

Platinum sensitivity: treatment by specific hyposensitization

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Summary

An analytical chemist developed respiratory tract and cutaneous allergy to complex salts of platinum in the course of his work.

Specific hyposensitization was achieved by means of intradermal injections of allergen given in increasing doses. During the course of injections he developed symptoms and signs suggestive of a serum-sickness reaction.

The immunological significance of these phenomena was investigated.

Introduction

Individuals who work with complex salts of platinum, such as ammonium hexachloroplatinate, are liable to develop symptoms relating to the skin and respiratory systems (Hunter, Milton & Perry, 1945; Roberts, 1951; Parrot *et al.*, 1969). These platinum salts are normally encountered only in the refining and analysis of platinum so that symptoms resulting from them are virtually confined to workers in the platinum industry. No symptoms arise through exposure to metallic platinum.

The cutaneous picture is usually one of transient urticaria or pruritic weals at the site of contact of solutions of the salts with the skin. Respiratory symptoms consist of rhinorrhoea, burning and itching in the eyes, cough, tightness in the throat and chest and episodes of overt asthma. The respiratory symptoms can be severe and at times disabling.

Case report

The patient, a healthy man of 35, works as an analytical chemist assaying the purity of platinum and other precious metals which have been obtained as by-products of nickel mining. He works mainly with ammonium hexachloroplatinate since the assay of platinum requires that the metal should be in a soluble form.

For the 7 years before his admission he had symptoms suggestive of hypersensitivity when he encountered complex platinum salts. Exposure to hexachloroplatinate or tetrachloroplatinate resulted in prompt sneezing, watering of the eyes, tightness in the chest and wheezing. If the salts came into contact with his skin he developed weals

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within a few minutes at the site of contact. It was often necessary for him to have time off work on account of his respiratory symptoms despite his taking great care to avoid spillage during the analytical procedure. He was suspected of allergy to platinum salts and on one occasion prior to being referred to this hospital he was prick-tested with what was said to be an 8% solution of ammonium hexachloroplatinate. A few minutes later he developed a reaction with severe tightness in the chest leading to transient unconsciousness. He recovered quickly with injection of adrenalin subcutaneously but felt unwell for at least 4 hr.

The patient reported that other workers in his firm have had similar symptoms and that the refinery workers are even more severely affected. Sometimes they are so disabled by respiratory symptoms that they require assistance into the open air to recover. Even passing the open door of the platinum refinery is sufficient to cause symptoms in those who are most sensitive. None of the workers have trouble with metallic platinum or with other precious metals or their salts.

The patient had no relevant past or family history and there was no history of an atopic tendency. Physical examination revealed a very healthy man with a low-grade *Trichophyton rubrum* infection of the left foot but with no other abnormalities. He is an instructor in swimming and diving in his spare time.



Fig. 1. Weal with pseudopodia 10 min after the intradermal injection of 10 ng of ammonium hexachloroplatinate.

Investigations

Hb 14.7 g/100 ml, WBC 6800/mm³ with normal differential, ESR 4 mm in 1 hour.

Skin tests. A single prick through a drop of ammonium hexachloroplatinate solution in a concentration of 1 µg/ml produced pruritus within 45 sec and a weal and flare reaction in 10 min. This was followed by an intradermal injection of 0.01 ml of this solution (10 ng) which resulted in an irregular weal with prominent pseudopodia (Fig. 1) and a surrounding flare. There were no systemic symptoms and by 1 hr the reaction had subsided and no further reaction at this site or elsewhere was seen over the course of the following 48 hr. A control subject injected intradermally with 100 µg of the salt showed no immediate reaction.

Progress and technique of hyposensitization

From the above investigations it was concluded that the patient was truly sensitive to the platinum salt used and that the observed manifestations were the result of interaction of the antigen with reaginic antibody with the liberation of histamine. It was

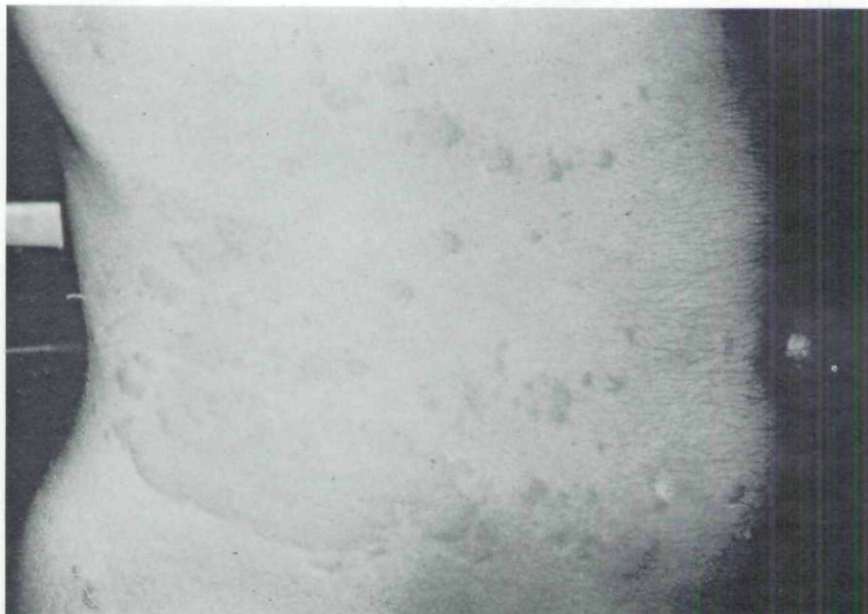


Fig. 2. Eruptive papules and plaques on abdomen. These appeared on several occasions during the course of injections. They began to appear about an hour after the forearm injection of platinum salt and persisted for up to 10 hr.

therefore decided to attempt modification of his sensitivity by injection of progressively increasing doses of antigen in the same way as one would attempt hyposensitization to pollen extracts in hay fever (Frankland, 1965) or to a drug causing anaphylactic allergy such as streptomycin (Levene & Withers, 1969).

He was given continuous antihistamine cover (chlorpheniramine maleate tablets, 12 mg q.d.s.) to minimize the effects of histamine release. Ammonium hexachloroplatinate solution in physiological saline was administered by intradermal injection into the flexor aspect of the forearm. If a particular dose caused a marked reaction, the

same dose was administered repeatedly until it no longer caused trouble. Three or four injections were given each day and the course was completed in just under a month. Each injection resulted in a prominent weal but the degree of flare tended to become less as the course of injections progressed. A noteworthy phenomenon was the appearance of transient induration and flare along the course of the lymphatics of the arm proximal to the site of injection. This occurred on numerous occasions throughout the course, it appeared about 15 min after injection and persisted for about half an hour.

A 200 ng dose on day 8 of the course caused coughing and wheezing after 10 min, but subsequent injection of the same dose and then higher doses caused only minor chest symptoms. On day 12, after a 5 μ g dose, he started to develop features of a serum sickness-like reactions. About an hour after the injection, the weal and flare having subsided, he produced pink, scattered, symmetrical, 'urticarial' papules and

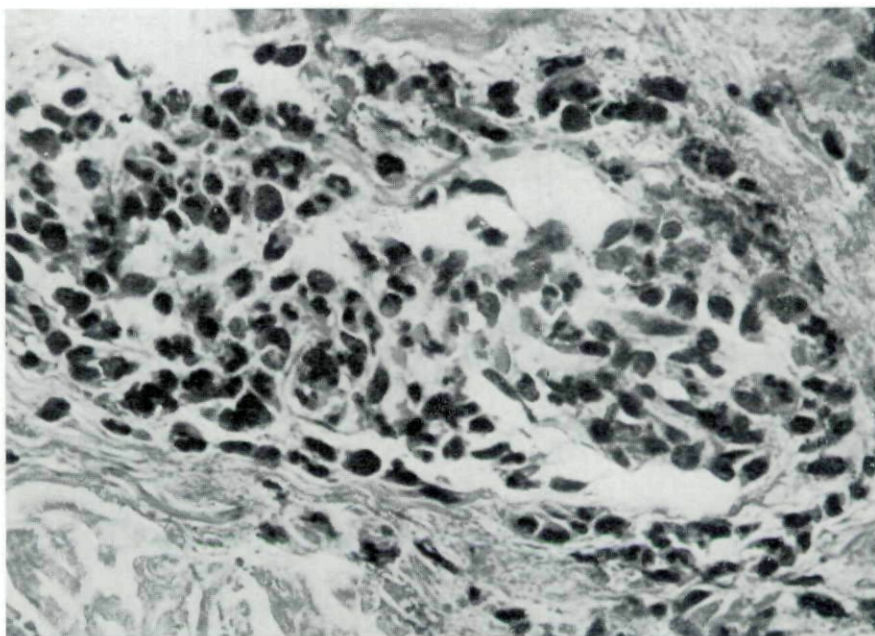


Fig. 3. Biopsy of an eruptive papule on the thigh 2 hr after a forearm injection of platinum salt. A dermal blood vessel is shown with intense polymorphonuclear infiltration, mainly of eosinophils.

plaques particularly on the neck, abdomen (Fig. 2) and thighs, burning and suffusion of the face, pressure in the ears, and tender swelling of the wrists, all of which persisted for several hours. The following day (day 13), with a dose of 10 μ g he had a similar episode with, in addition, tender swelling of the joints of the fingers and toes. Owing to personal commitments he then had a 5 day break from hospital. On his return, doses of 5 and 10 μ g were completely without untoward systemic effect but the injection site became indurated and brownish-pink from about 2 hr after administration. With higher doses scattered symmetrical red tender papules again began to appear from about an hour after injection. Biopsy of an eruptive papule on the right thigh taken 2 hr after the forearm injection showed a perivascular infiltration of polymorphonuclear cells, mainly eosinophils (Fig. 3). Biopsy of an eruptive papule taken 7 hr after

injection showed perivascular accumulation of neutrophils and eosinophils with scattered red cells and platelets consistent with the morphology of a vasculitis.

On day 22 he had his highest injected dose of ammonium hexachloroplatinate, i.e. 100 μg . This caused a transient local weal and irritation at the site of injection within a few minutes and moderate coughing and wheezing for an hour, and a tender papular rash on the neck, trunk and thighs starting 2 hr after injection. There was a further episode of pain and swelling of the finger joints. A further injection of the same dose was without respiratory side-effects. The injection sites developed into pink tender papules after an hour or so, but instead of subsiding as previously induced papules had done they became larger and much more tender over the following 24 hr and by 48 hr their central portions had become necrotic. The histology of one of these sites at 18 hr after injection showed that the vessel walls were infiltrated and occluded by an intense inflammatory reaction in which eosinophils predominated. A control subject injected with 100 μg of the platinum salt demonstrated a slightly raised and mildly erythematous area at 24 hr which subsided completely by 48 hr.

At this time it was decided that since the patient's immediate reactions had become minimal and had been replaced by a systemic reaction starting at least an hour after injection, the object of the course of injections had been achieved. Consequently on the twenty-ninth day after starting his course of injections a 'mock-up' of his working conditions was prepared in the laboratories of The Institute of Dermatology and he carried out his usual analytical procedure with ammonium hexachloroplatinate dissolved in acid. He was deliberately extremely sloppy in his technique to ensure maximum exposure and skin contact with the salt. Despite this the most he was able to provoke in the way of reaction was transient urticaria on the cheek. He had no chest symptoms from a degree of exposure which previously would have been guaranteed to make him incapable of work for the rest of the day. Even rubbing some of the platinum salt as powder into a fresh cut on a finger resulted in only local irritation lasting for 20 min. Having passed this crucial test he was discharged from hospital (12 May 1969).

He then returned to work and was able to perform all his usual techniques with ammonium hexachloroplatinate without any special precautions and completely without symptoms. Perhaps surprisingly, however, a chance exposure to ammonium tetrachloroplatinate caused sneezing, watering of the eyes and urticaria of the face lasting for 20 min. The patient then volunteered the information that a fellow worker in the laboratory had no symptoms with the tetrachloroplatinate but gave all the usual symptoms of sensitivity when exposed to the hexachloroplatinate.

The patient remained symptom-free for several months. However, in the late summer of 1969 there was a strike of nickel workers in Canada and as a consequence no supplies of platinum salt came his way for about 3 months. When he started using platinum salts again in November 1969 he had a recurrence of all his previous symptoms which became worse day by day, although they never achieved their previous severity. On account of this relapse it was decided to readmit the patient for a further course of hyposensitization injections to ammonium hexachloroplatinate. This was done during the first 3 weeks of 1970. The local and systemic responses to this course of injections followed the same pattern as those of the first course. A series of injections of ammonium tetrachloroplatinate was given in parallel with the above. Lesions produced by this salt were similar to those produced by hexachloroplatinate but were less marked. By the end of January 1970 the patient was able to handle both

of these platinum salts with impunity. He was advised on discharge from hospital to maintain a daily exposure to these salts to prevent the possibility of another relapse. He again returned to work and has remained symptom-free since.

Special investigations

Passive haemagglutination. Haemagglutination plates were set up using group O human erythrocytes conjugated with glutaraldehyde (Avrameas, Taudou & Chuilon, 1969) to hexachloroplatinate, tetrachloroplatinate and to ammonium tetrachloroplatinate-human serum albumin, prepared according to the method of Freedman & Krupcy (1968). Pre- and post-hyposensitization serum was added to these cells and progressive dilutions in physiological saline. No evidence of antigen-specific haemagglutination was obtained.

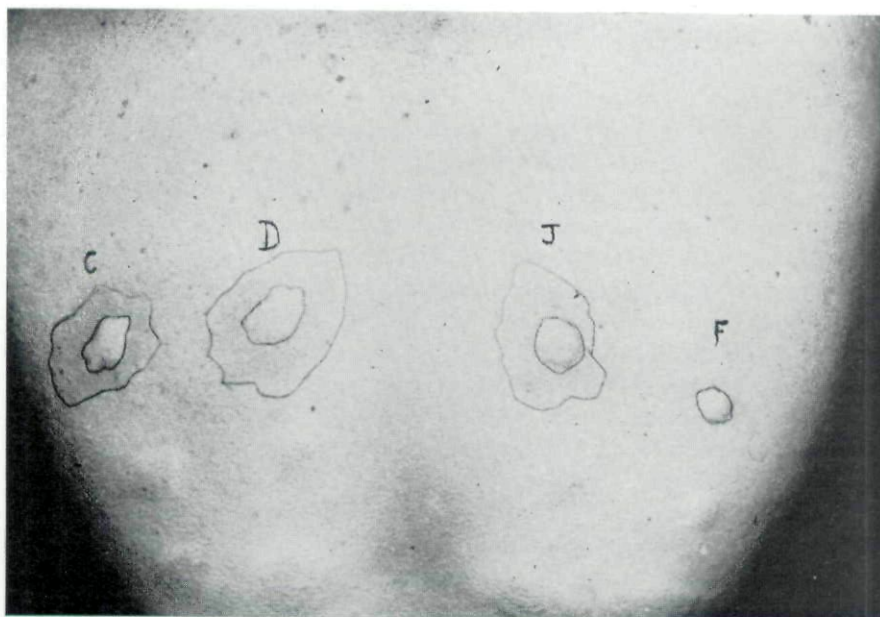


Fig. 4. Passive transfer test (see text) carried out 1 month after hyposensitization. Weal and flare reactions are outlined. C, platinum salt only (10 ng); D, platinum salt incubated with serum from December 1969 (pre-sensitization); J, platinum salt incubated with serum from January 1970 (during hyposensitization); F, platinum salt incubated with serum from February 1970 (post-hyposensitization). Incubation of platinum salt with post-hyposensitization serum has resulted in a much reduced response.

Double diffusion in Agar (Ouchterlony, 1964). Various dilutions of the two platinum salts and tetrachloroplatinate-albumin conjugate were set up against pre- and post-hyposensitization sera. No precipitation lines were observed after 48 hr.

Lymphocyte transformation. *In vitro* lymphocyte cultures were prepared as in Levene *et al.* (1969). To them was added ammonium hexachloroplatinate in saline solution in concentrations of 1–30 $\mu\text{g/ml}$ of culture for 6 days. No increase in [^{14}C] thymidine uptake was observed in cultures containing platinum salts compared with control cultures with no additions. The tetrachloroplatinate-albumin conjugate was

likewise without effect. Phytohaemagglutinin (PHA) added for 3 days to cultures prepared at the same time gave [^{14}C]thymidine uptake in the low normal range.

Passive transfer study. 0.1 ml of ammonium hexachloroplatinate solution in various concentrations was incubated for 30 min at 37°C with 0.1 ml samples of patient's serum obtained before, during and after the second course of hyposensitizing injections. Following incubation 0.05 ml of each sample was injected intradermally across the patient's back. It was found that 20 min after injection the weal given by the platinum salt solution incubated with the post-hyposensitization serum was appreciably smaller than those obtained using serum taken earlier, and that no flare was visible (Fig. 4).

Discussion

Reactions to platinum salts are distressing, occasionally dangerous and threaten the sufferers' livelihoods. Roberts (1951) investigated reactions in employees of a platinum laboratory and refinery in Malvern, Pennsylvania, seen over a period of 5 years. He used the term 'platinosis' for the syndromes he encountered and asserted that *all* the employees had the condition with 60% of them exhibiting clinical manifestations and the remainder having only minor involvement. He noted the variable times which workers were exposed to platinum salts before they developed significant symptoms and he observed that once disabling symptoms arose in any one case that person never again became asymptomatic in a platinum-salt-containing atmosphere. These findings concurred exactly with the previous findings of Hunter, Milton & Perry (1945) in London and both reports advised that sufferers from the effects of platinum salts should be transferred to other work.

It is necessary to consider evidence for the contention that the respiratory symptoms of platinosis in humans are those of an allergic reaction rather than those of non-specific histamine release, particularly since non-specific histamine release by platinum salts has been demonstrated in experimental animals (Parrott, Saindelle & Tazi, 1963; Parrott *et al.*, 1969). The evidence may be summarized as follows:

1. The duration of exposure to complex platinum salts before symptoms arise in any individual case is very variable.
2. There is often an increase in the severity of symptoms with repeated exposure.
3. It is reported that symptoms of platinosis are more likely to appear in people with an atopic disposition (Roberts, 1951; Parrott *et al.*, 1969).
4. In the case described here there was a marked immediate weal and flare reaction to a 10 ng dose whereas a control subject had no immediate reaction to a 100 μg dose.
5. The patient responded to a hyposensitization procedure with the platinum salt which was causing his symptoms in a manner analogous to that found using antigen producing known anaphylactic allergy.

It is also of interest to consider the possible immunological events associated with the observed reduction in anaphylactic-type hypersensitivity responses in this patient. It is suggested that repeated intradermal injections of the allergen has stimulated the production of non-anaphylactic IgG antibody ('blocking' antibody) which combined preferentially with the platinum antigen and thus prevented the anaphylactic symptoms associated with his previously dominant IgE type antibody. The strongest evidence in favour of the production of antigen-specific IgG antibodies is the emergence of physical signs which are strongly suggestive of a serum sickness-type reaction, i.e. the development of a generalized papular eruption and joint pains and swelling within a

few hours of administration of antigen and subsiding within 24 hr. The histology of the eruptive papules and the injection site showed a vasculitis with a perivascular polymorphonuclear infiltrate which is consistent with immune-complex deposition or an Arthus-like reaction in the dermis. However, it was not possible to demonstrate haemagglutinating or precipitating antibody by serological techniques. Nevertheless, incubation of antigen with post-hyposensitization serum and skin-testing with this material resulted in a very attenuated response compared with the reaction obtained using antigen incubated with pre-hyposensitization serum and pure antigen alone as a control. This indicates that antigen was being inactivated in its capacity to produce an immediate weal and flare and the hypothesis that such inactivation was the result of blocking antibody appears to be the most likely explanation.

The clinical picture and time-relationship of the start of lesions to injection of antigen were not in favour of a cell-mediated immune response in this patient and the lack of lymphocyte response *in vitro* to antigen in various forms and concentrations fails to provide any support for a delayed hypersensitivity response. Furthermore, there was no evidence at any time of an allergic contact dermatitis in this patient, a phenomenon known to be the result of a cell-mediated immune reaction.

Finally, in view of the fairly unpleasant reactions provoked during the courses of hyposensitization one must ask whether this form of treatment is justifiable in an otherwise healthy patient. The authors feel that since the patient has thereby been able to continue his skilled and highly paid occupation with no further symptoms it is justifiable to attempt this technique.

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