This lack of agreement has probably been due to two variable factors. In some experimental trials water-soluble vitamin-K preparations were regarded as effective when the anticoagulant was given in minimum active quantities. There is good evidence that this is so (Shapiro *et al.*, 1943), but little that they are effective against therapeutic doses of dicoumarol. The second variable factor has been the expected response to administration of vitamin K. Many writers have considered adequate a response demonstrable in the course of days and have been content to advise the use of the water-soluble preparations. Our own findings on the inadequacy of these preparations and the greater reliability of vitamin K₁, together with evidence presented by others on the use of vitamin K₁ or its oxide, seem to justify the conclusion that there are only two known effective means of treating hypoprothrombinaemia induced by dicoumarol or tromexan. These are by transfusion of blood or by administration of vitamin K₁ or its oxide.

In view of the fact that transfusion, to be effective, involves the use of blood or of frozen fresh plasma from possibly more than a single donor, and that thereby delay may often occur in beginning adequate treatment, there is some justification for regarding a suitable preparation of vitamin K₁ or its oxide as an essential material in any department in which treatment by dicoumarol or tromexan is being carried out. Neither vitamin K₁ nor its oxide is available commercially, but it could doubtless be made so, and, as has been shown (Shoshkes *et al.*, 1950), a convenient, effective, and stable emulsion can be prepared for intravenous use. No reliance should be placed on the use of larger doses of the synthetic water-soluble vitamin-K analogues. The action of vitamin-K preparations against the hypoprothrombinaemic effect of dicoumarol or tromexan is not simply a matter of dosage. There is a difference in the action of water-soluble and oil-soluble preparations which has not so far been explained except that it has been related to the presence of the "phytyl" group in the molecule of vitamin K₁ (Miller *et al.*, 1950).

Summary and Conclusions

The effect of certain substances with vitamin-K activity in modifying the action of dicoumarol and tromexan has been investigated in the human subject. The vitamin-K preparations employed were vitamin K₁, menaphthone, acetomenaphthone, kapilon, synkavit, and water-soluble K analogue (Boots).

Apart from vitamin K₁, these substances have been shown to possess a minor and inconstant ability to modify the action of these anticoagulants. Vitamin K₁, on the other hand, is a reliable and efficient antidote, and is capable of completely blocking the action of therapeutic doses of dicoumarol and tromexan, and capable of restoring to safe levels within a few hours excessive hypoprothrombinaemia due to these drugs.

Since these differences between the vitamin-K preparations are not merely a question of dosage, of all the substances tested here only vitamin K₁ can be regarded as a reliable antidote for a hypoprothrombinaemic emergency.

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ACQUIRED SENSITIVITY TO PARA-AMINOSALICYLIC ACID

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Since the widespread use of *para*-aminosalicylic acid (P.A.S.), either by itself or in conjunction with streptomycin, in the treatment of pulmonary tuberculosis, reactions have occurred which indicate that it is possible to distinguish two groups of cases.

First there are those patients with a natural intolerance to P.A.S. who develop gastro-intestinal symptoms during the first few days of treatment. As reported by Lehmann (1947) nausea is the symptom most frequently encountered, and may be accompanied by vomiting and diarrhoea in cases which exhibit a greater intolerance to the drug. Nagley and Logg (1949) pointed out that these effects are often due to impurities in the preparation of the drug and are seldom so severe as to cause abandonment of P.A.S. therapy.

Secondly, there are a few patients who develop an acquired allergic sensitivity to P.A.S. In these cases the onset of symptoms is characteristically sudden and usually occurs between two and four weeks after the beginning of treatment. Drug fever, with a rise of body temperature to 100–103° F. (37.8–39.4° C.), and symptoms of a marked constitutional disturbance are the usual features of this type of reaction and are commonly accompanied by a pruritic skin eruption as reported by Kierland and Carr (1949). Other toxic effects which have been recorded include renal damage (Nagley and Logg, 1949), hepatitis and enlargement of lymphatic nodes (Cuthbert, 1950), and lowering of the serum potassium (Cayley, 1950).

Case Report

The following case of an unusually severe sensitivity reaction to P.A.S. recently occurred at the Brompton Hospital.

A draughtsman aged 29 was admitted with the following history. He had developed pulmonary tuberculosis involving the right lung in 1944, for which he was treated by rest for 10 months at the Royal National Sanatorium, Ventnor. During this time a right artificial pneumothorax was induced, but this was abandoned after two months owing to the formation of an effusion. He subsequently returned to work and remained well until January, 1951, when, following a febrile coryza, he had a sudden haemoptysis of about 1 oz. (28 ml.).

Treatment consisted of rest in bed at home, and in March he began treatment with P.A.S., 18 g. daily by mouth. Three weeks later he had an evening rise of temperature, followed in two days by nausea, vomiting, and headache, and four days later by a morbilliform rash and pyrexia rising to 104° F. (40° C.). P.A.S. was discontinued, and the pyrexia and rash subsided on treatment with mepyramine hydrogen maleate ("anthisan").

One week later, while still receiving mepyramine, 100 mg. thrice daily, he was given two 3-g. doses of P.A.S., and within six hours the temperature rose to 102° F. (38.9° C.) and the rash returned. Despite discontinuation of P.A.S. the pyrexia and rash persisted, and five days later there was tender enlargement of the cervical, axillary, post-occipital, inguinal, and epitrochlear lymphatic nodes accompanied by sore throat, epigastric pain, and tenderness. The following

day he was clinically jaundiced, with a tender liver enlarged to 1 in. (2.5 cm.) below the costal margin. The rash, which became confluent on the face and neck while remaining morbilliform on the trunk, was accompanied by severe pruritus. The spleen was not palpable.

Investigations.—Urine: No albumin; excess urobilinogen and a small amount of bilirubin present. Serum bilirubin 4.5 mg. per 100 ml. Direct positive Van den Bergh reaction. Paul-Bunnell test, negative without absorption. Wassermann reaction and Kahn tests, negative. A blood count showed: Hb, 73%; red cells, 4,100,000; C.I., 0.9; white cells, 14,300 per c.mm. (polymorphs 34%, lymphocytes 48%, monocytes 2%, eosinophils 15%, basophils 1%).

Treatment was changed to diphenhydramine hydrochloride ("benadryl"), 50 mg. four times daily, and he responded with slow but steady improvement. Calamine lotion successfully relieved the pruritus. Within 10 days the temperature fell by lysis, the glands mostly subsided, clinical jaundice disappeared, and the liver became normal in size and no longer tender.

During the first week of treatment with benadryl the rash faded, pruritus ceased, and desquamation began on the face and neck, followed by desquamation on the trunk during the second week and on the arms and legs during the third week. Some glandular enlargement of the inguinal and axillary groups persisted until the desquamation on the limbs was complete.

By the end of the third week the serum bilirubin was 1.3 mg. per 100 ml., and the white blood cells numbered 16,400 per c.mm., but the lymphocytosis had subsided and the eosinophilia showed a decrease (polymorphs 60%, lymphocytes 20%, monocytes 10%, eosinophils 8%, basophils 2%).

Patch Tests.—At the conclusion of treatment, when clinically no manifestation of the sensitivity reaction remained, patch tests were performed (see Table). Two cases were selected as controls. Control 1 was a patient who had never received P.A.S. Control 2 was a patient receiving P.A.S., 18 g. daily, who had shown no manifestations of sensitivity.

Patch Tests

Test	Patient Before Desensitization	Patient After Desensitization	Control 1	Control 2
Aqueous solution of P.A.S. 5% ..	++	0	0	0
Chloroform ..	0	0	0	0
Aniline ..	++	+	0	0
Para-aminobenzoic acid ..	+	0	0	0
P.A.S. 5% solution in chloroform ..	+++	0	0	0
Meta-aminophenol ..	++	0	0	0
Benzoic acid ..	0	0	0	0
Salicylic acid ..	+	0	0	0

For these tests P.A.S. was prepared as a 5% solution and the other reagents as equimolecular solutions in chloroform.

Desensitization.—The patient was successfully desensitized by giving graduated doses of P.A.S. by mouth. A single dose of 50 mg. was given on the first day, and this was increased by 50 mg. each day in divided doses. If pyrexia occurred the dose was halved the following day and then increased as before from the reduced level. When the daily dose of P.A.S. reached 1 g. it was increased by 0.5 g. each day until a satisfactory therapeutic dosage of 15 g. daily was obtained. After desensitization the patch tests (see Table) were repeated; they proved negative with the exception of a doubtful positive reaction to aniline.

Discussion

Patients who show intolerance to P.A.S. or associated impurities should be distinguished from those who develop an allergic sensitivity by the differences described above

in the mode of onset and severity of the reaction. Early recognition is important, because P.A.S. therapy may be continued safely despite mild gastro-intestinal symptoms, but should be withdrawn immediately if an allergic sensitivity develops, as otherwise it may be practically impossible to control the reaction.

Antihistamine drugs are generally found useful in the treatment of the sensitivity reaction once P.A.S. has been withdrawn, but, as Horne (1949) observed, they are insufficient to control it if P.A.S. therapy is resumed before the patient has been desensitized. Once sensitivity has developed, even a small dose of P.A.S. is enough to provoke a severe reaction. Madigan *et al.* (1950) reported this effect after a dose as small as 0.5 g. In the case reported above two 3-g. doses of P.A.S. were given after the patient had become sensitized, and, despite an adequate dosage of an antihistamine drug being maintained, a reaction of considerable severity occurred.

In sensitized patients, skin tests usually show a positive reaction to dilutions of P.A.S. of 5% and upwards and to dilutions of meta-aminophenol of 1% and upwards, as observed by Climie (1950). Positive results are still obtained with patch tests even after the clinical termination of a sensitivity reaction. After desensitization, however, patch tests become negative in most cases, although Climie reported a persistent reaction to meta-aminophenol.

The method of performing skin tests may influence the results obtained. The technique used in the cases reported here consists in applying to the skin a measured quantity of the reagent in solution in chloroform by means of a pipette and drying it in a current of air. The area is then covered with adhesive plaster, which is removed after 24 hours, and readings are made at 48 hours. This method has been found to give accurate results, and is relatively simple to carry out.

Patients who have developed sensitivity may be desensitized by giving small quantities of P.A.S. by mouth and gradually increasing the dose. A scheme beginning with 0.1 g. of P.A.S. daily was suggested by Madigan *et al.* (1950); this will improve the tolerance of the patient by slow stages until an effective daily dosage of P.A.S. is reached. In desensitizing the case reported above it was considered advisable, in view of the severity of the reaction, to use a modified method beginning with 50 mg. daily, and to increase the dose of P.A.S. more gradually up to the required therapeutic level of 15 g. daily.

Summary

A severe case of P.A.S. sensitivity is described. The manifestations were pyrexia, sore throat, pruritus, morbilliform rash, generalized glandular enlargement, jaundice, hepatomegaly, and epigastric pain, accompanied by a marked lymphocytosis and eosinophilia.

The response to antihistamine drugs and to desensitization is recorded.

Skin tests with P.A.S. and certain related chemical compounds were positive, but became negative after successful desensitization. The technique used for these tests is described.

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