Volume 3.: The toxic effect of the sulphonamide drugs

CLINICAL STUDIES IN SULPHONAMIDE CHEMOTHERAPY.

VOLUME 3.

THE TOXIC EFFECTS OF THE SULPHONAMIDE DRUGS.

S U M M A R Y.

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The toxic effects are discussed under five main headings.

(a) Cyanosis. A general incidence of ten per cent. is noted. The rate varies with the different drugs and seems highest with sulphanilamide, possibly because of the number of cases which received a high preliminary dosage, and, in general, of the longer duration of treatment.

(b) Disturbances of the Central Nervous System. A general incidence of just under two per cent. is noted. This includes a few cases of violent delirium for which the drugs seem to have been responsible.

(c) Disturbances of the Gastrointestinal Tract. These are noted in less than eight per cent. of all the cases. With sulphapyridine this form of toxic effect is not only more common but more severe.

(d) Disturbances of the Urinary System. Haematuria or ureteric colic is noted in less than one per cent. of cases which receive sulphapyridine. No case receiving the other drugs has developed such a toxic reaction.

(e) The Occurrence of Toxic Rashes and of Fever. These occur in just less than four per cent. of all the cases. Charts are appended which show that individuals who develop rash and fever may show an allergic type of reaction to a single dose of the drug administered after a short lapse of time.

It is shown that toxic reactions (excluding cyanosis) are less frequent in children under ten years of age. They are seen with greater frequency in females than in males. In the patients with erysipelas who show a toxic reaction, the lesion may cease to spread rather more slowly; the primary pyrexia, however, is definitely prolonged.

None of the toxic effects noted is serious or causes harm to the patients. The most interesting and important of the toxic reactions is the occurrence of a rash or of fever. A parallel is drawn between "serum disease" and these drug rashes and drug fever. It is suggested, on the basis of the clinical findings and after discussion of experimental work, that the sensitization may be due to the formation in the blood of a drug-protein conjugate.

CHAPTER I.

Introduction.

Introduction.

I do not intend to attempt a review of the literature that has been written on this subject. My reason for not so doing is because such reviews convey a quite false impression of the dangers of the drugs. Few writers who report an unusual or serious side effect, include any details which would permit one to estimate how frequently such an event might occur. (It is as if someone reported that fifty fatal accidents had been noted at a certain crossing. The occurrence of such a large number (perhaps in one year) might cause one to use that crossing with caution, but it is exceedingly important to know whether five hundred or five thousand persons used the crossing in that period). As the present report will reveal, the toxic effects of this useful group of drugs have been greatly over-emphasised. Further, it might be suggested that the consultant physician or surgeon called in, as he often is, to the unusual case, may see so many "accidents" that he too tends to exaggerate their importance, forgetting that many other patients have received the drugs without untoward reaction.

In addition to those cases which have been described in the present report, I have been responsible for the management of many different types of infection for which sulphonamides have been prescribed. Since the records of the present cases were closed I have treated a further 500 cases of erysipelas and as many cases of pneumonia. In addition, the drugs have been used in some four to five hundred cases of meningococcal meningitis; while the effect of the drugs has been /

been tested in cases of scarlet fever, measles, whooping cough, pneumonia in infants, typhoid, paratyphoid, the dysenteries, and smaller numbers of cases of septicaemia, septic sore throat and puerperal infection. Although it is difficult to estimate the correct total number, at least 6,000 cases of different infections, in all age groups, have received sulphonamides under my direct supervision. Such a large series of cases permits one to be somewhat dogmatic regarding the occurrence of the different side-effects.

In the following analysis I shall describe the toxic effects which were noted in the series of erysipelas and pneumonia cases described in the preceding chapters. Since these records were closed, I have seen only two forms of toxic reaction which were not encountered among the present series, namely, one case of acute granulocytopenia and one case of acute haemolytic anaemia.

Three features which are common to all my cases may first be mentioned. These are —

1. All received their sulphonamides while at rest in bed.
2. Practically all started therapy with a polymorphonuclear leucocytosis.
3. As part of the general nursing treatment of fever patients, fluids were administered lavishly. As a rule, the quantity of bland fluid consumed daily by a person over 15 years of age was from four to six pints.

These three common factors are, I am sure, important, and they may go far to explain the relative absence of serious toxic reactions in my experience. In regard to the first, the incidence of toxic reactions in cases of gonorrhoea (which are nearly always treated ambulantly) seems to be much higher than in pneumonia or erysipelas (McGregor Robertson; /

(McGregor Robertson; personal communication). Second, French (1939) has reported a depressant effect of the sulphonamides upon the neutrophil cells of the blood. However, using the drugs in full dosage over a prolonged period in cases of scarlet fever, where a primary polymorphonuclear leucocytosis was always present, at no time was the fall in neutrophil cells such as to cause anxiety. Logically, it would seem natural that the case which begins therapy when his blood contains a high proportion of these cells, is in better shape to withstand the depressant effect of the drugs upon his bone marrow.* Thirdly, it has already been explained that the largest proportion of the drugs is excreted through the kidneys. The varying solubility of the different sulphonamides, and the fact that a proportion is excreted in the acetylated form (as a rule, even less soluble than the parent drug) both emphasise the importance of a high urinary output.

* It is not, of course, implied that the presence of a leucopenia at the onset of treatment is necessarily dangerous. I have observed cases of pneumonia in which the white cell count was as low as 3,000 per c.mm. initially, and where the number of cells gradually increased during the period of administration of sulphonamide drugs.

CHAPTER II.

The Incidence of Toxic Effects.

The toxic effects noted in the present series of cases may be summarised under the following headings:-

(a) Cyanosis.

(b) Disturbance of the Central Nervous System.

(c) Disturbance of the Gastrointestinal Tract.

(d) Disturbance of the Urinary System.

(e) The occurrence of rashes or of unexplained pyrexia.

(a) Cyanosis.

The unusual colour which developed in patients receiving sulphonamides was the first noticeable feature caused by the drugs. In cases of erysipelas, even before frank cyanosis was noted, it was found that the lesion "stood out" more obviously in those cases which received the drugs; the line of demarcation between inflamed and healthy skin was much more intense. I am inclined to think that this was an early grade of cyanosis which was more obvious in the engorged plaque of inflammation. The presence of generalised cyanosis was usually easily noticed, since it gave the patient an unnaturally "ill" appearance. This was often worrying in the early days, not only to the patient's relatives but to the nursing staff and myself. In these earlier patients treatment was frequently stopped when cyanosis of any intensity developed; but, as experience with the drugs increased, even severe degrees of cyanosis were discounted and therapy continued. The /

The figures which follow therefore must be regarded as referring to those patients whose degree of cyanosis gave rise to comment. The presence of a slight cyanotic tinge was often not noted, especially in the later stages of the experiment, since its occurrence seemed in no way to upset the patient.

The incidence of cyanosis with the different drugs used was as follows:-

Drug.	No. of Cases treated.	No. of Cases showing cyanosis.
Sulphonamido-chrysoidin	381	17 (4.5)
Sulphanilamide	317	105 (34.3)
Benzyl-sulphonamide	70	5 (7.1)
Carboxy-sulphonamido-chrysoidin	89	1 (1.1)
Sulphapyridine	481	5 (1.04)
Total:-	1338	133 (10.0)

(The figures in brackets are percentages of the total cases in the group).

It is clear that the incidence of cyanosis varies considerably with the different drugs, being highest with the radicle sulphanilamide (34 per cent.) and lowest with sulphapyridine (1.0 per cent.). It is difficult to explain this variation. Cyanosis may be due to the development of methaemoglobin or sulphaemoglobin. In some cases, however, which show clinical cyanosis, these two pigments cannot be defined; this undefined pigment may be formed by the drugs themselves (Marshall and Walzl, 1937).

Although /

Although, in the earlier stages, a number of spectroscopic examinations of the blood was made upon suspicious cases, in only two was the presence of sulphaemoglobinaemia proved. Two other cases (not examined spectroscopically) were suspected later in the experiment on account of the severity and prolonged duration of the cyanosis. All four received sulphanilamide.

During one stage of the experiment precise enquiry was made as to whether the patient had or had not taken a sulphate purgative within forty-eight hours of admission. Seventy (29 per cent.) of 242 patients gave such a history. The incidence of cyanosis in this group was 32.8 per cent., whereas in those who had not taken a saline purgative the incidence was 29 per cent. In no case did the intensity of the cyanosis suggest a sulphaemoglobinaemia.

There seems little doubt that in some cases (Paton and Eaton, 1937; Archer & Discombe, 1937) there is a causal relation between premedication with saline purgatives and the occurrence of sulphaemoglobinaemia; and it has been suggested that the fluidity of the contents of the large bowel is the factor of etiological importance. Cyanosis of a degree to suggest sulphaemoglobin has only been noted by me on, at the most, four occasions. The rarity of its occurrence might suggest that the peculiarity which causes its formation lies in the patient. Although, to begin with, great care was taken to exclude such articles as eggs and onions from the diet (since they contain small amounts of sulphur), in later periods no such precautions were enforced; and the incidence of severe grades of cyanosis did not appear to be affected.

The /

The following case history, however, does suggest that in some persons at least, sulphur-containing preparations may be dangerous.

"A ward maid, 19 years of age, was seen late on her first day of illness with an inflammatory area over the pre-patellar bursa. There was a small laceration overlying the bursa. The condition was diagnosed as a septic pre-patellar bursitis and she was admitted to the erysipelas ward. She had been given a dose of magnesium sulphate by mouth, and when admitted to the ward, as the case was not regarded as an erysipelas, dressings of glycerine and magnesium sulphate were applied. On the following morning, unaware of the type of dressing which was being applied, I re-examined the knee and found that the condition was in fact an erysipelas. Spread had taken place since the earlier examination and the raised border was now very definite. She was accordingly entered into the erysipelas series and was given sulphanilamide. During the next eighteen hours she received a total of 9.0 grams of the drug, when her condition suddenly became alarming. An intense violet cyanosis appeared, overlying what appeared to be an ashen pallor. The pulse rate rose rapidly to 120 and was of poor quality. The respirations were sighing and shallow. Examination of the blood by the spectro-microscope revealed the presence of sulphaemoglobin. For the next 24 hours her appearance was somewhat alarming but thereafter she slowly recovered, although the cyanosis was still evident for about four weeks. There seemed little doubt that in this case the sulphaemoglobinaemia was related to the use of a saline purgative and possibly also to the local dressings which contained magnesium sulphate."

(b) Disturbances of the Central Nervous System.

Another early observation made in the erysipelas cases suggested that the sulphonamides had a depressant effect upon the nervous system. Quite frequently when the morning visit was being paid it would be found that the patients receiving sulphonamide drugs were still asleep, or dosing. Some, on awaking, seemed slightly confused or disorientated. Enquiry among the more intelligent patients often elicited the information that the drugs made them feel "dizzy" and unable to concentrate. In a few cases, the patient exhibited a sudden delirium, not accounted for by the severity of his illness.

"A female, 58 years of age, had received sulphonamido-chrysoidin during the acute stage and early convalescence of a recurrent attack of facial erysipelas. Upon the twelfth day of illness (nine days after admission) she was noted to have a severe shivering. After this she became very noisy, tore her spectacles from her face, broke them and threw them at her neighbour. She was very abusive to the nursing staff for a short time (surprising, because she had previously appeared a very mild-tempered woman). Just as suddenly she subsided, fell asleep, and on waking, had no recollection of the occurrence."

A similar type of reaction was noted in a male who suddenly jumped out of bed, seized a siphon which was on his locker, flung it through a nearby window and then attempted to follow it.

In neither of these cases did the delirium seem to be explained by the erysipelas, the healing of which was in fact well advanced; nor by a history of alcoholism. The sulphonamide drugs seemed to be the only reasonable explanation.

Including /

Including all varieties of disturbance from severe drowsiness or dizziness to mental confusion or delirium, the incidence with the different drugs was as follows:-

Drug.	Total No. of Cases.	Total showing mental disturbances.
Sulphonamido-chrysoidin	381	11 (2.9)
Sulphanilamide	317	10 (3.1)
Benzyl-sulphonamide	70	0 (0)
Carboxy-sulphonamido-chrysoidin	89	4 (4.5)
Sulphapyridine	481	1 (0.2)
Total:-	1338	26 (1.9)

(The figures in brackets are percentages of the different totals).

There is little actual difference here between any of the drugs. The standard error of difference between the highest incidence (4.5 per cent.) and that for all cases (1.9 per cent.) is ± 2.24, so that the difference is not significant. The rate for sulphapyridine, however, seems surprisingly low.

(c) Disturbances of the Gastrointestinal Tract.

The commonest toxic effects noted were nausea, vomiting, epigastric pain and diarrhoea. The incidence of these in patients receiving the different drugs was as follows:-

Drug.	Total Cases Treated.	Total showing Toxic Effects.
Sulphonamido-chrysoidin	381	26 (6.8)
Sulphanilamide	317	10 (3.2)
Benzyl-sulphonamide	70	1 (1.4)
Carboxy-sulphonamido-chrysoidin	89	3 (2.4)
Sulphapyridine	481	60 (12.4)
Total:-	1338	100 (7.5)

(The figures in brackets are percentages of the different totals).

It is clear that sulphapyridine is not the only sulphonamide which can give rise to gastrointestinal upset. It should, however, be made clear that the symptoms with this drug are much more intense than with the other four. Many patients reached a stage when they refused to accept another dose of sulphapyridine; this situation was never encountered with the other drugs.

(d) Disturbances of the Urinary System.

No case of erysipelas was encountered where there was any apparent damage to the urinary tract from the drugs given. In fact, the drugs were given, without ill effect, to patients who showed an acute nephritis on admission to hospital. In four cases of pneumonia that received sulphapyridine, however, such a disturbance was noted. In three cases haematuria was found and in the fourth there was a complaint of pain — in site and nature very suggestive of ureteric colic. In this last case no haematuria was noted although the urine was repeatedly examined microscopically. The incidence is thus 0.83 per cent. In each of these cases the patient had been unco-operative and his fluid intake had been unsatisfactory.

It is clear that the solubility of the drug is here a factor of great importance. Although many urines were examined, the earlier drugs were always dissolved in the urine as passed; but with sulphapyridine, when the urine cooled, crystals were often easily seen under the microscope.

With sulphonamido-chrysoidin the urine (and the faeces) was always coloured a bright brick red. This caused a very "fast" staining of the bed-linen but seemed to have no effect upon the patient. Curiously, with the other red dye, carboxy-sulphonamido-chrysoidin, the urine was not coloured.

(e) The Occurrence of Toxic Rashes and of Fever.

The incidence of these conditions with the five drugs used is shown in Table 1.

TABLE 1.

The Occurrence of Drug Rashes and Drug Fever with various Sulphonamide Drugs.

Drug.	Rashes with Febrile Disturbance.	Febrile Disturbance only.	Combined figures for both Toxic Effects.	Total Cases Treated
Sulphonamido-chrysoidin	7 (1.8)	7 (1.8)	14 (3.7)	381
Sulphanilamide	6 (1.9)	15 (4.7)	21 (6.6)	317
Benzyl-sulphanilamide	2 (2.8)	2 (2.8)	4 (5.7)	70
Carboxy-sulphonamido-chrysoidin	1 (1.1)	0 (0)	1 (1.1)	89
Sulphapyridine	7 (1.5)	2 (0.4)	9 (1.9)	481
Total:-	23 (1.7)	26 (1.9)	49 (3.7)	1338

(The figures in brackets are percentages of the total in the group).

Rashes. The usual rash noted closely resembled that of rubella. The elements of the rash consisted of rather small, maculo-papules which tended to coalesce. The colour was a bright pink. In the majority of cases the skin was very irritable. The rash, as a rule, appeared after treatment had continued for some 7-12 days. The distribution of the rash was very variable. In some cases it was generalised and profuse; in others the rash was confined to certain areas. As a rule, the extensor aspects were particularly involved, the elbows and knees being rarely spared. The back of the trunk, the /

the flanks and buttocks usually showed a profuse cropping. The rash was often noted on the face and when this occurred the circumoral region was not spared. Finally, it was not infrequent to find slight oedema and redness of the eyelids; pinkness of the conjunctivae served to complete the close resemblance to rubella. A certain amount of febrile disturbance usually accompanied the eruption. The temperature as a rule did not exceed 99° or 100° Fahrenheit, but in some cases high fever up to 103° Fahrenheit was noted.

Fever. When the results obtained with different dosage of the drugs in erysipelas were reported, I advanced the suggestion that the primary fever might be prolonged when large doses were administered. I am in no doubt that one occasionally sees this prolongation of primary pyrexia as a direct toxic effect. Sometimes, in cases of meningococcal meningitis, fever has continued despite the fact that the physical signs and examination of the cerebrospinal fluid indicated that the infection was under control. The decision to stop the drug in such cases is sometimes reached with difficulty. Much more frequently, however, this toxic effect makes its appearance when the primary pyrexia has ceased and after an interval of normal temperature of from three to five days; that is, on the fifth to tenth day of treatment. In these cases no rash is to be seen, and when administration of the drug is stopped the fever subsides fairly rapidly.

The causation of these two conditions, namely, late rashes and late fever, seem to me to be related. The temperature charts shown in Figures 1 and 2 (which could be repeated by many others) may supply a clue to their origin. It will be seen that the administration of a /

Explanatory Legend to Fig. 1.

This patient was admitted to hospital as a case of measles. On admission, Rubella was suspected; but a history was obtained that sulphapyridine had been administered for several days prior to admission. As the chart shows, the subsequent administration of a single dose of 0.5 gm. of this drug was responsible for a very acute reaction characterised by high temperature, shivering, headache, suffused eyes and a bright generalised morbilliform rash.

DAY OF ILLNESS
TIME.
5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23
AM PM
TEMPERATURE °F
PULSE.
RESPIRATION.
On Admission, Acutely ill; Eyes Suffused; Face Swollen; Headache and Shivering.
Rash Still Present.
ON ADMISSION
STRONGLY SUGGESTED RUBELLA
DRUG RASH SUSPECTED
NOTE EFFECT OF SULPHAPYRIDINE
0·5 GM AFTER ONE WEEK.
At 6 P.M.
At 6 P.M.
Sulphapyridine Gms 2·0 at 2 P.M. Feveled &
Marked Shivering; Eyes Suffused & Watery Cough.
Bright General Rash at 9 P.M.

Explanatory Legend to Fig. 2.

This patient was admitted as a case of pneumonia in his 5th day of illness; the diagnosis was confirmed. Sulphadiazine was given but although the consolidation did not spread and no complication was noted, the pyrexia continued and the patient remained toxic. On the eighth day of treatment the appearance of a typical drug rash suggested the cause of the continued fever: stoppage of the drug caused a rapid subsidence of the fever. Later, a single dose of the drug produced a typical sensitisation reaction.

The chart is an excellent illustration of the continuation of primary pyrexia as a toxic effect of the drug, already referred to in Volume I.

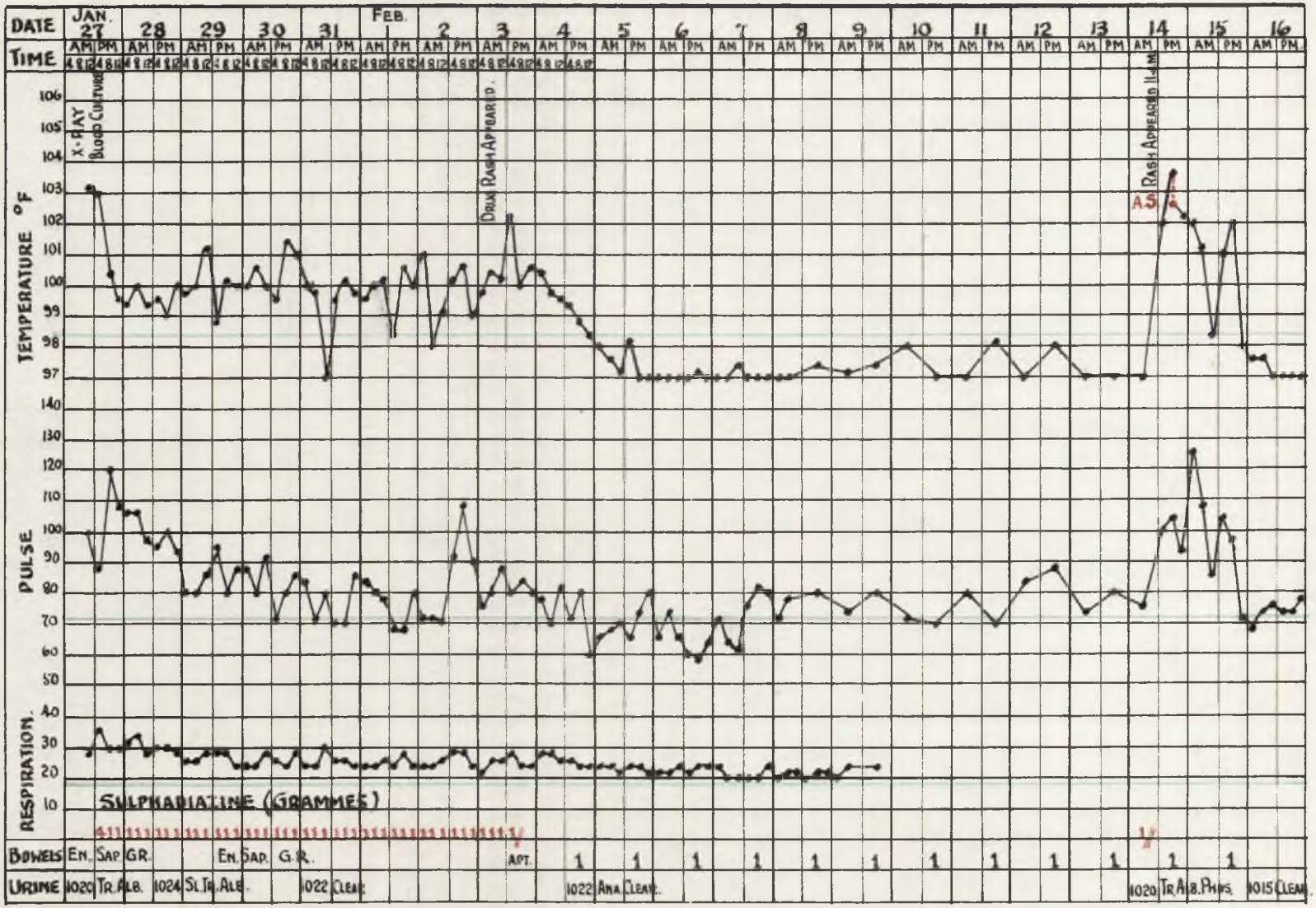
CHART OF PNEUMONIA SHOWING DELAY IN FALL OF PRIMARY PYREXIA DUE TO DRUG FEVER

NOTE EXHIBITION OF DRUG IN CONVALESCENCE FOLLOWED BY IMMEDIATE RISE.

DATE :- 27.1.43
DAY OF ILLNESS: 5TH.
NAME :- R.K. (MALE)
AGE :- 57 YEARS.
SPUTUM :-
TYPE XVIII

BLOOD CULTURE :-
NEGATIVE

SULPHADIAZINE :-
XLIV GRAMMES.



a single dose of the drug at a later date has induced an immediate repetition of the earlier toxic signs. This finding suggests that rash and fever are due to sensitisation. It has been suggested that photo-sensitisation is a factor in the causation of drug rashes (Erskine, 1942; Park and Platts, 1942), and that they show a tendency to be most profuse on parts of the body commonly exposed to sunlight. In my own series of cases this has not occurred, and as I have stated above, the rash was usually most profuse on the elbows and knees, the buttocks and flanks. Further, it should not be forgotten that 49 cases of erysipelas received combined treatment with sulphonamido-chrysoidin and ultra-violet light from a mercury vapour lamp (Snodgrass and Anderson, 1937) Although several doses of artificial sunlight were given to many of the cases, not a single one developed any kind of rash — either local or general.

From the figures given in Table 1, it is clear that the incidence of both rashes and fever varies little with different drugs of the sulphonamide series. In regard to the occurrence of rashes, the figures show a close resemblance varying from 1.1 per cent. to 2.8 per cent., with a mean for the whole series of 1.7 per cent. In regard to the occurrence of fever, there is rather more disagreement. For all but sulphanilamide the figures may be regarded as essentially similar. The difference between the incidence per cent. for sulphanilamide and that for the whole series (2.8 per cent.) has a standard error of $\pm$ 1.25. If a difference greater than twice the standard error is accepted as significant, then "drug fever" is more frequent in patients who receive sulphanilamide. As a possible explanation of this may be advanced the fact that in

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in stages 2 and 3 of the experiments upon erysipelas, sulphanilamide was frequently administered in what I would now regard as an excessive dose, namely, 2.0 grams four-hourly during the acute stage. Finally, in comparing the figures obtained with the four drugs as used in the treatment of erysipelas, and sulphapyridine as used in the treatment of pneumonia, it should be remembered that with the latter the treatment period was slightly shorter. In the case of pneumonia, it was unusual for treatment to extend beyond the seventh day in hospital, whereas in erysipelas (with the exception of the first stage of the experiment), treatment was often continued until the fourteenth or fifteenth day.

Summary.

A survey of 1,338 cases that received a sulphonamide drug shows that a wide variety of toxic effects occurred. No case showed serious toxicity, although in two patients who developed sulphaemoglobinaemia the clinical appearance initially was somewhat alarming. The appearance of a rash or fever formed the most interesting group of toxic reactions. Charts are shown which suggest that these effects may be of the nature of a sensitisation to the drugs.

CHAPTER III.

An Examination of the Relation between Certain Characteristics and the Occurrence of Toxic Effects.

In this analysis I shall confine myself to the study of the figures obtained with the three drugs mainly used, namely, sulphonamido-chrysoidin, sulphanilamide and sulphapyridine. Only with these three are the figures large enough to permit satisfactory deductions to be drawn.

(a) The Effect of Age upon the Occurrence of Toxic Effects.

TABLE 2.

Incidence of Toxic Effects with three Sulphonamides at different ages.

Age Group Years	S.C.		S.A.		S.P.		All drugs.	
	Col. 1	Col.2	Col.1	Col.2	Col.1	Col.2	Col.1	Col. 2
0-10	25	1	79	6	-	-	104	7 (6.9)
11-40	137	24	103	15	280	44	520	83 (16.0)
41 +	219	26	135	20	201	28	555	74 (13.4)
	381	51	317	41	481	62	1179	164 (13.9)

Note: Col. 1 - Total cases receiving that drug.

Col. 2 - Actual number of toxic effects arising, cyanosis excluded.

S.C. = Sulphonamido-chrysoidin.

S.A. = Sulphanilamide.

S.P. = Sulphapyridine.

(The figures in brackets are percentages).

The analysis in respect of age with the three drugs is shown in Table 2. Cyanosis has been excluded because, although it must be regarded as a toxic effect of the drugs, its appearance is of such slight importance that it may usually be disregarded.

Study of Table 2 draws attention in accurate figures to the low incidence of toxic effects in the young, for the incidence is only a half of that noted in the adult. This low rate seems to be associated only with childhood, for the rates for those between 11 years and 40 years and those over the age of 40 are essentially similar for all the drugs. This is a point of some importance. In some infections, for example, erysipelas and meningococcal meningitis, the severity is greater in young children. It is satisfactory to know that the drugs may perhaps be used with greater freedom in this period of life. The cause of the difference is not easy to explain. The first point of importance may be that, relatively, children absorb much more fluid than adults. I have already stated my belief in the importance of a high fluid intake. In the very young children who formed the bulk of the erysipelas patients under the age of 10 years, the diet was, naturally, almost entirely fluid. It would further seem natural that, in young children, the excretory apparatus is unlikely to show even the slight degenerative changes that may appear as age advances. If this were the whole explanation, however, one would expect the incidence of toxic reactions to increase with age. The similarity of the incidence above and below forty years would not support such a view.

(b) The Effect of Sex upon the Occurrence of Toxic Effects.

The same set of figures is subdivided into the two sexes in Table 3.

TABLE 3.

The Incidence of Toxic Effects with three drugs in the two sexes.

Sex	S.C.		S.A.		S.P.		Combined drugs.	
	Col.1	Col.2	Col.1	Col.2	Col.1	Col.2	Col.1	Col.2
Male	187	17	168	13	330	38	685	68 (9.9)
Female	194	34	149	28	151	37	494	99 (20.0)
Combined	381	51	317	41	481	75	1179	167

Note: S.C., S.A., and S.P. represent Sulphonamido-chrysoidin, Sulphanilamide and Sulphapyridine, respectively.

Col.1 — Total cases in treatment group.

Col.2 — Actual number of toxic effects, excluding cyanosis.

(The figures in brackets are percentages).

Study of Table 3 shows that with each of the three drugs toxic effects are more common in females than males. When the figures for the three drugs are combined, we find a difference in favour of males of 10.1 per cent. The standard error is $\pm$ 2.14 which suggests that the difference is significant. Even when one concentrates upon the occurrence of a rash or fever (which I have already suggested may possibly be due to sensitisation) the figures show a similar distribution. Forty-three patients showed rash, fever or both combined; of these thirty-two occurred in females. In other words, nearly 75 per cent. of those who showed such toxic reactions were females although just less than 42 per cent. of the total cases were of this sex.

I can offer no explanation for this surprising difference.

(c) An Examination of the Results of Treatment obtained in cases which showed some toxic effect.

It has occurred to me to be worth while to examine the results obtained in those cases which displayed some toxic reaction to the drug and to compare them with the results which were given in the earlier part of this report. In order to compare two groups as nearly alike as possible, I shall confine the analysis to those cases of erysipelas which received sulphonamido-chrysoidin or sulphanilamide. It will be remembered that a comparison was made between the results of treatment obtained with ultra-violet light and these same two drugs in the preliminary assessment of the results in erysipelas (see p. 41). These cases will now be used as the control group for comparison. The relevant figures are shown in Table 4.

TABLE 4.

Duration, in days, of Spread and Primary Pyrexia in cases (a) unselected, (b) showing toxic effects. (Treatment : Sulphonamido-chrysoidin or Sulphanilamide).

Character-istic.	Group	Duration, in days, till Cessation.									Total
		0	1	2	3	4	5	6	7	over 7	
Spread	A	161 (51.8)	120 (38.5)	25 (8.0)	5 (1.6)	1 (0.3)	0	0	0	0	312
	B	69 (37.1)	88 (47.4)	26 (14.0)	3 (1.6)	0	0	0	0	0	186
Primary Pyrexia	A	19	127 (43.4)	109 (37.2)	34 (11.6)	12 (4.1)	8 (2.7)	3 (1.0)	0	0	312
	B	4	53 (29.2)	75 (41.5)	32 (17.6)	14 (7.7)	5 (2.7)	1 (0.5)	1* (0.5)	1* (0.5)	186

* In both cases the fever was prolonged by the drug:

Group A: Those cases treated in stages 1, 2 and 4 (i.e. with sulphonamido-chrysoidin or sulphanilamide) of the original experiment and already reported (p. 47).

Group B: Those cases from the whole series which received sulphonamido-chrysoidin or sulphanilamide and which showed a toxic reaction, including cyanosis.

(The figures in brackets are percentages).

Examination of Table 4 shows that of Group A, 90.3 per cent. ceased to spread within twenty-four hours of admission; the equivalent figure for Group B was 84.5 per cent. The difference (5.8 per cent.) has a standard error of $\pm$ 3.14, so that it might have arisen by chance.

In Group A, 80.6 per cent. of the cases (excluding those apyrexial on admission) ceased to show fever after 48 hours in hospital; in Group B, the equivalent rate was 70.7 per cent. The difference (9.9 per cent.) has a standard error of $\pm$ 4.1 per cent., so that it may be regarded as outside the limits of chance variation.

It would thus seem that the fall in temperature may be slightly delayed in those cases which show a toxic reaction to the drug. Such a finding adds point to the conclusion drawn from the use of the drugs in erysipelas, that prolongation of primary pyrexia may result from excessive dosage.

Summary.

The occurrence of a toxic effect (other than cyanosis) due to the drug is examined in relation to (i) the age, (ii) the sex and (iii) the rapidity of abatement of certain clinical characteristics. It is shown that toxic symptoms are less common in young children than in adults. This may be due to the larger relative intake of fluid in young children. Toxic symptoms are found to arise more frequently in female than in male patients: no explanation can be afforded for this finding. Finally, in cases of erysipelas, it is found that there is a prolongation of fever in those who show evidence of toxicity.

CHAPTER IV.

Discussion.

Discussion.

The cases described represent the only toxic effects discovered in a series of 1,338 cases receiving some form of sulphonamide. With the exception of the early cases of sulphaemoglobinaemia, none gave rise to any anxiety. Indeed, cyanosis I would now regard as a natural accompaniment of sulphonamide therapy which should not permit any interference with the scheme of treatment. Once experience with the drugs had increased, I paid no attention to its development and continued administration of the drug; often to find that, as treatment continued, cyanosis appeared to lessen.

Severe mental disturbance was so unusual that it, too, could well be overlooked, at least when the drugs were being given to a recumbent patient. I would advise that their occurrence, however, should induce care when the drugs are given to ambulant persons.

With sulphapyridine, vomiting was frequently a very distressing toxic effect. I found that no form of therapy reduced its incidence. Further, it occurred in a case receiving the drug entirely by the intravenous route; such a finding suggests that the gastrointestinal disturbance might be of central origin. Haematuria occurred only with sulphapyridine and even then in but a handful of patients. Microscopic examination of many specimens of urine from patients under treatment failed to reveal the presence of more than a few red blood cells. It seems reasonable to suggest that the large quantities of fluid imbibed were responsible for the low incidence of this toxic effect.

The /

The occurrence of drug rashes and drug fever can be disturbing. Quite apart from the difficulty of diagnosis from measles or rubella (and in an infectious diseases hospital this may be important), it might have serious consequences if, subsequently, the patient should require sulphonamides for a serious infection. I think it is worth stressing their relatively lower incidence with sulphapyridine and suggesting again that the reason is the shorter duration of treatment. To review the case at the end of seven days with a view to terminating treatment would appear to be a wise rule.

The temperature charts which have been shown emphasise the feature of sensitisation. In my view, after long experience of the administration of serums and antitoxins in different diseases, the resemblance between "serum disease" and these toxic effects with the sulphonamides is very striking. The incubation period, for example, is similar, for in the "normal" type of serum reaction the duration between the infection of the foreign material and the appearance of the reaction is about six to twelve days. One might in fact, with drug fever and drug rash, parallel fairly well the three classical forms of serum disease, the "normal", the "accelerated" and the "immediate". (Muir and Ritchie's Manual of Bacteriology, 10th ed., 1937).

A. Normal. 1. Serum Disease: Here there is no history of previous serum injection and the patient is not spontaneously sensitive. The incubation period is from 6 - 12 days.

2. Drug reaction: The normal reaction of the appearance of rash and/or fever about 9 - 12 days after the commencement of administration of the drug fits this description well.

B. /

B. Accelerated. 1. Serum Disease: This form is more common in persons who have had previous experience of antiserums. The incubation period is shorter, from 2 - 5 days.

2. Drug reaction: This description might fit the form of reaction which I have described as a prolongation of the normal pyrexia. One would imagine that the pyrexia of the original disease will account for the first two days, so that the drug fever only dates from about the second or third day of treatment. It might be suggested that this will occur in persons who have had previous experience of the sulphonamide drugs or of chemicals containing similar groupings.

C. Immediate. 1. Serum disease: Here the reaction occurs instantaneously on the administration of the foreign protein. This reaction undoubtedly occurs rarely and probably indicates either spontaneous sensitivity or previous sensitisation with a similar foreign protein.

2. Drug reaction: The temperature charts which I have supplied have both shown an immediate response on the later oral administration of the sulphonamide responsible for the original reaction.

Now such reasoning might seem to rest upon somewhat slender evidence. But recently, Rich (1942) and Rich and Gregory (1943) have produced pathological evidence which supports a belief in the similarity between the two conditions. Rich reported the autopsy findings in seven patients who died from serum disease or after the administration of sulphonamides. Five of the cases had received serum with, in addition, sulphapyridine, sulphathiazole or /

or sulphadiazine; one had received serum alone; and one had received sulphathiazole alone. The microscopic picture in all was the same, namely, an acute arteritis and peri-arteritis which involved the smaller vessels of a large variety of organs. Rich stated that the picture was essentially that of a periarteritis nodosa. Similar lesions were thus noted in (a) those who had received both serum and drug, (b) the patient who had received serum alone and (c) the patient who had received sulphathiazole alone; it seems reasonable to suppose that there is a relationship between the two toxic effects. In their later paper, Rich and Gregory reported that they had been able to reproduce essentially similar lesions in rabbits. Finally, Lyons and Balberor (1942) have reported that 19 out of 53 patients who were given two or more courses of sulphathiazole showed an immediate response in the shape of fever or rash. Clearly, therefore, there is a form of acute reaction to the drugs which may arise from previous sensitisation. The avoidance of drug fever and drug rashes is therefore of some importance since it may vitiate later treatment.

That these reactions may be specific for the drug administered is shown by the following experience, reported by one of my resident medical staff (Smith, 1944).

"At one time in the hospital a number of adult female patients were receiving in high dosage one of the sulphonamide series, namely, sulphaguanidine. Of these, twenty developed a drug rash, often with some fever. Later four groups of three volunteers in each were given a single 1.0 g. dose of (a) sulphanilamide, (b) sulphapyridine, (c) /

(c) sulphathiazole and (d) sulphaguanidine. Only those who were given sulphaguanidine showed an immediate reaction by the development of a rash. Later still, the nine girls who had failed to respond to the single dose of the other sulphonamides were each given a single dose of sulphaguanidine. Seven of them developed an acute reaction with widespread rash, fever and sickness."

Such an experience certainly emphasises the marked specificity of the reaction which is again in keeping with the experience of serum disease. Sensitisation to chemicals is, of course, not new, for Landsteiner and Jacobs (1936) have reported the sensitisation of guinea-pigs to arsphenamine and neo-arsphenamine so that anaphylactic shock followed their intravenous injection.

Attention might be drawn to one further parallelism between the two conditions. Weaver (1909) drew attention to the fact that the occurrence of serum disease was related to the amount of foreign serum administered: the reaction was more likely to develop in those who received the larger amounts. A greater tendency for the development of drug rashes or drug fever in those who receive excessive or prolonged dosage of the sulphonamides is certainly suggested from the experience with sulphaguanidine reported above; nearly 50 per cent. of those who were given an excessive dose of the drug developed fever or rash. I have already indicated that the slightly lower incidence with sulphapyridine may be due to the shorter duration of treatment in pneumonia compared with erysipelas. Finally, I have shown that with excessive dosage of the drugs in the treatment of erysipelas the primary pyrexia was prolonged.

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All of these experiences point to a similarity between the two conditions — "serum disease" and sulphonamide rash or fever. The question remains — to what is the patient sensitised?

In the first place, sensitisation is unlikely to be due to the common factor to all the drugs, namely, the sulphonamide radicle: for were this the case the reaction would not be drug-specific. (Sulphanilamide itself may, of course, induce its own specific sensitisation). It might be thought that the allergy was induced by each particular chemical. But, against this deduction can be brought the fact that skin tests (using lint soaked in the drug strapped to the skin by adhesive plaster) have always, in my experience, failed to produce a local reaction. Such evidence is not absolute, for it might well be necessary for the antigen to be absorbed enterally . A third possibility may be advanced. It is possible that after absorption, the drugs combine with proteins in the blood; and that these protein complexes are the offending anaphylactogens. Two recent reports tend to support such a view. Gerber and Gross (1944) have recently shown that sulphonamide protein conjugates can be prepared which produce a specific allergy; in guinea-pigs demonstrated by the occurrence of anaphylaxis; and in rabbits by the Schwarzman phenomenon. More recently, Leftwich (1944) has devised a test for sensitisation. The serum of persons who have been receiving a sulphonamide drug for five to seven days without ill-effect is used for performing an intradermal test. The injection of 0.05 c.cmm. causes a wheal which develops to a maximum in about fifteen to twenty minutes in persons who are sensitised to the drug. The injection of the drug alone, or of the individual's serum after /

after sulphonamide has disappeared from the blood, produces no result. Such evidence strongly supports the view that the etiological agent is a sulphonamide conjugate.

The importance of such a form of toxic effect should not be exaggerated. The incidence figures reported here do not indicate that they occur with great frequency. Nevertheless their occurrence and the possible mechanism of their causation deserve some emphasis; more especially if it is true, as I have suggested, that they are likely to occur more frequently when the period of treatment is prolonged. Such a finding may point a way to their avoidance.

From the evidence produced, therefore, it can be concluded that the drugs are of surprisingly low toxicity in the dosage usually given to man; especially when it is remembered how much they contribute to the more effective clinical control, not only of the infections described in the preceding volumes, but of other such important diseases as meningococcal meningitis and gonorrhoea. This low incidence of serious side-effects is combined with an ease of administration which should permit optimum benefit to follow their use, even in comparatively inexpert hands. It is unfortunate that the toxicity of the drugs has often been exaggerated by the reports of isolated and serious effects from their use. For it has occasioned their timorous application in general practice, where they can, in fact, be given as effectively as in hospital. It might indeed be said that no great skill is required for their administration; the skill required lies in making the correct diagnosis of the diseases in which they are known to exert a beneficial effect; and, more particularly, in realising when their administration should be stopped.

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