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## Cryoglobulinemia in Raynaud's Phenomenon due to Vinyl Chloride

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**Summary.** Raynaud's phenomenon was described in 22 workers engaged in vinyl chloride polymerization. Within this group, prodromal signs have been seen in 6 persons, typical Raynaud's syndrome in 10 persons. In the remaining 6 persons in addition to Raynaud's phenomenon sclerodermalike changes in upper extremities and acro-osteolysis of distal phalanges of fingers were observed.

Immunoelectrophoretic findings displayed increase in the levels of orosomucoid, ceruloplasmin, total lipids, and lipoproteins. Latent cryoglobulinemia, detectable after Sephadex G-200 filtration, was found in 18 sera (81.6%). The majority of precipitates was polyclonal, chiefly composed of immunoglobulin A and G. In 5 cases including 3 with acro-osteolysis a substantial increase in serum IgG level was seen. The authors express the opinion that Raynaud's phenomenon due to the toxic effect of vinyl chloride is conditioned by cryoglobulinemia. It is assumed that the toxic mechanism of vinyl chloride is due to disturbances in humoral resistance of the organism.

**Key words:** Vinyl chloride disease - Cryoglobulinemia - Raynaud's phenomenon.

Raynaud's phenomenon is the most frequently observed symptom of vinyl chloride disease; consequently sclerodermalike skin changes particularly in distal parts of extremities, acro-osteolysis of distal phalanges, thrombocytopenia, periportal liver fibrosis accompanied by secondary esophageal varices and pulmonary insufficiency may be seen [6,12,14,22].

Recently not only experimental investigations [23] but also clinical observations indicate, that vinyl chloride (v.c.) may have carcinogenic properties [4,23,24].

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Raynaud's phenomenon appears to be the earliest symptom of pathologic disturbances caused by vinyl chloride intoxication. The pathogenesis of vinyl chloride disease, and Raynaud's phenomenon particularly, is unknown.

This paper presents results of studies on pathogenesis of Raynaud's phenomenon due to vinyl chloride.

#### MATERIALS AND METHODS

Raynaud's disease has been found in 22 workers employed in polymerization of vinyl chloride. There were 18 men and 4 women. Affected personnel ranged in age from 22 - 61 years (average 34.2). Only 3 persons were over 50. The time of professional exposure to v.c. varied between 2 and 10 years (average 4.7). At the time of medical examination, 15 people have not been working with v.c. for periods of 2 weeks to 18 months. Five workers retired due to professional disease. In all the patients general medical and neurologic examination as well as capillaroscopy of nail beds were carried out.

The laboratory investigations have been directed toward detecting changes in serum proteins. They included total serum protein concentration, paper electrophoresis, immunoelectrophoresis with estimation of prealbumin, orosomucoid, anti-trypsin, haptoglobin, ceruloplasmin, and transferrin fractions. Other immunologic studies covered heterologic antiglobulins for sheep erythrocytes sensitized with rabbit antibody (SSE), homologous antiglobulins for latex covered with human gamma-globulin (latex fixation test), cold agglutinins [15], cryoglobulins in serum detectable by spontaneous precipitation at +40°C, as well as latent cryoglobulins, detectable after filtration of the serum through a Sephadex G-200 column and incubation of the effluent at +40°C [8].

The cryoglobulins were identified by their immunoglobulin set-up by immunoelectrophoresis double diffusion precipitation in gel in micromodification according to Scheidegger [21]. For immunoglobulin identification specific antisera for IgA, IgG, IgM Biomed-Poland have been used.

The concentrations of serum immunoglobulins A, G, M have been determined by single radial diffusion method using Behringwerke (GER) partigen plates.

#### RESULTS

According to the degree of clinical changes, 3 groups of patients could be observed. They display, respectively:

1. prodromal signs of Raynaud's phenomenon (n = 5);

2. typical
3. Raynaud's

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2. typical Raynaud's phenomenon (n = 6);
3. Raynaud's phenomenon, scleroderma-like skin changes and acro-osteolysis (n = 6).

There were 6 people in the first group. Four of them continued working with v.c., and the other 2 remained unexposed to v.c. for the last month. All patients reported that spontaneous coldness provoked numbness as well as having hypersensitivity to cold. Capillaries of nail beds in 1 case were spastic with atonic component, in another gigantic Raynaud's loops could be seen. Apart from hypoaesthesia of the dorsal part of the hand in 1 patient, no other neurologic disturbances have been found.

Among the 10 patients of the second group, 2 continued working with v.c., the others were removed from the professional exposure to v.c. for several weeks to 18 months. Apart from the same troubles as in the first group, here Raynaud's phenomenon was described as skin-blanching distal parts of upper and even lower extremities. This symptom occurred most frequently by cooling, rarely spontaneously in room temperature. The patients complained also of drowsiness, hyperexcitability, pains in the heart area, dizziness, periodic muscular and joint pains, stiffness of the hands. Capillaries of nail beds were spastic in 7 persons, with atrophic component in 2 of them. There were moderate vegetative skin changes in the distal parts of upper and lower extremities: the skin was unusually damp, cool, and pale. Hypoaesthesia of the fingers was found in 4 patients.

There were 6 persons in the third group; 5 of them retired on the grounds of suffering from professional disease and left the job with v.c. for periods from 6 - 18 months. Subjective symptoms were similar to those in the previous group. Apart from skin-blanching the patients complained of paroxysmal cyanosis and a feeling of stiffness of the fingers. Giant Raynaud's loops were observed in 3 persons, in 1 of them atrophic changes too. There were severe trophic troubles in distal parts of extremities. The skin was cyanotic, dry, or exceedingly damp, usually cold, fingers were thicker than normal, distal phalanx swollen, or shortened. In some patients the matrix of the fingernails was lacking.

Three patients had ropelike stiffening of the forearms, muscular atrophy of hands and forearms. Roentgenographically, acro-osteolysis in distal phalanges of fingers in all 6 patients has been found.

Concerning investigations of serum proteins the most frequent disturbances were cryoglobulinemia (83.8%), increased albumin in immunoelectrophoresis accompanied by unchanged albumin to globulin ratio (63.6%), increased oros mucoid

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Table 1. Vinyl chloride disease serum protein disturbances in 22 cases

| Kind of changes                                 | No. of cases |      |
|-------------------------------------------------|--------------|------|
| Cryoglobulinemia                                | 18           | 81.8 |
| Increase of albumins                            | 14           | 63.6 |
| Increase of orosomucoid                         | 12           | 54.5 |
| Increase of ceruloplasmin                       | 8            | 36.3 |
| Decrease of $\alpha_2$ - and $\beta$ -globulins | 8            | 34.3 |
| Increase of IgG concentration                   | 5            | 22.7 |
| Decrease of haptoglobin                         | 2            | 9.0  |
| Increase of haptoglobin                         | 1            | 4.5  |
| Decrease of antitrypsin                         | 1            | 4.5  |
| Increase of IgM concentration                   | 1            | 4.5  |

(54.5%) and ceruloplasmin (36.3%) fractions. The proteinogram displayed a small drop in the  $\alpha_2$ - and  $\beta$ -globulin fractions (36.3%) and increased immunoglobulin IgG level (22.7%) (see Table 1).

An increased level of total lipids (61%) and  $\beta$ -lipoproteins was noted as well.

At the stage of prodromal signs of Raynaud's disease, cryoglobulinemia was a general finding except in 1 person. Immunoelectrophoretic hyperalbuminemia with normal albumin to globulin ratio was coexistent with a threefold increased orosomucoid and a twofold increased ceruloplasmin level. In a single case a substantial increase of the immunoglobulin IgM (218.2 mg%) has been found (Table 2).

In advanced Raynaud's syndrome (second group), in addition to cryoglobulinemia (9x), the following changes were seen: Increased orosomucoid (6x) and ceruloplasmin (4x), both increased and decreased haptoglobin, decreased  $\alpha_2$ - and  $\beta$ -globulins (4x), as well as a clear increase of the immunoglobulin IgG level (2x) (Table 3).

In the third group (sclerodermalike changes) again cryoglobulin was evident (4x) as well as increased orosomucoid (3x) and ceruloplasmin (2x). The drop in the  $\alpha_2$ - and  $\beta$ -globulins was more frequent (4x). Special attention should be paid to the increase of class C immunoglobulins in 50% of the cases of this group (Table 4). In 2 sera no cryoprecipitates were found.

One of the sera belonged to a worker whose exposure to v.c. was stopped 18 months earlier. In the second case cryoprecipitates had been positive 12 months earlier. Since then exposure to v.c. had been stopped as well.

Table 2. Vinyl chloride disease. Clinical data in patients with prodromal signs of Raynaud's phenomenon

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Table 2. Vinyl chloride disease. Clinical data in patients with prodromal signs of Raynaud's phenomenon

| Case no. | Present case | Age | Exposure (yrs) | Total lipids (mg %) | S-lipoproteins (mg %) | Total protein (g %) | Paper electrophoresis (%) |          |          |            |            |         |          |                 | Immunoelectrophoresis |         |             |             |               |      |       |       | Cryoglobulins | Cold agglutinins |
|----------|--------------|-----|----------------|---------------------|-----------------------|---------------------|---------------------------|----------|----------|------------|------------|---------|----------|-----------------|-----------------------|---------|-------------|-------------|---------------|------|-------|-------|---------------|------------------|
|          |              |     |                |                     |                       |                     | Albumin                   | Globulin | Rate A/G | $\alpha_1$ | $\alpha_2$ | $\beta$ | $\gamma$ | $\alpha/\alpha$ | Prealbumin            | Albumin | Orosomucoid | Haptoglobin | Ceruloplasmin | IgG  | IgA   | IgM   |               |                  |
| 1        | 1            | 28  | 5              | 780                 | 459                   | 7.5                 | 71.0                      | 29.0     | 2.41     | 3.3        | 5.5        | 8.8     | 14.0     | 0.62            | N                     | +       | +           | N           | N             | 1327 | 170.5 | 218.2 | +             | -                |
| 2        | 2            | 61  | 6              | 780                 | 405                   | 7.3                 | 69.6                      | 30.4     | 2.28     | 3.3        | 5.2        | 7.2     | 14.6     | 0.58            | N                     | +       | N           | N           | +             | -    | -     | -     | +             | -                |
| 3        | 4            | 26  | 5              | 1050                | 414                   | 7.3                 | 68.6                      | 31.8     | 2.13     | 3.7        | 4.9        | 8.7     | 15.5     | 0.55            | N                     | N       | N           | N           | N             | 1370 | 177.2 | 127.7 | +             | -                |
| 4        | 14           | 24  | 4              | 920                 | 413                   | 7.1                 | 72.0                      | 28.0     | 2.57     | 4.2        | 5.7        | 7.1     | 11.2     | 0.87            | N                     | +       | N           | N           | +             | 1370 | 257.6 | 71.3  | +             | -                |
| 5        | 17           | 30  | 4              | 1440                | 738                   | 7.3                 | 69.0                      | 31.0     | 2.22     | 3.2        | 5.8        | 9.3     | 12.7     | 0.70            | N                     | +       | N           | N           | N             | 1327 | 198.0 | 114.3 | +             | -                |
| 6        | 21           | 44  | 4              | 1780                | 930                   | 7.1                 | 58.5                      | 41.5     | 1.40     | 3.8        | 8.4        | 13.9    | 15.2     | 0.80            | N                     | N       | +           | N           | N             | 1083 | 205.1 | 101.4 | -             | -                |

Table 3. Vinyl chloride disease. Clinical data in patients with typical Raynaud's phenomenon

| Case no. | Present case | Age | Exposure (yrs) | Total lipids (mg %) | $\beta$ -lipoproteins (mg %) | Total protein (g %) | Paper electrophoresis (%) |          |          |            |            |         |          |                 | Immunoelectrophoresis |         |             |             |               | Cryoglobulins | Cold agglutinins |       |     |     |
|----------|--------------|-----|----------------|---------------------|------------------------------|---------------------|---------------------------|----------|----------|------------|------------|---------|----------|-----------------|-----------------------|---------|-------------|-------------|---------------|---------------|------------------|-------|-----|-----|
|          |              |     |                |                     |                              |                     | Albumin                   | Globulin | Rate A/G | $\alpha_1$ | $\alpha_2$ | $\beta$ | $\gamma$ | $\alpha/\gamma$ | Prealbumin            | Albumin | Orosomucoid | Haptoglobin | Ceruloplasmin |               |                  | IgG   | IgA | IgM |
| 1        | 3            | 25  | 2.5            | 1040                | 540                          | 7.6                 | 66.0                      | 24.4     | 1.91     | 5.5        | 5.7        | 9.5     | 13.3     | 0.94            | N                     | +       | +           | N           | +             | 1415          | 138.5            | 77.1  | +   | -   |
| 2        | 5            | 34  | 10             | 1780                | 873                          | 7.6                 | 67.9                      | 32.1     | 2.11     | 3.8        | 4.7        | 6.6     | 17.0     | 0.50            | N                     | N       | N           | N           | +             | 2166          | 227.0            | 194.0 | +   | -   |
| 3        | 6            | 26  | 6              | 1360                | 585                          | 7.9                 | 57.0                      | 43.3     | 1.33     | 5.7        | 7.4        | 10.7    | 18.2     | 0.71            | N                     | N       | N           | N           | N             | 1591          | 351.0            | 170.8 | +   | -   |
| 4        | 7            | 22  | 5              | 1000                | 441                          | 6.9                 | 66.2                      | 33.8     | 1.95     | 3.1        | 4.3        | 7.4     | 19.0     | 0.39            | N                     | +       | +           | -           | -             | -             | -                | -     | +   | -   |
| 5        | 11           | 51  | 5              | 1100                | 450                          | 7.9                 | 64.5                      | 35.5     | 1.81     | 3.5        | 6.5        | 9.4     | 16.1     | 0.62            | N                     | +       | +           | +           | +             | 1924          | 265.5            | 141.8 | +   | -   |
| 6        | 12           | 23  | 3              | 800                 | 325                          | 8.6                 | 74.5                      | 25.5     | 2.92     | 2.5        | 4.6        | 7.0     | 11.4     | 0.62            | N                     | +       | +           | +           | +             | 1546          | 281.6            | 77.1  | +   | -   |
| 7        | 13           | 25  | 3              | 1100                | 495                          | 7.3                 | 71.0                      | 29.0     | 2.44     | 5.3        | 4.4        | 7.1     | 12.2     | 0.79            | N                     | +       | +           | N           | +             | 1501          | 289.8            | 101.4 | +   | -   |
| 8        | 15           | 32  | 6              | 1440                | 756                          | 6.9                 | 72.0                      | 28.0     | 2.57     | 3.6        | 5.2        | 9.2     | 10.0     | 0.88            | N                     | +       | N           | N           | N             | 1244          | 157.4            | 77.1  | +   | -   |
| 9        | 20           | 41  | 4              | 1260                | 423                          | 7.6                 | 63.0                      | 37.0     | 1.70     | 3.6        | 6.2        | 10.0    | 14.2     | 0.69            | N                     | +       | +           | N           | N             | 1203          | 265.5            | 89.0  | +   | -   |
| 10       | 23           | 26  | 4              | 940                 | 342                          | 6.3                 | 65.0                      | 35.0     | 1.85     | 4.7        | 7.5        | 9.2     | 13.6     | 0.89            | +                     | N       | N           | N           | N             | 1083          | 219.6            | 77.1  | -   | -   |

Table 4

Vinyl chloride disease. Clinical data in patients with Raynaud's phenomenon, scleroderma-like changes and acro-

10 23 26 4 940 342 6.3 65.0 35.0 85 4.7 7.5 9.2 13.6 0.89 † N N N N 1083 219 77.1

Table 4

Vinyl chloride disease. Clinical data in patients with Raynaud's phenomenon, scleroderma-like changes and acro-osteolysis

| Case no. | Present case | Age | Exposure (yrs) | Total lipids (mg %) | β-lipoproteins (mg %) | Total protein (g %) | Paper electrophoresis (%) |          |          |                |                |      |      |      | Immunoelectrophoresis |         |             |             |               |      |       |       | Cryoglobulin | Cold agglutinins |
|----------|--------------|-----|----------------|---------------------|-----------------------|---------------------|---------------------------|----------|----------|----------------|----------------|------|------|------|-----------------------|---------|-------------|-------------|---------------|------|-------|-------|--------------|------------------|
|          |              |     |                |                     |                       |                     | Albumin                   | Globulin | Rate A/G | α <sub>1</sub> | α <sub>2</sub> | β    | γ    | α/γ  | Prealbumin            | Albumin | Orosomucoid | Haptoglobin | Ceruloplasmin | IgG  | IgA   | IgM   |              |                  |
| 1        | 8            | 56  | 6              | 1440                | 765                   | 7.6                 | 68.3                      | 31.7     | 2.15     | 3.6            | 5.4            | 8.3  | 14.4 | 0.62 | N                     | †       | N           | N           | N             | 1778 | 163.9 | 178.4 | +            |                  |
| 2        | 9            | 31  | 2              | 880                 | 297                   | 7.6                 | 67.2                      | 32.8     | 2.04     | 3.7            | 4.1            | 7.2  | 17.8 | 0.43 | N                     | N       | †           | N           | N             | 2012 | 351.0 | 170.8 | +            |                  |
| 3        | 10           | 39  | 3              | 940                 | 449                   | 8.2                 | 71.8                      | 28.2     | 2.54     | 2.7            | 3.8            | 7.6  | 14.1 | 0.46 | N                     | †       | N           | N           | N             | 2166 | 265.5 | 107.8 | +            |                  |
| 4        | 18           | 36  | 2              | 1190                | 666                   | 8.25                | 74.0                      | 26.0     | 2.84     | 2.2            | 4.1            | 7.2  | 12.5 | 0.50 | N                     | †       | †           | †           | †             | 1285 | 163.9 | 71.3  | +            |                  |
| 5        | 22           | 30  | 5              | 1110                | 540                   | 7.9                 | 63.2                      | 36.8     | 1.71     | 4.2            | 6.6            | 10.4 | 15.6 | 0.69 | N                     | N       | †           | N           | N             | 1370 | 298.1 | 155.9 | -            |                  |
| 6        | 24           | 27  | 4              | 920                 | 441                   | 6.6                 | 61.0                      | 39.0     | 1.56     | 5.6            | 8.8            | 8.6  | 16.0 | 0.90 | N                     | N       | †           | N           | †             | 1546 | 177.2 | 155.9 | -            |                  |

In none of the investigated cases were cold agglutinins found. Immunoelectrophoretic identification of 12 cryoprecipitates was performed using anti-IgA, anti-IgG, and anti-IgM sera. The remaining 6 cryoprecipitates have not been investigated because of the small amounts of cryoglobulins obtained. This was most evident in the third group (Table 4).

Two cryoprecipitates were monoclonal, that is composed of IgG exclusively; the other 10 were polyclonal. They were composed of class A, G, and M immunoglobulins in 1 case, in the remaining ones a clear IgA + IgG band was visible. It should be added that cryoprecipitation was present in fractions 5-12 of sera belonging to the first group, in fractions 5-11 in the second one and in fractions 5-8 exclusively in the third group.

#### DISCUSSION

It follows from these observations that Raynaud's phenomenon is the dominant clinical sign in vinyl chloride intoxication [3]. Raynaud's phenomenon is known as accompanying many systemic diseases especially those marked as autoaggression diseases conditioned by alterations in the reactivity of the organism [8,9].

The most frequent cause of apparent pathologic changes during cooling down are cryoglobulins or cold agglutinins [19]. The presence of cryoglobulins at great concentrations is manifested by a characteristic clinical picture: In addition to Raynaud's phenomenon, aseptic finger necrosis, and skin ulcerations, other symptoms such as stasis in the retinal blood vessels, hemorrhagic diathesis, and alterations in blood vessels of the lungs, the kidney, the coronaries, and even brain and trophic nerve trunk vessels can be seen [1,4,5,18].

The similarity in syndrome between chronic vinyl chloride intoxication and the above described cryoglobulinemia prompted the search for a connection between the 2 diseases. The investigation confirmed this assumption. Cryoglobulins were found in the sera of 81% of cases examined. According to numerous authors, spontaneous and latent cryoprecipitation may be distinguished [8,16]. The latter does not result in a spontaneous precipitation in serum after cooling. It can only be detected after filtration through a Sephadex G-200 column.

In this investigation latent cryoprecipitation in serum was found exclusively.

The polyclonal character of most cryoprecipitates testifies undoubtedly to their pathologic nature [10]. Quantitatively

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larger precipitation was seen during the first 2 phases of Raynaud's phenomenon; it receded in 1 case after a 12-months period. These observations are in accord with the transient nature of cryoglobulinemia in different pathologic conditions [2].

The presence of cryoglobulins shows that the reactivity of the organism has been altered. It is assumed that the production of cryoglobulins is caused by a fault in the synthesis of immunoglobulin [11,17]. Most probably the engagement of anti-globulin antibodies arising in the process of hyperimmunization plays also an important role [10].

These considerations justify the assumption that the mechanism of the toxic effect of vinyl chloride in general and of Raynaud's phenomenon in particular lies in the altered immunologic response of the organism. This is also confirmed by the finding of increased serum immunoglobulin levels both in the cases mentioned in this report as well as in those described by Lange et al. [15]. In the prodromal period of Raynaud's syndrome a net increase of IgM in 1 case was seen whereas increased class IgG levels were observed in patients with advanced pathologic symptoms, particularly scleroderma-like changes and acro-osteolysis. Similarly, in the cases described by Lange et al., high IgG levels were found in 6 out of 7 persons with acro-osteolysis. The increase of serum glycoproteins as well as of orosomucoid and ceruloplasmin levels which are considered a sign of exacerbation in collagen diseases may also be interpreted as signs of a general pathologic process [7].

According to the authors' observations the humoral immunity is stimulated under the toxic action of vinyl chloride. On the other hand, participation of cellular immunity may not be excluded if we keep in mind the generation of malignant tumors in people exposed to vinyl chloride (liver angiosarcomata) [4].

Investigations on the pathogenesis of vinyl chloride intoxication should be continued not only for theoretic reasons. It may be anticipated that this will create a basis for successful treatment and prophylaxis.

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