Original Articles

TOXIC COMPLICATIONS OF SULPHANILAMIDE THERAPY

(AN ANALYSIS OF 6,070 CASES TREATED IN THE VENEREAL DEPARTMENT OF THE GOVERNMENT GENERAL HOSPITAL, MADRAS)

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THE extensive use of sulphanilamide and its derivatives in the chemotherapy of coccal and bacterial infections has resulted in a certain incidence of toxic reactions. An increasing volume of literature has been appearing in the medical press regarding the frequency and the severity of these toxic side-effects. The routine treatment of a large number of cases of gonorrhœa, chancroids and venereal lymphogranuloma with sulphanilamide in the venereal department of the Government General Hospital during the past three years has afforded us an opportunity for clinical study of the toxic manifestations of the drug.

The majority of the cases undergoing treatment in the department are ambulatory and only those whose illnesses are very acute or who develop a serious toxic complication are admitted to hospital. During the three-year period (October 1937 to October 1940) 6,070 cases were under treatment, of whom 5,076 were males and 994 females. A smaller number of female children were treated in the clinic, but are not included in this paper. Sulphanilamide is the drug in routine use and the costlier, though therapeutically more effective, sulphapyridine was used only in a very small number of cases.

Table I gives an analysis of the toxic reactions noted.

Fever.—This is the commonest of the toxic reactions observed in the course of sulphanilamide therapy and occurs in the majority of the cases between the fifth and the tenth day of treatment. Fever either occurs alone or is associated with the development of some other complication such as dermatitis, leucopænia, or breathlessness. Four types of fever were recognized among the cases :

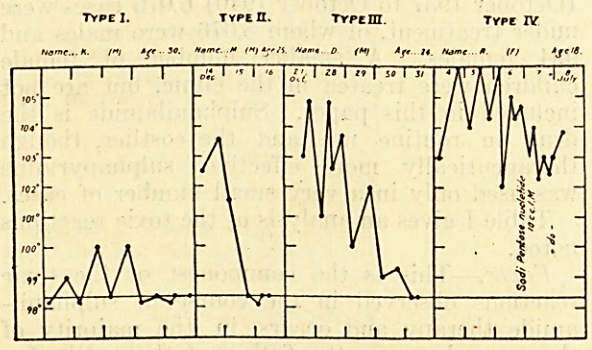
1. A low intermittent fever, the temperature rarely going beyond 100°F., with the evening rise and morning remission, lasting for a few days.
2. A sudden rise of temperature to 103°F. or 104°F., preceded by a chill and coming down by crisis in about 24 hours.

TABLE I

	Cases	Complications	Percentage
Total number	6,070	1,765	29.08
Males	5,076	1,512	29.79
Females	994	253	25.45

Serial number	Complications	Males	Females	Total	Percentage		
					Males	Females	Total
1	Fever	619	96	715	12.20	9.66	11.78
2	Dermatitis	48	9	57	0.95	1.00	0.94
3	Leucopænia with or without granulocytopænia.	23	3	26	0.45	0.30	0.43
4	Agranulocytosis	1	2	3	0.02	0.20	0.05
5	Mild anæmia	7	2	9	0.14	0.20	0.15
6	Bleeding from the nose	6	4	10	0.12	0.40	0.16
7	Profuse menses	..	2	2	..	0.20	0.20
8	Bleeding from the bowel	..	1	1	..	0.10	0.015
9	Hæmoptysis	2	..	2	0.04	..	0.03
10	Bleeding from the gums	1	..	1	0.02	..	0.015
11	Breathlessness with or without cyanosis	53	1	54	1.04	0.10	0.89
12	Numbness and tingling of fingers and toes	57	12	69	1.12	1.20	1.14
13	Herpes zoster	..	1	1	..	0.10	0.015
14	Diminished acuity of vision	6	..	6	0.12	..	0.10
15	Vestibular dysfunction—vertigo, tinnitus and slight deafness.	5	..	5	0.10	..	0.08
16	Gastro-intestinal upset (diarrhœa)	44	8	52	0.86	0.80	0.86
17	Headache	96	14	110	1.89	1.40	1.81
18	Giddiness	171	30	201	3.37	3.00	3.31
19	Nausea, with or without vomiting	102	13	115	2.01	1.32	1.89
20	Anorexia	68	3	71	1.34	0.30	1.17
21	Pain in chest	53	5	58	1.04	0.50	0.96
22	Pain in abdomen	58	10	68	1.14	1.00	1.12
23	Pain in joints	22	1	23	0.43	0.10	0.38
24	Muscular weakness	59	29	88	1.16	2.92	1.45
25	Sore throat	11	7	18	0.22	0.70	0.30

3. The third type is similar to the second except that the fever continues for about three days, slowly coming down to normal on or about the fourth day.
4. In this type, there is severe shivering followed by high fever 104°F. or 105°F.; patient looks very ill and toxic. Blood count reveals a profound granulocytopænia or agranulocytosis.



Graphs showing different types of febrile reaction.

The development of fever is indication for stoppage of therapy and it is our practice to admit these cases as in-patients for observation, and performance of blood count. Only in about 6 per cent of these cases did the blood count show any abnormality. The resumption of treatment brought on the fever of a more severe form in the majority of the patients. In a few cases, change to another derivative of the drug failed to produce the fever and the treatment was continued successfully. It is our impression that the fever in all the cases may not be directly due to the toxic effect of the drug, but may be caused by the liberation and circulation of toxins from some buried focus of infection. The drug fever should be carefully distinguished from fever incidental to the infection for which sulphanilamide is administered. For example, in metastatic complications of gonorrhœa and in venereal lymphogranuloma, fever of varying degree is usually present even before the treatment is started.

Cutaneous reactions.—There were 57 cases of drug eruptions in our analysis, of whom 48 were males and nine females. Table II gives a detailed description of the type and distribution of the rash, the dosage of the drug, the day of appearance of the rash, etc.

The eruptions appeared any time from the third to the fourteenth day of sulphanilamide therapy; but in the majority of cases the rash developed between the seventh and the twelfth day of treatment. Two distinct types of rash were observed from the point of view of distribution. The first one (26 cases) was a diffuse eruption involving the trunk, face and limbs. The second type (22 cases) was a localized rash, confined to the parts exposed to direct sunlight—face, neck, extensor aspects of the forearms and hands and dorsal aspects of the feet. A third type (nine cases) complained of intense itching all over the body without any visible eruption.

The following is the classification of eruptions observed :—

Morbilliform	18
Urticarial	12
Follicular	6
Papulo-macular and papular ..	5
Erythematous	4
Scarlatiniform	1
Bullous	1

The morbilliform type of eruption seems the commonest. Constitutional disturbance, such as fever and malaise, was present in many of the cases. Ten per cent of these patients with eruptions showed a definite leucocytosis, the leucocytes ranging from 12,000 to 21,000 per c.mm. One case developed a slight leucopænia and in two severe cases, there was a leucopænia with granulocytopænia. Most of the eruptions disappeared in a few days on cessation of therapy. In one case of diffuse urticarial eruption, marked breathlessness, and mental confusion were associated features. A moderate desquamation was observed in four cases of severe diffuse type.

From the table it may be seen that the cutaneous intolerance due to sulphanilamide therapy does not depend so much on the total dose of the drug ingested as on the time factor, seventh to twelfth day of therapy appearing to be the most favourable period for the development of the eruption. The question of resumption of therapy in these cases could not be studied with any precision as many of these patients failed to report again. But in quite a few cases of the light-sensitization type, who reported after a few months for treatment either for the original uncured venereal infection or a fresh infection, we were able to administer the same drug, with a warning to the patients not to expose themselves to direct sunlight, without the recurrence of the skin trouble. Patch tests were not performed to determine the sensitiveness.

Another observation we have made is the relation between the severity of the skin reaction and the therapeutic response of the infection to the drug. In many cases of the diffuse severe type, no matter on what day of treatment they developed, the therapeutic response, particularly in gonorrhœa, was very dramatic and the clinical and bacteriological cure was permanent.

A third of the cases of drug eruption, in our series, were of the light-sensitization type; this is in contrast to the relative infrequency of such eruptions reported by other clinicians from the temperate regions of the world. The strong and powerful sunlight prevalent during the greater part of the year in these latitudes will easily account for the increased incidence of this type of rash. It is our impression that even some of the diffuse types of eruption belong to this light-sensitization type, as many of our

TABLE II

Serial number	Type of cutaneous eruption	Day of rash	Total dose of sulphanilamide (gm.)	Distribution of rash	REMARKS
1	Follicular	3	12	Trunk and limbs	Diffuse and symmetrical.
2	Morbilliform	9	30⅔	Trunk, face and limbs.	Do.
3	Do.	6	23	Chest, neck and upper limbs.	Diffuse.
4	Do.	5	13⅓	Trunk, face and extremities.	Diffuse (slight leucopænia).
5	Do.	5	30	Trunk, face and limbs.	Do.
6	Follicular	8	33	Chest and back	Leucocytosis.
7	Do.	12	30	Trunk and face	Do.
8	Morbilliform	10	29	Hands, face and forearms.	Light sensitive. Marked leucocytosis 20,625.
9	Do.	4	12	Face only	Photo sensitive.
10	Erythematous	4	18	Trunk and limbs	Diffuse.
11	Maculo-papular	10	39	Do.	Do.
12	Morbilliform	10	39	Face, neck, feet and forearms.	Light sensitive.
13	Do.	12	45	Face only	Light sensitive (five months later was put on streptocide without developing rash).
14	Macular	9	36	Do.	Light sensitive (leucocytosis).
15	Erythematous	7	21	Face, forearms and feet.	Light sensitive.
16	Do.	7	22	Face and neck	Do.
17	Erythemato-macular.	7	21	Face, hands and feet.	Do.
18	Morbilliform	9	37½	Face, neck and forearms.	Do.
19	Do.	8	34½	Trunk, limbs and face.	Diffuse.
20	Papulo-urticarial	11	43½	Face only	Light sensitive.
21	Urticarial	9	37½	Trunk, limbs and face.	Breathlessness and mental confusion—leucocytosis.
22	Morbilliform	8	24	Exposed parts—face and forearms.	Light sensitive.
23	Scarlatiniform and urticarial.	7	31½	Trunk, limbs and face.	Leucopænia with granulocytopænia. Marked desquamation.
24	Morbilliform	9	27	Trunk, face and arms.	Diffuse.
25	Do.	9	37½	Face, trunk and limbs.	Diffuse. Leucocytosis 18,750. Marked desquamation.
26	Bullous dermatitis, with extensive mucosal lesions.	9	37½	Trunk, face, limbs, mouth, lips, eyelids, conjunctiva and cornea.	Initial high fever, leucocytosis followed by leucopænia—marked exfoliation—pigmentary scars all over—ulcer cornea.
27	Morbilliform	10	40½	Exposed parts—face, neck, forearms and limbs.	Light sensitive. Leucocytosis.
28	Do.	7	31½	Face, neck, forearms and hands.	Light sensitive.
29	Urticarial	3	8	Trunk and limbs	Diffuse.
30	Do.	9	36	Do.	Do.
31	Do.	3	13½	Trunk	Three months after tolerated streptocide without rash.
32	Do.	9	34½	Trunk and limbs	Diffuse.
33	Do.	4	18	Distal half of the extremities.	Light sensitive.
34	Do.	4	13½	Trunk	
35	Do.	14	60½	Face only	Light sensitive.
36	Do.	7	21	Face and hands	Do.
37	Do.	5	22½	Trunk and limbs	Fever, pain in the limbs.
38	Do.	8	34½	Trunk, limbs and face.	
39	Pruritus	7	30	All over the body	
40	Do.	6	22½	Exposed parts—face and forearms.	Light sensitive.
41	Do.	11	43½	All over the body	
42	Pruritus and stomatitis.	4	18	All over the body. Herpetiform ulcers on the buccal mucosa, pain stomach.	

TABLE II—*concld.*

Serial number	Type of cutaneous eruption	Day of rash	Total dose of sulphanilamide (gm.)	Distribution of rash	REMARKS
43	Pruritus	7	21	All over the body	
44	Do.	8	33	Do.	
45	Do.	3	9	Do.	
46	Do.	9	40½	Do.	
47	Do.	5	22½	Do.	
48	Do.	8	33	Do.	
49	Morbilliform	12	36	Trunk, face and limbs.	
50	Follicular	6	18	Forearms and hands.	Light sensitive.
51	Morbilliform	21	63	Trunk, face and limbs.	Marked desquamation.
52	Follicular	7	21	Face, forearms and feet.	Light sensitive.
53	Morbilliform	9	24	Face only	Do.
54	Follicular	3	9	Face and forearms	Do.
55	Papular and pustular.	7	21	All over the trunk and limbs.	
56	Urticarial	10	30	All over the body	
57	Urticarial and papular.	5	15	Exposed parts—face and hands.	Light sensitive.

poorer patients wear only a loin cloth exposing the greater part of their skin to direct sunlight.

According to Tedder (1939), three factors are involved in the causation of sulphanilamide

Morbilliform rash (sulphanilamide). Anterior view.

rash :—1. Sensitization. 2. Toxic effect. 3. Light sensitization. Erskine (1939) is of opinion that these eruptions, occurring mostly towards the end of the first week of therapy, bear a close family resemblance to the ninth-day erythema met with the arsenobenzene compounds. Another theory put forward by the same author (1938) is the activation of some buried focus of infection by sulphanilamide liberating toxins from the focus.

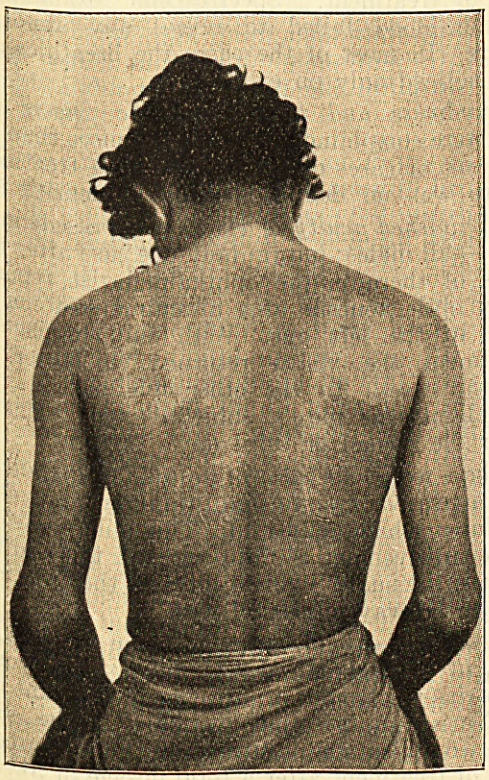
We have not encountered a case of true allergy, in which a single dose of the drug has induced the cutaneous intolerance. The theory of sensitization is advanced on two grounds :—1. In such allergic cases, a normal elimination of the drug in the urine is demonstrated. 2. They remain sensitive to the drug for months and a single small dose brings on the rash in a few hours. In our opinion, the toxic factor appears to be the more important cause of drug rash, particularly of the generalized type in which retention of the drug occurs in the body, due to faulty or inefficient elimination in the urine. The associated or coexistent constitutional disturbance of malaise and fever observed in the majority of cases of generalized eruptions in our analysis lends support to the toxic factor as being the main cause of the diffuse type of drug eruptions.

Rimington and Hemmings (1938) have shown that during sulphanilamide therapy there is an increased production of porphyrin together with coproporphyrin I. This latter substance is a photo-sensitizer and its production varies in degree in different individuals. Epstein (1939) distinguishes true light sensitization from photo allergy. The former is a direct light sensitization caused by the drug and the latter is indirectly due to the drug by the production of porphyrin and coproporphyrin I. The relative infrequency of the photo-sensitive type of drug eruptions noted by clinicians in temperate latitudes, where powerful sunlight is a desideratum, is accounted for by the variation in the production of porphyrin in individual cases.

The greatly increased incidence of this type of cutaneous reaction in our latitudes suggesting that the increased production of photo-sensitizing substance during sulphanilamide therapy may be dependent more upon the sunlight than upon individual bodily tissue reaction; or it may be that the cases of light-sensitization type of eruption in our series are cases of true light sensitization caused directly by the drug.

The notes of our only severe case of cutaneous and mucosal lesions caused by sulphanilamide is given below :—

The patient, a male, aged 30 years, was admitted to the wards of the venereal department on 23rd August, 1940, with a purulent urethral discharge, acute strangury, and difficulty in micturition. Investigation showed him to be suffering from an acute gonococcal urethritis with prostatitis. He was put on sulphanilamide tablets at the rate of 4½ gm. daily. He received

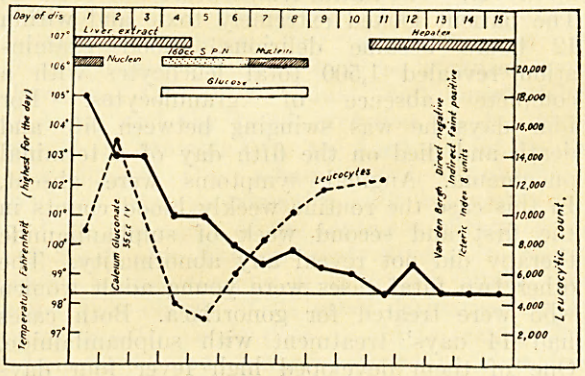


Morbilliform rash (sulphanilamide). Posterior view.

4½ gm. daily for seven days and 3 gm. daily for two more days and as his condition greatly improved, he was discharged from the wards on 31st August, 1940, and advised to continue treatment as an ambulatory patient. He had taken 37½ gm. of the drug in nine days.

On 2nd September, two days after discharge from the wards, he reported very ill and was immediately admitted. On examination, he had extensive eruptions all over the face, trunk, limbs and genitals. The lesions were pleomorphic on the first day, consisting of papular and bullous types, the latter predominating. He had severe cheilitis, stomatitis with fissures and ulcers on the lips, palate, pharynx with a considerable œdema so that the patient was scarcely able to open the mouth. Intense conjunctivitis with blepharitis in both eyes was present. The patient looked extremely toxic with an initial temperature of 105°F., pulse 132 and respiration 40. Within 48 hours the entire skin of the body, face and limbs was covered with grouped and confluent bullous lesions, of varying sizes and shapes, which rapidly burst leaving large raw weeping areas. The eyelids were swollen, shut with discharge and crusts. The mucous membrane of the lips, tongue and palate was grossly inflamed, fissured, ulcerated and easily bleeding. The blood count showed an initial leucocytosis on the first two days of admission but suddenly dropped to 4,000 and 2,750 leucocytes on the fifth and sixth day after admission. The other findings of the blood were normal.

After about five days' treatment the patient turned the corner and started to mend. The temperature came down, the leucocyte count went up, the skin lesions started drying up and exfoliating. The inflammation of the mucous membranes with the exception of the right eye showed a gradual subsidence. An acute ulcer of the right cornea developed with prolapse of the iris which ultimately seriously compromised the vision in that eye. During the involution stage of the skin lesions the patient shed all his nails, and the skin of the palms and soles was coming away in thick flakes. A few subcutaneous abscesses were opened and drained. The healed bullous lesions on the skin of the trunk and face left pigmented, mottled and vitiliginous patches. Towards the end of the second week, recovery was almost complete except for the eye condition. The accompanying chart shows the progress in the temperature and blood findings and also the treatment adopted in the case.



Leucopœnia and granulocytopœnia.—A reduction of the total leucocyte count or granulocyte count, or both, was discovered in about 26 cases. In all the patients, the drug was immediately stopped and they were kept under observation. Regular daily leucocyte counts were performed on them. All the cases, after a few weeks, completely returned to normal. In a few of them, sulphanilamide therapy was restarted without their developing any recurrence of this blood dyscrasia. In three cases, the reduction in leucocytes was observed towards the end of the first week of therapy, the rest occurring at the end of the second week.

Agranulocytosis.—This grave complication of sulphanilamide therapy is reminiscent of a similar grave intoxication of arsenobenzene therapy, *i.e.*, encephalitis, in that both conditions are almost unpredictable and occur with startling and dramatic suddenness from an almost unclouded sky without any premonition. It is usually asserted that the clinician will be forewarned of the grave complication if daily blood counts are performed on patients receiving sulphanilamide therapy. Our observations on the very large number of cases receiving

sulphanilamide in the venereal clinic of the General Hospital do not bear out this contention. There seems an inevitability about the development of agranulocytosis, which appears to occur on a basis of individual idiosyncrasy, rather than as a toxic manifestation. The rarity of this complication, considering the thousands of patients treated with this drug all over the world for the past few years, is evidence of an as yet undetermined susceptibility in a few individuals. In the three years of routine sulphanilamide therapy in the venereal clinic of the Government General Hospital, approximately 2,70,000 grammes of sulphanilamide were administered to about 6,000 patients. Three cases of acute agranulocytosis, in one male and two females, occurred during the period under review. All the three cases ended fatally in spite of treatment.

The male patient, who was receiving treatment for acute gonorrhœa, completed three weeks' course of sulphanilamide totalling 72 grammes. The day after the last day's sulphanilamide the patient suddenly took ill with shivering and fever. The initial temperature was 105.6°F. The patient looked extremely toxic and within 12 hours became delirious. Blood examination revealed 1,500 total leucocytes with a complete absence of granulocytes. For four days he was swinging between life and death and died on the fifth day of a terminal pneumonia. Anginal symptoms were absent. In this case the routine weekly blood counts in the first and second week of sulphanilamide therapy did not reveal any abnormality. The other two fatal cases were young adult women who were treated for gonorrhœa. Both cases had 14 days' treatment with sulphanilamide. One of them developed high fever four days and the other six days after cessation of therapy. The leucocyte count in one was 500 and in the other 1,600, with complete absence of granulocytes in the former and 3 per cent in the latter. One of the women suffered also from a severe angina of the throat. In spite of treatment with sodium pentose nucleotide, glucose and blood transfusion, both cases terminated fatally, the one five days and the other three days after onset of the illness.

A mild anæmia has been noted in nine cases during therapy, with a reduction in the red cell count and hæmoglobin content. We have not regarded these cases of mild anæmia as grave toxic manifestations. Temporary cessation of therapy with administration of iron by mouth has enabled us to restore the defect and then continue the therapy without any ill effect. No case of hæmolytic anæmia was encountered in our series.

A number of cases of *unexplained bleeding* from different orifices of the body was observed in our cases :—ten cases of epistaxis, two of profuse menses, two of hæmoptysis, one of bleeding from the rectum and one of bleeding from the gums. In all these cases the bleeding stopped with the cessation of therapy, but recurred with resumption of treatment. Examination of the blood failed to reveal any abnormality. It is curious that there was no case of hæmaturia in our series treated with sulphanilamide.

Slight breathlessness with or without cyanosis was present in about one per cent of the cases and with a marked predominance in the male patients. It was observed as early as the second day of therapy or was delayed up to the end of the second week. This complication was usually associated with slight fever, dry throat, and retro-sternal pain. In almost all the cases the treatment was continued without any mishap. In two cases of marked cyanosis with breathlessness, the patients were admitted to hospital for a few days with cessation of treatment. Spectroscopic examination of the blood failed to reveal any abnormal bands. In most of the cases the breathlessness was noticed only on exertion.

Numbness and tingling of the fingers and toes were complained of by a little more than one per cent of cases of either sex during treatment. There was no definite peripheral neuritis.

Diminished acuity of vision was present in six cases—all males; but, in only one case after four days of therapy, the ophthalmologist reported early optic neuritis with a central scotoma for blue in the left eye. With the stoppage of treatment the vision returned to normal in all the cases. In the other five patients, the complaint was purely subjective and came on after the second or third day's therapy.

There were four cases of *vestibular dysfunction* characterized by vertigo, tinnitus and slight deafness, which passed off. This mild occasional toxic involvement of the optic and the auditory nerves, is usually evanescent and the treatment was in no way interfered with.

A solitary case of *herpes zoster* in the distribution of the seventh dorsal nerve in a woman who was treated for a particularly resistant type of Neisserian infection was seen in the clinic. The complication occurred on the seventeenth day of treatment after a total dosage of 51½ gm. of sulphanilamide. The condition was accompanied by mild fever, headache, severe neuralgic pain along the nerve and intense burning over the crops of herpetic vesicles. Treatment was stopped and the condition subsided gradually with forcing of fluids and glucose and exhibition of vitamin B_1.

Clinical acidosis has not been encountered in any of our cases since it has been the routine practice to prescribe an alkaline mixture to be taken along with the sulphanilamide.

In about 0.8 per cent of either sex, gastro-intestinal upset and diarrhœa were prominent minor reactions of the drug.

Some of the minor reactions like *giddiness, headache, nausea* and *vomiting* were complained

of by the patients in the first two or three days of therapy, but tended to disappear with the continuation of the treatment.

A minority of patients complained of pain in different parts of the body, chest, abdomen, joints and muscles.

Mental disturbance, a sort of toxic psychosis, in the form of mental confusion was observed in one case of drug dermatitis associated with breathlessness. Muscular weakness was found to be twice as common in women patients as in men, but it did not interfere with the maintenance of therapy.

Toxic hepatitis with or without jaundice was conspicuously absent with sulphanilamide in our series, but two cases of jaundice were met with among a smaller number of selected paying cases treated with sulphapyridine in the clinic. As only 30 cases were under sulphapyridine treatment during the period under review the toxic complications of this drug are not included in this study.

Comment.—The incidence of the toxic complications of sulphanilamide seems to be almost equally distributed between the sexes with a slight preponderance of the blood dyscrasias in women. Taking agranulocytosis alone, the incidence in women is one in about 500 patients, whereas in men it is about one in 5,000 patients. The danger of this often fatal complication seems to be ten times more frequent in women. It is obvious from the analysis of the toxic reactions that with the single exception of agranulocytosis the other toxic effects of sulphanilamide therapy are not grave reactions jeopardizing life. In most of these cases the treatment could be safely continued with proper precautions with or without a certain interval of rest. We are also convinced that, with the exception of agranulocytosis, the other toxic manifestations occurring in the first two weeks of therapy can be recognized by daily and careful observation of the patients. An attitude of over-cautiousness seems to prevail among sections of the medical profession regarding the dangers of the new chemotherapy. It is our opinion that sulphanilamide and its derivatives should be used with greater resolution than has hitherto been shown and that clinicians should not hesitate to administer this drug in therapeutically adequate doses. Having said so much it is essential to emphasize that patients receiving sulphanilamide or one of its derivatives should be kept under daily and careful observational control. Enquiry should be made for symptoms such as fever, headache, malaise, vomiting and pain. Examination of the skin for rash, of the mucous membrane for pallor or jaundice, and observation of the temperature for drug fever, should form part of the daily routine of sulphanilamide therapy. As many of the toxic manifestations occur towards the end of the first week of treatment, observation of the patient should be more detailed and careful from and after the end of the first week.

It has been our routine practice to have a blood count performed at the end of the first and second weeks of therapy, or whenever the patient develops fever, rash, breathlessness, or suffers from the persistence or increase in severity of a minor toxic manifestation such as headache or vomiting, etc. Daily blood counts are no doubt ideal, but, in the exigencies of the out-patient venereal practice, when 200 to 300 patients have to be dealt with and disposed of daily, blood examination on an average of 100 patients who would be receiving sulphanilamide for one or the other of the venereal diseases, would be a terrible strain on the medical staff of the department.

Since our analysis of the drug rash has shown that nearly a third of the skin eruptions is of the light-sensitive type, patients should be strictly warned not to expose their naked skin to direct sunlight during sulphanilamide treatment.

In conclusion, the clinician should bear in mind that if a patient has drug fever, rash, leucopænia, cyanosis, or persistence of a seemingly minor trouble such as vomiting and diarrhœa, the drug should be immediately stopped; and the rapid excretion of the drug should be promoted by the ingestion of fluids and glucose. Oral administration of nicotinic acid has been recommended both for prevention and the treatment of the toxic complications of sulphanilamide and its derivatives. In cases where further therapy is indicated, either the same drug or one of its other derivatives in a much smaller single dose should be cautiously administered and a watch should be kept for the recurrence of the toxic manifestations.

SUMMARY

1. An analysis of the toxic complications of sulphanilamide therapy in the venereal department of the Government General Hospital is attempted.

2. Over 6,000 cases of both sexes who had received between them 2,70,000 grammes of sulphanilamide are reviewed.

3. Some of the complications are discussed in detail, particularly the cutaneous reactions and the blood dyscrasias.

4. The much greater frequency of the light-sensitive type of sulphanilamide rash is noted.

5. A plea is made for an optimistic attitude towards the new therapy and for the use of the drug in therapeutically adequate doses.

6. Necessity for daily careful observation of the patients receiving the new therapy aided by frequent blood count estimation is stressed.

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A STUDY OF CARDIAC SOUNDS AND MURMURS IN SEVERE ANÆMIA

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THE presence of cardiac murmurs in cases of severe anæmia is a very common finding. The murmur is mostly a systolic one, heard best at the mitral area. So frequent is its occurrence in cases of anæmia, that this murmur is called a hæmic murmur.

In the present series of cases an attempt was made to study the cardiac sounds and murmurs in anæmias, and also to see the frequency and character of the diastolic and pre-systolic murmur in these cases. Again, an attempt was made to correlate the blood picture with these murmurs. With this end in view, frequent blood counts were made and the cardiac changes recorded daily or less frequently.

An interesting finding was the presence of diastolic murmurs. These diastolic murmurs in cases of anæmia have always been regarded sceptically by clinicians, and their *modus operandi* is not well understood. It was found in some cases that a pericardial rub was also detected with the diastolic murmur. Both the rub and diastolic murmur cleared up on treatment of the anæmia, showing that they were not due to any organic lesion of the heart. In cases where a definite diastolic murmur was detected, an electro-cardiogram and teleradiogram were taken to find out if there was any chance of the lesion being an organic one.

Technique

1. *Selection of cases.*—Only cases of very severe anæmia likely to give a total red cell count of about a million per c.mm. were selected. Ankylostome cases were preferred because they present varying grades of anæmia, are mostly free from other complications and are more amenable to treatment. Cases of other types of anæmia were also included and thus the report represents fairly the conditions prevalent in this part of the United Provinces.

Cases of anæmia of pregnancy were avoided because of the alteration in cardiac findings in these cases due to enlarged abdomen. For this same reason cases with ascites had to be excluded.

2. *Examination of cases.*—After a careful clinical examination a detailed blood study was undertaken. All blood studies were carried out by using counting chambers and pipettes which were certified by the United States Bureau of Standards to be correct. For hæmoglobin estimations, Hellige's hæmometer was selected using Sahli's standardized scale so that 14.5 gm. were equivalent to 100 per cent (Wintrobe, 1930).

The detailed blood investigation consisted of the following observations repeated bi-weekly, or less frequently:—Total red cell and white cell counts, hæmoglobin estimation, differential leucocyte count and the general blood picture, the average cell diameter by Eve's halometer, and the reticulocyte percentage; the last named was repeated daily during the early stages of anti-anæmic treatment.

3. *X-ray findings.*—Teleradiogram and electro-cardiogram were taken under standard conditions in the *x*-ray department of King George's Hospital. For the teleradiogram, the patient was kept in the erect posture; he was instructed to take shallow breaths. After his initial excitation, due to new surroundings, had passed off, he was instructed to hold his breath in mid-inspiration when the plate was exposed (White, 1937).

Observations

A very frequent finding was the presence of murmurs, mostly systolic, which either disappeared altogether or altered in character with the improvement of anæmia. The murmur was systolic, as mentioned above, and was best heard on left side of chest about the fourth intercostal space, though in a fair number of cases it was equally well heard in the pulmonary area. However, murmurs other than systolic were also found.

Three cases in the series presented a definite diastolic murmur which was sharply localized to the apex. These cases were carefully observed and electro-cardiograms and teleradiograms taken (plate XVII, figs. A, B, and C and plate XVIII, figs. 1, 2, and 3) but no evidence of any organic lesion could be found. On the contrary, it was shown that the murmurs were functional only, since they disappeared a few days after admission. In two of these cases the murmur disappeared on improvement of anæmia, while in one case it developed after blood transfusion, and disappeared a week later.

One case (case 2) presented a pericardial rub along with a diastolic and systolic murmur at the apex. She looked a typical case of mitral lesion with secondary failure but electro-cardiogram and teleradiogram showed no mitral involvement. The case proved to be a functional one by the complete disappearance of all signs and symptoms on her regaining the normal blood count, and when seen eight months

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