SECONDARY SYNDROME OF CHEMOTHERAPY

A CASE OF SULPHONAMIDE HYPERSENSITIVITY

BY

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Lewi (1949) has grouped a number of cutaneous and visceral incidents (ninth-day erythema, toxic rash, agranulocytosis, nephritis, hepatitis, encephalopathy, etc.) occurring in patients during chemotherapy under the name of "secondary syndrome of chemotherapy." This syndrome is a clinical expression of an alteration of bodily response to certain chemotherapeutic agents resulting in generally well-known manifestations of drug-hypersensitiveness. All the factors involved in the pathogenesis are not yet fully understood, but it is clear that the final clinical picture is the resultant of the specific reactions of organs and tissues involved. That this is so will be clearly seen from the history of the case reported below.

To simplify the description of the case history the clinical facts have been grouped into five stages. It is realized that this subdivision into stages is in a way an artificial one, if only for the fact that, chronologically, different phases overlapped, as will be seen from the dates given with each stage.

Case Report

A building-labourer aged 41 was admitted to hospital on July 31, 1949, suffering from severe dermatitis of his arms, legs, and face. There was nothing relevant in his past history; he had never had sulphonamides before, nor had he had any allergic reactions. The history of his present illness was as follows: Following exposure to strong sunlight on a hot July day his face, neck, forearms, and hands became seriously burned. He consulted his doctor, who on July 27 prescribed sulphanilamide powder for infection prophylaxis; the powder was applied locally to the affected skin for three consecutive days. On July 31 the skin condition became unexpectedly worse, and the patient was advised to seek admission to hospital.

Stage 1 (July 31 to August 10): Sensitization Dermatitis.—The dermatitis affected only those parts of the skin surface of the body which, unprotected by clothes, sustained sunburns. The forehead, face, neck, forearms, and hands showed acute weeping eczematous lesions with bullae and oedema. There was slight pyrexia (99.2°F — 37.3°C .), but the general condition was unaffected except for exhaustion from lack of sleep. The urine was normal, though a trace of porphyrins was found on two occasions. Treatment included rest in bed, removal of remaining sulphanilamide powder from the skin, lotio glyc. plumbi subacetat. in daytime and zinc cream at night. He was also given "benadryl" 50 mg. t.d.s., phenobarbitone $\frac{1}{2}$ gr. (32 mg.) t.d.s., and intramuscular injections of crystalline penicillin (this was discontinued after three days). The response to treatment seemed satisfactory.

Stage 2 (August 4–10): Toxic Erythema.—On the fourth day after admission an erythematous rash appeared and spread to all parts of the body. The eruption was particularly noticeable on the chest, shoulders, and abdomen. No special treatment was prescribed. The rash started to fade after August 10.

Stage 3 (August 15–20): Bronchial Asthma.—Whilst the skin continued to improve, a sudden rise of temperature to 102°F . (38.9°C .) occurred on August 15, and the patient complained of a sore throat, headache, dry cough, pain in the chest, and dyspnoea. Auscultation revealed the presence of rhonchi and sibili, and a chest skiagram showed generally streaky lung fields. In the evening of August 16 the temperature rose still higher (104°F .— 40°C .) and the chest symptoms became more pronounced. The R.M.O. saw the patient and ordered sulphatriad, an initial dose of 2 g. being given, followed by 1 g. four-hourly.

Not unexpectedly, after the fifth dose weeping reappeared on the face, neck, and forearms; and the almost completely faded erythema spread and formed in new areas. Asthmatic attacks supervened with marked respiratory distress, tachypnoea, wheezing, and spasmodic cough. Physical signs in the chest were consistent with bronchial asthma. A differential white blood count showed leucocytosis (26,000 per c.mm.) with pronounced eosinophilia (21% eosinophils).

Stage 4 (August 20–23): Migraine.—Even before August 20 the patient complained of occasional headache, but now the pain in the head and temples became severe, paroxysmal, and obstinate, and was accompanied by photophobia and nausea. This headache was not unlike migrainous cephalalgia. Examination of the central nervous system was negative.

Before the fifth and final phase of the syndrome appeared the patient seemed to progress satisfactorily. He became afebrile, the eczema stopped weeping, and the erythematous eruption had disappeared and been replaced by fine desquamation seen on the trunk and limbs. Mild asthmatic attacks, however, continued to recur at irregular intervals, but these were now easily controlled by adrenaline injections.

Stage 5 (August 23 to September 7): Periarthritis Nodosa.—Haematuria was first noticed on August 23, and thereafter red blood cells and leucocytes were found repeatedly in the urine. On August 24 the patient drew my attention to painful swellings on his legs and thighs. Closer examination showed that they were formed by subcutaneous nodules, 0.5–2 cm. in diameter, reddish and tender. Scanty at first, they became more numerous towards the end of August, at which time nodules in various stages of development and healing could be demonstrated. It is unfortunate that no biopsy of a nodule could be made; thus no histological verification of periarthritic lesions can be given. Clinically, the skin lesions were very suggestive of the condition and were like those seen by me in a proved case (Suchett-Kaye, 1948); they corresponded also to the description given by Nicaud (1946). At this stage the patient ran a slight temperature (99 – 100°F .— 37.2 – 37.8°C .), and blood examination showed both leucocytosis and eosinophilia of marked degree (August 26: white cells, 42,000 per c.mm.—polymorphs 28%, eosinophils 57%, lymphocytes 12%, monocytes 3%).

On September 2 the temperature returned to normal and remained so during the rest of the patient's stay in hospital. On September 9 he was free from eczematous lesions, headache, and asthma, and his urine contained only an occasional red blood cell. On the lower limbs the subcutaneous nodules disappeared and were replaced by a brownish pigmentation over which the skin felt somewhat leathery. This pigmentation could still be found six weeks later, though it was much less pronounced.

After his discharge from hospital on September 9 repeated examinations showed that the blood and urine were perfectly normal. It should be noted in particular that the eosinophilia completely disappeared. The patient has returned to his normal work.

Discussion

What is the mechanism by which sulphonamides are capable of producing a sequence of clinical events as described in this patient? So far as the early eczematous and erythematous lesions are concerned, there is no doubt that the burns caused by solar irradiation contributed greatly to their onset by facilitating percutaneous sulphanilamide absorption.

The cutaneous sensitization phenomena and other manifestations of sulphonamide hypersensitivity, such as bronchial asthma, migraine (? encephalopathy), blood eosinophilia, and periarthritis nodosa, have for some time been considered to be due to anaphylaxis and allergy. The allergic and anaphylactic factors have come recently into prominence through the observations published by Rich (1942a, 1942b) and Rich and Gregory (1943). The warning given by Rich that repeated administration of a sulphonamide after symptoms of hypersensitivity have appeared

carries the danger of producing vascular damage of the periarteritis nodosa type was borne out by the present case.

The oral administration on August 16 of a few grammes of sulphatriad followed by the alarming signs described in stage 3 was of almost experimental value in demonstrating the abnormal bodily response as seen in anaphylaxis. That this should have expressed itself clinically by fever, prompt reappearance of the rash, bronchial spasm, eosinophilic leucocytosis, periarteritis-nodosa-like skin lesions, and haematuria is in complete agreement with observations by Rich and many other workers. The way in which sulphonamides act has been clarified by Wedum (1942). He suggested that sulphonamides can attach themselves to plasma proteins and form antigens capable of sensitizing the body specifically. Such a combination of sulphonamides with human serum proteins had been effected in the laboratory (Wedum, 1942).

In recent years attempts have been made to find a common pathogenic basis for manifestations of drug hypersensitiveness and certain haemorrhagic phenomena occurring during or shortly after specific fevers (for example, purpura fulminans in scarlet fever). The search has led to the rediscovery of the role of the Sanarelli and Schwartzman phenomena in human pathology (Lewi, 1948, 1949; Boelter and Hatoff, 1949). Alechinsky (1939) has repeated Sanarelli and Schwartzman's experiments and demonstrated that the two phenomena are identical and not dependent on allergy or anaphylaxis. It is Lewi's merit to have introduced the conception of sanergy (San(arelli) and -ergy, to denote reaction) to describe an altered bodily reaction to certain drugs and bacterial toxins; the reaction is thought to be produced in a manner similar to that operating in the experiments on animals performed by Sanarelli in 1894 and by Schwartzman in 1927. It seems that the autonomic nervous system is the principal mediator in the Sanarelli-Schwartzman type of reaction, but the intimate mechanism of this mediation is not yet quite clear. The problem became more complex when it was realized that allergic sensitization may supervene on top of the Sanarelli-Schwartzman phenomenon.

In the above case the clinical manifestations described in stages 1 and 2 were undoubtedly due to allergic sensitization; but, in the light of Lewi's concept, it could be argued that the sulphonamide administered to the patient on August 16 acted as a precipitating sanergen, producing in a highly sensitized subject a sanergic reaction (the locally applied sulphonamide powder was the sensitizing sanergen), with such complications as toxic rash, bronchial asthma, and periarteritis nodosa. In the absence of histological verification of the latter, the existence of sanergic periarteritis nodosa is very problematical.

It is well, however, to bear in mind that in some patients receiving chemotherapy (antibiotics should be added) a state of sensitization can sometimes be established in which further treatment with the same or related compounds will result in a sanergic, as distinct from anaphylactic, reaction—that is, in essentially haemorrhagic lesions. These would be either of a general nature (Sanarelli), such as haemorrhagic purpura, visceral haemorrhagic lesions, vascular necrosis, nephritis, etc., or local in extent (Schwartzman), such as skin lesions at the site of application of the sensitizing sanergen. In other words, some patients during chemotherapy, when certain favourable factors are operating, can behave in the same manner as the suitably prepared rabbits in the Sanarelli-Schwartzman experiments. It is hoped that elucidation of these facts may lead to rational

treatment and especially to prevention of the secondary syndrome of chemotherapy.

Summary

An unusually severe case of sulphonamide hypersensitivity is reported, and its clinical manifestations are described under the name of the secondary syndrome of chemotherapy (Lewi, 1949). The pathogenic mechanism is discussed with reference to the theories of allergy and Lewi's sanergy.

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ANAESTHESIA FOR CARDIAC CATHETERIZATION IN CHILDREN

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The use of cardiac catheterization and angiocardiology in the investigation of children with congenital cardiac defects is increasing rapidly as its value becomes apparent.

It has been considered by us that children under the age of 5 and in all probability up to the age of 12, depending on their mental development and temperament, require an anaesthetic to allow the investigations to take place, and it is hoped that this article may be of value to anaesthetists when first confronted with this problem.

The investigation entails the passage of a catheter into a vein, usually an antecubital one, and thence into the right heart and the vessels arising therefrom, under x-ray control. Blood samples are taken for gas analysis and pressures are recorded at suitable points. If an angiogram is required the catheter is withdrawn until a few inches remain in the vein, when an adequate dose of contrast medium is injected and rapid serial radiographs are taken of the heart and great vessels. This may be done in the antero-posterior position, in either oblique position, or, where it is considered necessary, any two may be done consecutively. The whole investigation may last from 1½ to 2 hours.

In attempting to devise a safe yet simple technique of anaesthesia for these cases certain problems had to be overcome: (1) the use of an x-ray plant precludes the use of all explosive anaesthetic mixtures; (2) the technique of blood gas analysis necessitates the use of non-volatile agents; (3) the subject, usually cyanosed, is a poor-risk patient; (4) despite this, except in an emergency, pure oxygen should not be administered, as the extra oxygen dissolved in the plasma may render the gas analysis inaccurate; and (5) the injection of the contrast medium may shock the patient.

When these problems were first tackled rectal bromethol ("avertin") was used. It was unsatisfactory because even with a dose of 0.12 g. per kg. of body weight—the