PRELIMINARY COMMUNICATIONS

Immunological Studies on the Mechanism of Gold Hypersensitivity Reactions

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British Medical Journal, 1973, 3, 676–678

Summary

Immunological studies were performed on 12 patients with rheumatoid arthritis who developed reactions to gold. IgE levels were found to be raised in 10 of 11 patients tested at the time of the gold reaction, returning to normal on stopping therapy. Two of 12 patients with gold reactions had positive in-vitro lymphocyte transformation responses to gold.

It is suggested that dermatological side effects in particular are mediated by a type I hypersensitivity response.

Introduction

Gold was first reported to be of value in rheumatoid arthritis by Forestier (1929). His findings were not universally accepted and the therapeutic value of gold was disputed until the favourable report by the Empire Rheumatism Council on a multicentre control trial of gold in rheumatoid arthritis (Empire Rheumatism Council, 1960). The major limiting factor in chrysotherapy is the high incidence of toxic and potentially serious reactions to gold. In a review of 7,693 patients (Freyburg, 1966) the overall incidence of adverse reactions was 32%, this being similar to the incidence of 35% reported by the Empire Rheumatism Council (1961). While dermatological reactions account for most of the side effects reported, blood dyscrasia, proteinuria, and colitis may also occur.

Despite the widespread use of gold and the high incidence of side effects, relatively little is known about the mechanism of gold toxicity. There is some evidence to suggest that gold hypersensitivity is immunologically determined. Denman and Denman (1968) suggested that cellular immunity may be involved. No evidence has been provided to date to implicate other immunological mechanisms.

A high incidence of oesinophilia in our patients with gold reactions has led us to investigate the possible role of immediate (type I) hypersensitivity. Parallel studies, using the lymphocyte transformation test, previously used for drug hypersensitivity (Sarkany, 1967) have also been performed on our patients with gold reactions.

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Patients

Fifty-five patients have received gold therapy in our rheumatology clinics during the past six months. Each one was carefully screened during the course of treatment by routine blood counts, urine testing, and inquiry into any unusual symptoms or skin lesions. Twelve of these cases (22%) developed side effects attributed to gold. Three male and nine female patients have been investigated. Mean gold dosage received at the time of developing the side effect was 657 mg (range 210-1,320 mg). Eight patients developed rashes, one pruritus, one mouth ulcers, and nine developed eosinophilia—mean level 1,120 (range 420-2,550) cells/mm^3. In three patients eosinophilia was the only side effect noted. A "control" group was provided by patients receiving gold for rheumatoid arthritis but without side effects.

Methods

RADIOIMMUNOSORBENT TEST OF SERUM IgE

Immunoglobulin E levels were estimated by the radioimmunosorbent test. The anti-IgE antiserum was raised in rabbits against purified IgE myeloma proteins (thanks to the kindness of Dr. S. G. O. Johannson and Dr. O. R. McIntyre). The antiserum was rendered specific for IgE by exhaustive absorption with insolubilized normal human serum, and the globulin fraction was precipitated using 18% w/v sodium sulphate at 25°C washed and redissolved to the original volume of antiserum. A 100 µl sample of this was coupled to CNBr-activated microcrystalline cellulose (Merck). For IgE standard, pure IgE standardized against W.H.O. material (68/341) was used (Rowe *et al.*, 1970). Pure myeloma IgE 13 µg was labelled with 1 mCi of ^{125}I by the method of Hunter and Greenwood (1962).

LYMPHOCYTE TRANSFORMATION TEST

Peripheral lymphocytes were separated from defibrinated blood on a Triosil-Ficoll gradient (Vischer, 1966). Lymphocytes were adjusted to a 1×10^6/ml concentration with TC 199 (Wellcome). The following cultures were set up in triplicate: (*a*) unstimulated cells; (*b*) cells stimulated with non-specific mitogen, phytohaemagglutinin (PHA); (*c*) cells stimulated with myocrisin (May & Baker), 2 µg and 4 µg/ml concentration; and (*d*) cells stimulated with PHA and containing 2 µg/ml myocrisin to determine any inhibitory effects. Cultures were incubated till the fifth day when 1 µcI of tritiated thymidine (Radiochemical Centre, Amersham) was added, and the cells were harvested on the sixth day. The cells were precipitated with 10% trichloracetic acid, dried with methanol, and dissolved in 0·5 ml of methanol and 10 ml of scintillation fluid before counting. The mean value of triplicate counts was taken.

Results

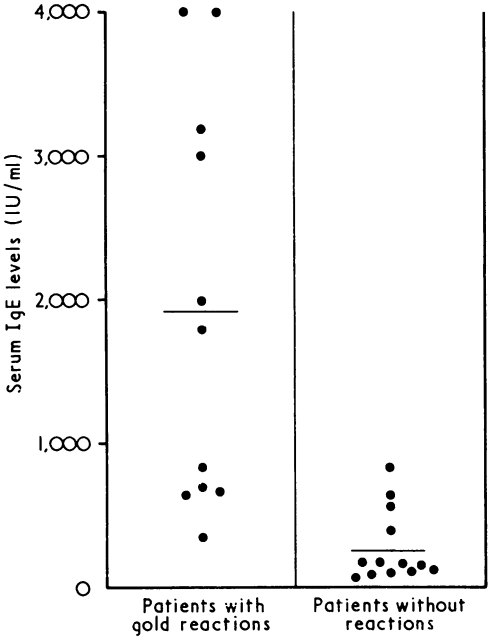
The IgE levels are given in the chart. Ten out of 11 patients who developed side effects while on gold had serum IgE levels above the 2 S.D. limit of normal ranging from 650 to > 4,000 IU/ml. When gold therapy was stopped all IgE levels fell to normal within two months. Only one of the patients in the control group had raised serum IgE at 850 IU/ml. None developed side effects.

The lymphocyte transformation results are shown in the table. Transformation was thought significant when stimulated

Lymphocyte Transformation Counts

Case Nlo	Unstimulated (Counts/min)	PHA (Counts/min)	PHA + Gold 2 μg (Counts/min)	2 μg Gold (Counts/min)	4 μg Gold (Counts/min)	Side Effects
Patients with gold reactions:						
1	664	1,043	1,320	1,251	589	Rash/eosinophilia
2	137	5,587	5,612	93	154	Rash/eosinophilia
3	114	2,830	2,624	46	73	Eosinophilia
4	33	11,409	7,669	11	50	Rash/eosinophilia
5	226	1,540	1,650	88	84	Mouth ulcers/eosinophilia
6	168	5,079	4,756	104	141	Eosinophilia
7	153	3,140	4,330	112	150	Eosinophilia
8	156	3,969	4,142	552*	476*	Eosinophilia
9	411	—	1,288	238	137	Rash
10	765	6,598	4,433	1,342	1,693*	Rash
11	343	6,628	6,165	290	239	Rash/eosinophilia
12	76	300	360	42	36	Rash
Patients without gold reactions:						
13	138	10.604	4,533	28	30	
14	316	1,635	940	300	109	
15	271	5,198	1,119	237	428	
16	113	1,280	1,030	124	121	
17	61	322	169	126	82	
18	171	7,370	6,787	174	133	

*Counts of double unstimulated counts.



Serum IgE levels in 11 patients with gold reactions compared with 13 patients on gold without reactions.

counts were at least double the unstimulated ones. This occurred in two of the 12 patients tested who had developed a gold reaction. Transformation in case 10 was noted two weeks before the development of the rash. No patient in the control group showed lymphocyte transformation.

Discussion

Raised IgE levels in patients developing gold reactions has not previously been reported. Abnormally high serum IgE levels together with eosinophilia acquired on gold therapy and remitting on gold withdrawal is suggestive of a type I hypersensitivity reaction. Type I reactions are well recognized in various allergic states and the combination of raised IgE and eosinophilia has been reported in tropical filariasis (Ezeoke *et al.*, 1973) and hay fever (Manners and Ezeoke, 1973).

Type I hypersensitivity reactions due to drugs are uncommon, though occasionally seen with penicillin reactions. The short half life of IgE may account for the rapid fall after stopping therapy, though eosinophilia may persist. At the present time there is no other explanation for the raised IgE levels in our patients. None of our patients was suffering from atopic states, there being no evidence of asthma, eczema, hay fever, or parasitic infection.

The lymphocyte transformation test has been widely used to determine patients' idiosyncracies to drugs (Sarkany, 1967). Previous studies of lymphocyte transformation to PHA on patients with rheumatoid arthritis receiving gold have produced conflicting results (Persellin *et al.*, 1967; Von Baenkler *et al.*, 1971). Our findings would support the view that gold therapy does not reduce lymphocyte transformation to non-specific mitogens.

The lymphocyte transformation test has been previously used to determine idiosyncracies to gold. Denman and Denman (1968) found positive lymphocyte transformation in all six patients who developed serious haematological reactions to gold and in one of six patients who developed rash while on gold. In addition, one of 12 patients who were receiving gold without reaction also had a positive rest tesult. This patient subsequently developed a rash. They concluded that their results supported an immunological basis for gold toxicity by showing the presence of lymphocytes involved in a delayed hypersensitivity response to gold. Von Schubert *et al.* (1971) reported positive transformation to gold in two patients developing dermatological reactions to gold, and in a single case report Waltzer *et al.* (1972) reported positive lymphocyte transformation in a patient who developed exfoliative dermatitis.

Positive lymphocyte transformation to gold was seen in only two of our 12 patients with gold reactions. It seems likely that most side effects in our patients were not mediated by type IV hypersensitivity.

In summary, our findings would support the theory proposed by Denman and Denman (1968) that most gold reactions are immunologically mediated. It appears likely that at least two separate immunological reactions are involved, and our findings suggest that dermatological side effects in particular are mediated by a type I response.

We are grateful to Professor E. G. L. Bywaters and to Dr. P. J. L. Holt for their encouragement and advice. This work has been supported by a grant from the North-West Metropolitan Regional Board.

We are grateful to Mrs. J. Andrews for secretarial help.

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MEDICAL MEMORANDA

Hypernephroma Presenting as Cardiomegaly

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British Medical Journal, 1973, **3**, 678–679

Hypernephromas are characteristically vascular tumours, and often contain numerous small arteriovenous fistulae and shunts. In most cases these shunts are not thought to be haemodynamically important, but occasionally they can be more extensive and give rise to cardiovascular manifestations. Up to June 1971 only 12 such cases had been described (Hamilton *et al.*, 1953; Myhre, 1956; Scheifley *et al.*, 1960; Abbott and Poutasse, 1961; Jantet *et al.*, 1962; Maldonado *et al.*, 1964; Nicoloff, 1964; Wise *et al.*, 1967; Norris *et al.*, 1971; Schoenfeld and Bernstein, 1971). We report a further case in which the presenting symptoms were related to the haemodynamic abnormality.

Case Report

A 51-year-old woman clerk was referred to Leith Hospital in September 1969. Routine chest *x*-ray pictures requested by her general practitioner had shown cardiomegaly. The patient admitted to only occasional exertional dyspnoea and slight cough. Previous medical history and family history were not relevant.

At examination she looked young for her years. She was not breathless or cyanosed. Pulse was 90/min, regular in time and force. B.P. 180/95 mm Hg, jugular venous pressure not raised. Apex beat not clinically displaced, but heaving in character. The pulmonary second sound was accentuated and a faint systolic murmur, maximal down the left sternal edge, was heard. There was no evidence of cardiac failure.

Investigations were: urine analysis, normal; full blood count, normal; E.S.R., 6 mm in the first hour; blood urea and serum electrolytes, normal. A chest *x*-ray picture showed well-marked cardiac enlargement, mainly of the left ventricle. Cardiac catheterization showed no evidence of valvular disease, but a high resting cardiac output of 10 l./min, and an oxygen saturation of 93% in the inferior vena cava. E.C.G. showed sinus rhythm with left ventricular hypertrophy.

At this time it became apparent that there was a mass about 10 by 8 cm palpable in the right hypochondrium, together with a thrill and audible bruit. Intravenous pyelography showed that the lower pole of the right kidney had been displaced upwards and laterally by an intrinsic mass.

Unfortunately the patient was temperamentally difficult and took her own discharge against advice.

In January 1971 she was again referred by her general practitioner, when there was no doubt that her condition had deteriorated. She was in congestive cardiac failure with atrial fibrillation and rapid ventricular rate; her B.P. was 130/80 mm Hg (several readings). The palpable vascular mass in the abdomen was now more obvious. She was readmitted and the cardiac failure was treated with diuretic and digoxin. At this stage she agreed to further investigation and treatment.

Arteriography showed a grossly dilated right renal artery plus a mass with abnormal circulation measuring roughly 15 by 15 cm in the right iliac fossa, with early filling of a greatly dilated renal vein.

The patient was transferred to the surgical unit of Leith Hospital, and nephrectomy through a right paramedian incision was performed in February. At operation all the branches of the renal artery could be identified exactly as shown in the aortogram. There appeared to be a fistula between the most medial (vertical) branch of the renal artery and the overlying renal vein. Sectioning of the kidney after operation showed it to consist of a rim of normal tissue balanced on a large "yellow sponge-like material," which on microscopical examination was shown to be carcinoma of clear cell (hypernephroma) type, with much vascularity.

The patient made good postoperative progress and was discharged home on 20 February on diuretic and digoxin. At that time her blood pressure was 120/70, and the E.C.G. showed controlled atrial fibrillation. She was subsequently followed up at the medical outpatient clinic and by July chest *x*-ray showed that the transverse diameter of the heart was reduced from 18 cm to 15 cm and the lung fields were clear. When seen in September her general condition was excellent. The diuretic was discontinued, but she still required digoxin.

Comment

Maldonado (1964) tabulated the clinical manifestations associated with arteriovenous fistulae in the functioning kidney. He recorded a total of 35 cases six of which were associated with renal carcinoma. A point to be noted from his series was the relatively low incidence of pain and haematuria among the clinical manifestations.

Of the reported cases of arteriovenous fistulae associated with renal carcinoma, the main clinical manifestations were intra-abdominal bruit, cardiomegaly, diastolic hypertension, and systolic cardiac murmur.

Obviously the findings are consistent with the haemodynamic changes found in all types of renal arteriovenous fistulae, but the most important fact drawn from these cases is that two-thirds of the patients with renal carcinoma did not present with urinary symptoms, but because of symptoms referable to the cardiovascular system.

The triad of mass, pain, and haematuria, which is the classical picture of renal carcinoma, was not an important finding in the patients and, as stated by Wise *et al.* (1967), "emphasizes the diagnostic importance of this manifestation, i.e. arteriovenous fistulae of renal carcinoma."

There was no doubt that selective renal arteriography played a major part in the diagnosis and subsequent surgical treatment of our case and the cases described by Wise *et al.* (1967).

Renal arteriography should therefore be regarded as an integral part of the investigations of all renal masses if arteriovenous anomalies are to be detected.

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I should like to thank Dr. R. F. Robertson and Mr. J. Cook for their advice and help in preparation of the case report, and for allowing me to use the information regarding their patient.