposed virus infection or to drugs. In such cases sulphonamides may not be so harmful, though they are not necessarily to be preferred to penicillin.

Puckey (1941) reported a hospital case in which granulopenia had developed after a leucocytosis due to pneumonia, treated with sulphapyridine; measles and infective hepatitis developed during the treatment. At the end of the pneumonia, after ten days on sulphapyridine and three days after the measles rash appeared, the white-cell count was 25,000 per c.mm. In spite of stopping sulphapyridine the white-cell count dropped steadily to 4,600 per c.mm.

(24% neutrophils) on the fourteenth day after the rash. How much of this leucopenia was due to sulphapyridine and how much to measles and infective hepatitis it is not possible to judge, but the question is one which undoubtedly needs to be examined again.

Conclusions

A fresh investigation of the problem of antibacterial prophylaxis in measles should be carried out soon by those with access to a large number of cases treated at home, bearing in mind the following conclusions which can be drawn from the present report of an outbreak in a country practice of 142 cases of measles, 90 of which were given prophylactics.

(1) The complications rate in untreated normal children during this outbreak was 4 out of 36 (11%), whereas in untreated catarrhal children it was 4 out of 5 (80%).

(2) Among all children, irrespective of age or past medical history, who were free of signs of bacterial infection at the onset of their measles, the complications rate was higher in those given sulphonamides prophylactically (17 out of 56=30%) than in the untreated (8 out of 41=20%).

(3) Some children already showed signs of bacterial infection when their measles began. This occurred in 24 out of 38 (63%) of catarrhal children, but in only 20 out of 104 (19%) of normal children.

(4) Twice as many such infections, already present, were graded as moderate or severe as opposed to mild in the catarrhal children, as compared with those in normal children.

(5) There was a seasonal variation in the amount of preliminary bacterial infection, especially among catarrhal children. In this outbreak the peak of such bacterial infection fell in March, though the peak of the measles epidemic passed during February.

(6) There was no evidence that the severity of the virus illness of measles was unduly marked in children under 3 so long as bacterial infection was absent; in fact, the impression was gained that such children suffered less from their measles than did some of their older siblings.

(7) There was evidence that the sulphonamides given had been acting curatively rather than prophylactically in those children who started measles showing signs of preliminary bacterial infection; but that in about half of these the dose had been insufficient.

(8) There was some evidence to suggest that the catarrhal state of a child was not something permanent, but that it might vary according to undefined circumstances both before and after the age of starting school.

(9) Since it appears from an analysis of the present observations that sulphonamides are of value to some children, but not to others, in preventing bacterial complications of measles, a further investigation is needed into the incidence, severity, and duration of any changes in the white-cell count of normal and of complicated measles, in both treated and untreated children, some receiving sulphonamides and some penicillin. Such an investigation might reveal ways of defining stages of the virus illness of measles in terms of leucopenia and the consequent risk of bacterial complications.

(10) Such an investigation, if also carried out in other diseases associated with leucopenia and apt to be followed by bacterial complications, such as influenza,

might further reveal a general principle of value in determining the choice of antibacterial drugs for prophylactic or curative use, especially in virus infections.

I wish to thank the librarian of the Royal Society of Medicine for his help in connexion with the references to previous work on this subject. Three colleagues, Dr. D. G. French, Dr. J. H. Hunt, and Dr. R. J. F. H. Pinsent, have offered valuable criticism of earlier drafts of this paper, and to them I would like to repeat my thanks.

REFERENCES

- Badr El-Din, M. K. (1951). *J. roy. Egypt. med. Ass.*, **34**, 340.
 Begg, N. D., Snellie, E. W., and Wright, J. (1947). *British Medical Journal*, **1**, 209.
British Medical Journal, 1952, **2**, 1196.
 Ibid., 1953, **1**, 605.
 Fry, J. (1953). *British Medical Journal*, **1**, 68.
 Gunn, W. (1951). *British Encyclopaedia of Medical Practice*, 2nd ed., **8**, 418. London.
 Haerem, A. T. (1943). *Milit. Surg.*, **92**, 306.
Lancet, 1954, **1**, 1283.
 Mawson, S., Gray, J. D., and Hewlett, A. B. (1953). *British Medical Journal*, **1**, 817.
 Price, F. W. (1947). *A Textbook of the Practice of Medicine*, 7th ed., p. 151. London.
 Puckey, M. C. (1941). *Med. J. Aust.*, **1**, 52.

Note.—Since this essay was presented, the College of General Practitioners has begun a two-year investigation into the value of sulphonamides and antibiotics in the prophylaxis of the bacterial complications of measles. The conclusions reached in this essay were made available to the College, which hopes to obtain records of 2,000 to 3,000 cases of measles by the end of 1955.

THE EARLY DIAGNOSIS OF SPINAL TUMOURS

BY

H. J. G. BLOOM, M.D., M.R.C.P.

Registrar, Meyerstein Institute of Radiotherapy, Middlesex Hospital; late Captain, R.A.M.C.

H. ELLIS, B.M., F.R.C.S.

R.S.O., Royal Infirmary, Sheffield; late Captain, R.A.M.C.

AND

W. B. JENNETT, M.B., F.R.C.S.

Surgical Registrar, United Liverpool Hospitals; late Captain, R.A.M.C.

(From the Military Hospital for Head Injuries, Wheatley, Oxford)

The first patient to be successfully treated for spinal tumour was a British Army officer who was operated on by Sir Victor Horsley in 1887 (Gowers and Horsley, 1888). He recovered from paraplegia and lived for twenty years before he died from an unrelated condition. Since this demonstration that at least some spinal tumours were surgically accessible, and indeed curable, it has been of the utmost importance to diagnose such neoplasms early in their course and to locate them accurately.

It is not the purpose of this paper to describe in detail the established clinical syndromes, excellent accounts of which already exist (Elsberg, 1941). Rather is it intended to make use of the opportunity afforded the Service medical officer of having patients under observation from an early stage, and to comment on the clinical picture and diagnosis at this stage. Failure to make an early diagnosis may lead to incomplete recovery or even permanent disablement, despite the removal of a benign tumour, due to prolonged cord compression.

This paper is concerned with primary and secondary tumours which involve the spinal cord or nerve roots; such lesions develop in the vertebrae or in the structures within the spinal canal. The material for the investigation consists of 36 verified cases of spinal tumour treated between January, 1940, and December, 1951, at the Military Hospital for Head Injuries, Oxford. During this period there were approximately 1,150 admissions with spinal symptoms, 813 bearing the label of prolapsed intervertebral disk. These cases were drawn from the three Services and therefore represent a special cross-section of the population in regard to age and sex. There were 32 males and 4 females, the ages ranging from 17 to 60 years, 30 of them being under 35 years (see Table III).

Pathology

The lesions met with in this series are given in Table I. The frequency of the histological groups may be compared with those in a civilian series of 275 cases reported

TABLE I.—Pathology

Present Series		Civilian Series (Elsberg, 1941)	
Tumour	No. of Cases	Tumour	No. of Cases
Neurofibroma ..	15 (41.6%)	Meningioma ..	73 (26.5%)
Metastatic ..	8 (22.2%)	Neurofibroma ..	64 (23.2%)
Vascular ..	4 (11%)	Sarcoma ..	31 (11.2%)
Ependymoma ..	3 (8.3%)	Glioma ..	14 (5%)
Glioma* ..	3 (8.3%)	Metastatic ..	11 (4%)
Osteoclastoma ..	2	Ependymoma ..	14 (5%)
Melanoma ..	1	Vascular ..	9 (3.3%)
		Others ..	59 (21.5%)

* Two histologically unverified.

by Elsberg (1941). Table I reveals two important differences between the two series in the relative incidence of these tumours. There are no meningiomas and there is a high proportion of metastases in the military series. These points require further comment.

Meningiomas are found most often in middle-age, and when they occur in the spine women are affected twice as often as men (Learmonth, 1927); this group of patients not being represented in the section of the population from which our cases are drawn thus accounts for their absence in this series.

Metastatic tumours occurred in no less than 22% (8 out of 36) of the patients in this series, mainly young adults; the oldest patient with a secondary tumour was 42, four patients were in the thirties, one was 19, and two were 17 years of age. However, the incidence of metastatic spinal tumours is doubtless underestimated in civilian series based on statistics from surgical explorations: many overtly metastatic tumours, frequently presenting in the terminal stages of malignant disease, never reach the neurosurgeon. Nevertheless, it is important to appreciate that a metastatic neoplasm cannot be ruled out on age alone, nor on the apparent absence of a primary growth.

In six patients (Cases 29–34) the histological sections of the spinal tumour revealed secondary anaplastic carcinoma, suggestive of bronchial origin. Although the presence of a primary bronchial carcinoma was later confirmed by a post-mortem examination in only one instance (Case 34), the available facts favoured a bronchial origin for the primary growth in all six cases. Pulmonary or hilar shadows were present in four of the five patients in whom x-ray films were available.

Another patient with a secondary neoplasm (Case 35) died elsewhere, and a post-mortem examination revealed anaplastic secondary carcinomatous deposits in the spine, liver, lung, and iliac glands; a primary tumour was not found. The final patient in this group (Case 36) had vertebral collapse associated with a tumour in the lower end of the humerus, the radiological diagnosis being "osteogenic sarcoma"; no further information about the pathology is available.