



## reviews

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# Dextran hypersensitivity

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*Dextran, a common plasma substitute, sometimes induces life-threatening hypersensitivity reactions. In this article Wolfgang Richter and Harriet Hedin discuss recent evidence that these Type III anaphylactic reactions, caused by natural antibodies, can be abolished by pretreatment of patients with monovalent hapten dextran.*

The search for more efficient and safer plasma volume expanders led to the introduction of partially hydrolyzed and purified dextrans into medicine in 1947 (Ref. 1). Clinical dextrans have a molecular size range comparable to that of plasma proteins and are prepared from native dextrans which are polysaccharides of mol. wt 10–100 millions. The latter are produced from sucrose by enzymes, mainly derived from bacteria of *Leuconostoc* spp (for review see Ref. 2). The dextran molecules consist of more or less branched chains of glucose units connected by  $\alpha$  1–6 bonds. The first generation of clinical dextrans had a moderate degree of branching and frequently caused immediate-type allergic reactions involving the skin, respiratory tract and circulation. However, clinical dextrans from European and American manufacturers had varying incidence of reactions and it was found that the conditions of manufacture i.e. the *Leuconostoc* strain, degree of hydrolysis, and extent of removal of high molecular weight constituents were important in diminishing reactions<sup>3</sup>. Since 1955, B 512 dextran – a linear dextran causing a minimum of allergic reactions and produced by *Leuconostoc mesenteroides* strain NRRL B 512 – has been in use worldwide. Until 1968 only a few cases of dextran-induced anaphylactoid/anaphylactic reactions (ARs) were reported. However, the more widespread use of clinical dextrans, e.g. for improvement of blood flow<sup>4</sup> and prophylaxis of postoperative pulmonary embolism<sup>5</sup> led to an increase in the number of ARs reported<sup>6</sup>. Since some of these reactions are life-threatening, efforts to eliminate them were desirable.

A collaborative study was carried out during 1968–1981 with the aim of elucidating the mechanisms underlying ARs and finding ways to prevent them. This included research on the immunogenicity of dextran, serological studies on normal individuals, and on those people who reacted to dextran, development of animal models of dextran anaphylaxis, hapten inhibition studies, and clinical multicenter trials to determine the incidence of ARs and the efficacy of hapten prophylaxis. This work was done by W. Richter, H. Hedin, K. Granath, B. Ingelman and H. Renck (Research Division, Pharmacia AB, Uppsala, Sweden), K. Messmer, J. Ring, C. Mandler and H. Laubenthal (Institute for Surgical Research Univer-

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## Immunology of dextran

The antigenicity of dextran was disclosed by its serological reactivity with antibodies to *Leuconostoc* and pneumococci of types II and XX (for review see Ref. 6). Later the immunogenicity of native dextrans of varying structure was demonstrated in man<sup>7</sup>. The immunogenicity of B 512 dextran has been shown to be dependent on its molecular weight, in man<sup>7</sup> and mouse<sup>8</sup>. The choice of a non-immunogenic mol. wt range of 40,000–75,000 for clinical dextrans has been influenced by these findings. It must be pointed out here that the amount of clinical dextran given to patients per infusion (30–100 grams) represents an 'overwhelming' dose, which most probably leads to immunological unresponsiveness as it is known to be induced by large doses of purified polysaccharides (cited in Ref. 9). Like other polysaccharides of repetitive structure, dextran induces a thymus-independent humoral IgM class response in mice<sup>10</sup> and is a polyclonal B-cell activator<sup>11</sup>. However, dextran can be converted to a thymus-dependent antigen by covalent coupling to protein<sup>9</sup>. Such conjugates elicit a strong IgG antidextran response upon immunization. Clinical dextran does not induce mitogenic stimulation of human lymphocytes *in vitro*<sup>12,13</sup>.

The antigenic determinants of different dextrans reflect their simple structure. They are constituted by oligosaccharides containing  $\alpha$ 1–6, 1–2, 1–3 and 1–4 linked glucosyl residues in varying proportions<sup>2</sup>. The clinically used B 512 dextran contains about 95%  $\alpha$ 1–6 linkages<sup>1</sup>. Inhibition studies indicated that combining sites of antidextrans are complementary to sequences

of 2-7 glucose residues, also suggesting the size range of its antigenic determinants<sup>13</sup>. Antidextran combining sites may react with terminal or non-terminal determinants<sup>15</sup>. The minimal size of the immunogenic determinants of B 512 dextran corresponds to two, and exceptionally single,  $\alpha$ 1-6 linked glucosyl residues<sup>2</sup>. In mice, the immune responses to the  $\alpha$ 1-3 and  $\alpha$ 1-6 determinants of dextran<sup>16,17</sup> have been shown to be under separate genetic control. Thus, high responder strains to the former may be low responders to the latter, and vice versa. In man, high and low responders to B 512 dextran can also be distinguished<sup>18</sup> but the genetic background has not been studied. Antidextrans in humans may belong to the IgG, IgA and IgM classes. Within the IgG class, the IgG<sub>1</sub> subgroup has been found to be predominant<sup>19</sup> as an expression of a restricted response.

Most people have natural dextran-reactive antibodies (DRA)<sup>3,18,20,21,22,23</sup>. They may be induced by dextran itself or by cross-reactive microbial polysaccharides. Native dextran is ingested as a regular

contaminant of sucrose<sup>6</sup>. Dextran is also a component of dental plaque, may occur in food, and is produced by microorganisms of the gastrointestinal tract (cited in Ref. 29). Recently, a ubiquitous antigen found in the tissues and sera of human beings was identified as native dextran. In patients with gastrointestinal disease, high levels of 40-260 ng/ml serum were demonstrable<sup>23</sup>. It is also of interest that in guinea pigs the permeability of the gastric mucosa to ingested dextran is increased by acetylsalicylic acid in therapeutic doses; the influx of dextran into the circulation was sufficient to induce passive cutaneous anaphylaxis<sup>24</sup>. Thus, ample opportunity exists for dextran to induce DRA in random human populations. On the other hand, hyperimmune animal sera to pneumococci, streptococci, *Salmonella*, and teichoic acids cross-react with dextran (cited in Ref. 20), so theoretically DRA could be induced by cross-immunization. In the case of cross-reactive pneumococcal polysaccharides, results of absorption tests on human sera did not support such a view<sup>22</sup> (Table I).

#### Clinical aspects of adverse reactions to dextran

Clinically ARs range from skin symptoms alone to circulatory shock. Grades of severity are recognized as follows:

| Grade of severity | Symptoms                                                                                                                                                              |
|-------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| I                 | Skin manifestations (flush, erythema, urticaria)                                                                                                                      |
| II                | Mild to moderate hypotension (reduction of systolic blood pressure with $\geq 20$ mm Hg down to $\geq 40$ mm Hg). Gastrointestinal disturbances. Respiratory distress |
| III               | Severe hypotension (blood pressure $< 40$ mm Hg). Severe bronchospasm                                                                                                 |
| IV                | Cardiac and/or respiratory arrest                                                                                                                                     |

Skin manifestations are most common and tend to be localized to the head, neck and chest regions. Severe reactions (grades III and IV) are characterized by a rapid fall in blood pressure. The circulatory symptoms are often combined with erythema, urticaria and bronchospasm.

The earlier a reaction appears after start of the dextran infusion the more severe it is likely to be. In a retrospective study covering a ten year period (Ljungström, Renck *et al.*, to be published) cardiac arrest always occurred within 10 mins. This emphasizes that patients must be closely supervised during the initial phase of the infusion. Patients with severe reactions are not abnormally prone to allergic disease but allergic disease is overrepresented among people with mild symptoms. Diabetes, heart disease, pulmonary disease and chronic inflammatory states are more common in patients with severe ARs than in

those with mild reactions. Elderly patients, especially males, are more prone to develop a severe reaction. Patients under anaesthesia or undergoing surgery are as liable as others to have severe ARs. Of those patients who have died of ARs during anaesthesia, all but one had had epidural or spinal anaesthesia.

When signs of ARs appear, dextran infusion should immediately be stopped. Generally, mild reactions do not require further therapy, whereas severe ones need adequate shock treatment. The retrospective study (mentioned above) has shown that vigorous fluid resuscitation and aggressive buffer therapy are mandatory for a positive outcome.

#### Incidence

It is difficult to determine the true incidence of adverse drug reactions, especially when the incidence is low. The number of reported adverse reactions to many drugs, including the various plasma substitutes, has risen in recent years but this may reflect improved reporting<sup>25</sup>. During the past decade, the reported incidence of ARs varied from 0.1-4.7% and that of severe ARs from 0.008-0.25%<sup>26,27</sup>. Differences may be explained by the design of the study, number of patients investigated, criteria used for classification of symptoms, and whether the incidence is given per bottle infused or per patient. In studies on a small number of patients<sup>28,29</sup> the phenomenon of 'clustering', i.e. the fortuitous accumulation of reactions, may distort the true incidence. For a statistically valid evaluation of the incidence of severe ARs more than 20,000 patients are required. Based on a total consumption of 682,633 units of clinical dextran, this incidence in Sweden in 1975-1979 was estimated to be 0.037-0.50% per patient (Ljungström, Renck *et al.*, to be published). These figures are calculated on the assumption that each patient on the average received 1.5 or 2 units of dextran. The incidence of severe DIAR was essentially the same for 'Rheomacrodex' (Dextran 40) as for 'Macrodex' (Dextran 70).

TABLE I. Microgranin antibody N precipitated per ml of serum from medical volunteers receiving subcutaneous injections of 1 mg of various native dextrans.

| Subject No. | Native dextran Code | Bleeding         | Anti-           |     |     |     | Antidextran after absorption with pneumococcal polysaccharides | Antidextran before absorption with pneumococcal polysaccharides |
|-------------|---------------------|------------------|-----------------|-----|-----|-----|----------------------------------------------------------------|-----------------------------------------------------------------|
|             |                     |                  | CI <sup>a</sup> | SH  | SXH | SXX |                                                                |                                                                 |
| 21          | CSG-N 279           | Pre-immunization | 0.3             | 1.1 | 0.9 | 1.0 | 0.2                                                            | 1.8                                                             |
|             |                     | Post- "          | 1.2             | 1.4 | 0.7 | 1.0 | 5.9                                                            | 6.0                                                             |
| 34          | Swerd. 3079         | Pre- "           | 0.9             | 0.5 | 0.9 | 0.5 | 1.1                                                            | 1.5                                                             |
|             |                     | Post- "          | 1.0             | 1.3 | 0.4 | 0.6 | 14.9                                                           | 16.2                                                            |
| 44          | NRRL-B 742          | Pre- "           | 1.5             | 0.0 | 0.6 | 0.6 | 3.0                                                            | 5.1                                                             |
|             |                     | Post- "          | 1.3             | 0.0 | 1.6 | 1.2 | 6.5                                                            | 6.3                                                             |
| 49          | NRRL-B 1254         | Pre- "           | 0.7             | 2.8 | 0.0 | 0.0 | 0.8                                                            | 0.5                                                             |
|             |                     | Post- "          | 0.5             | 2.9 | 0.4 | 0.7 | 4.1                                                            | 4.1                                                             |
| 51          | NRRL-B 512 F        | Pre- "           | 1.6             | 0.0 | 1.2 | 0.3 | 2.7                                                            | 3.1                                                             |
|             |                     | Post- "          | 1.2             | 0.0 | 0.0 | 0.5 | 19.4                                                           | 17.1                                                            |

<sup>a</sup> CI = C polysaccharide from type I pneumococcus

SH = pneumococcal polysaccharide specific for type II

SXH = pneumococcal polysaccharide specific for type XII

SXX = pneumococcal polysaccharide specific for type XX

From Ref. 22

### Pathogenetic mechanisms

#### Impurities

In adverse drug reactions, the drug itself, its metabolites, or impurities may be elicitors. With regard to dextran, the molecule itself was incriminated in severe ARs<sup>29,30</sup> rather than impurities<sup>31-33</sup> but the role of macromolecular contaminants in provoking mild reactions cannot be ruled out since traces of such material are demonstrable in the majority of clinical dextran preparations<sup>33</sup>. The removal of impurities is therefore desirable and one manufacturer has recently achieved this<sup>33</sup>. Benefits may be expected but demonstrating them will be difficult, for technical and biometric reasons.

#### Dextran reactive antibodies (DRA)

The theoretical risks of dextran infusion in individuals with high titers of circulating DRA were pointed out in 1950 (Ref. 34). A few years later, Kabat *et al.*<sup>3</sup> demonstrated a positive relationship between skin tests to native dextran, high specific precipitin levels, and a propensity to systemic allergic reactions upon infusion of non-B 512 and B 512 clinical dextrans into 101 volunteers. The results indicated that DRA participate in elicitation of such reactions. However, Jacobsson<sup>21</sup>, concluded that DRA have no pathogenic importance, since the great majority of volunteers with high DRA levels tolerate B 512 dextran infusion. Despite the many published case reports of ARs immunological observations are rare and give no clear picture of the underlying mechanisms. We therefore studied the levels and composition of DRA in sera from many patients who had experienced ARs of varying severity and from normal individuals. Sera were collected over 12 years from different countries.

In anaphylactic shock in humans, specific IgE-class antibodies are often considered responsible for the

development of clinical signs, but IgG-mediated anaphylaxis has also been documented<sup>25</sup>. No DRA of IgE-class could be found before or after ARs by passive cutaneous anaphylaxis in monkeys, the radioallergo-sorbent technique, and the modified radioactive red-cell-linked antigen-antiglobulin reaction<sup>29,30</sup>. Thus, ARs do not conform to the concept of IgE-mediated anaphylaxis.

Sera of dextran reactors were also examined for DRA by passive hemagglutination<sup>29</sup>. In this way, total activity of the Ig-classes G, A, M and D is determined. It is apparent from Fig. 1 that the titer of DRA is positively related to the degree of severity of ARs. All patients with severe reactions have high titers. It should be emphasized that these results have been obtained from serum samples fortuitously collected from patients shortly before ARs occurred. If sera drawn soon after ARs are examined, erroneously low titers are found, due to neutralization of DRA by the infused dextran.

A comparison between DRA-titer distributions in patients with severe ARs and in a random population shows that 76% of the dextran reactors and only 4% of normals had high titers of 512 or more (Fig. 2). Clearly, the group at risk is a small subpopulation of high responders to dextran. However, comparison of the incidence of severe ARs (0.05%) and the frequency of high titers of DRA in normal people shows that only a small proportion of those with high titers develop ARs. This is in accord with Jacobsson's results<sup>21</sup> and may be explained by several sets of factors<sup>18</sup>. Some of these are: Ig-class and subgroup composition, affinity and concentration of DRA, platelet fragility and responsiveness of the patient's vascular system.

For further analysis of DRA, the modified red-cell-linked antigen-antiglobulin reaction was employed to determine Ig-class and subgroup composition<sup>30</sup>.

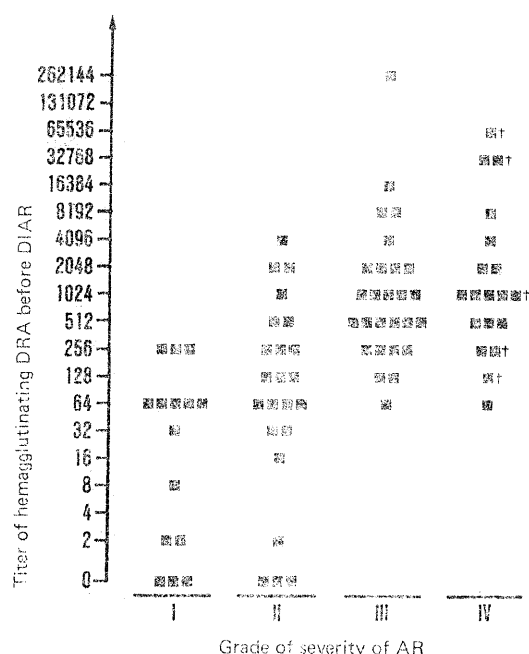


Fig. 1 Relationship between serum titers of hemagglutinating DRA and grade of severity in patients with ARs. Samples were collected prior to the dextran infusion ( $n = 84$ ). + = fatal outcome.

(From Hedin and Richter, in press)

Dextran-reactive IgG antibodies of high titer were regularly found in patients with severe reactions. IgG-titer strongly correlated with grade of severity; four lethal cases all belonged to the highest titer range of 16,384 to 32,768. This corresponds to 0.4 mg DRA per ml serum. In addition, high IgA-titers were sometimes found, whereas IgM levels were low and IgD antibodies were absent. All four subgroups of IgG were demonstrable but the contribution of IgG<sub>2</sub> was considered the most important.

Skin tests with clinical B 512 dextran were positive in 32% of dextran reactors and often correlated with high titers of hemagglutinating DRA<sup>20</sup>.

The best predictive diagnostic test for dextran hypersensitivity is determination of dextran reactive IgG. However, such a test can only delineate a risk group of a few per cent in a random population, and cannot predict individual predisposition.

#### Complement

Since native dextran can activate the alternative pathway of complement *in vitro*, it was suggested that ARs might be triggered in a similar way (for review see Ref. 31). Complement profiles were established for dextran reactors to study this possibility. In addition, serum carboxypeptidase B levels were determined, since low levels might lead to high concentrations of anaphylatoxin with potential shock producing activity. The most important finding was a significant

decrease in the levels of C1q in severe ARs<sup>31</sup>. Concentrations of the other complement proteins and of serum carboxypeptidase B were normal. These results indicate that the classical pathway is being activated in dextran reactors by immune complexes and accord with the presence of high titers of DRA in patients with severe reactions. Available evidence does not favour the activation of the alternative pathway by infusion of clinical dextran.

#### Lung histopathology

Histological examination of sections of lung tissue from patients with fatal ARs showed occlusion of pulmonary vessels (Ref. 36 and unpublished data). The occluding material consisted of platelets, leukocytes and hyaline globuli with the staining properties of fibrin. These findings are interpreted to suggest that

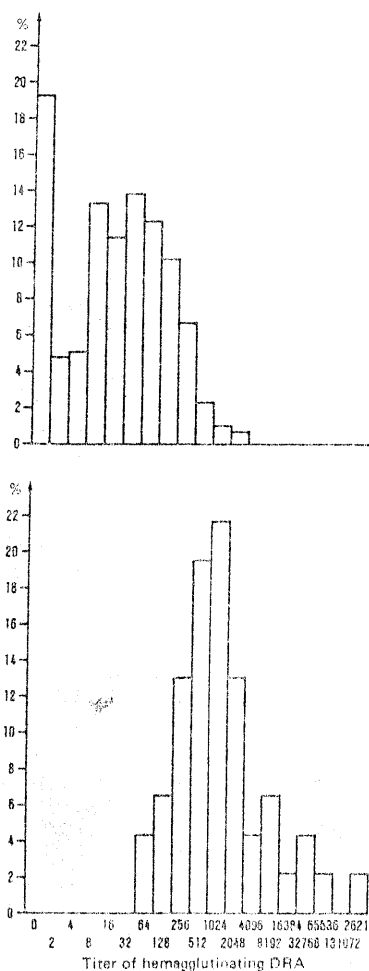


Fig. 2 Distribution of serum titers of hemagglutinating DRA in individuals with no history of ARs,  $n = 1,408$  (upper graph) and in patients with ARs of grades III to IV,  $n = 46$  (lower graph).

(From Hedin and Richter, in press)

insoluble antigen-antibody complexes have been deposited in the lungs and bound leukocytes and platelets by an interaction between Fc-receptors on cells and Fc-pieces of DRA. The fibrin deposits appearing as globular microthrombi are thought to be due to activation of the coagulation system via its connection with other plasma enzyme systems, e.g. the complement system.

#### Conclusion

All these findings taken together strongly support immune complex (Type III) anaphylaxis as the mechanism of severe ARs. Mild reactions may be antibody-dependent or not. The sequence of events leading to antibody-dependent reactions may be envisaged as follows. In a small subpopulation of individuals with high titers of preformed DRA of IgG-class, infusion of clinical dextran generates harmful immune complexes. They activate complement and aggregation of leukocytes and platelets occurs. The aggregated material is sequestered in the lung and release of vasoactive mediators leads to the anaphylactic symptoms. Since antigen-antibody complexes are of crucial pathogenic importance, interference with their formation by hapten inhibition was proposed as a means of preventing ARs<sup>38</sup>.

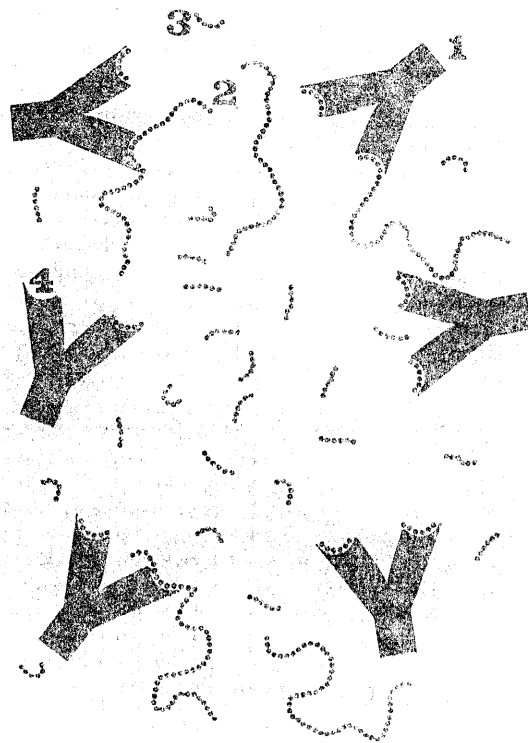


Fig. 3 Illustration of the hapten inhibition principle. Monovalent haptendextran, i.e. Dextran-I (3) binds competitively to combining sites (4) of DRA (1) thus preventing formation of large complexes between polyvalent clinical dextran (2) and DRA (1).

#### Hapten inhibition

A hapten is a substance capable of binding to antibodies with corresponding specificity but which cannot induce antibody formation. Haptens may be polyvalent or monovalent with regard to the number of antigenic determinants. A polyvalent hapten may form complexes with antibodies, as an antigen does, but a monovalent hapten can bind only to individual combining sites of antibodies. Fig. 3 illustrates the inhibition of immune complex formation by a monovalent hapten.

#### In-vitro studies

Hapten inhibition of precipitation in the dextran-antidextran system has been extensively investigated by Kabat and co-workers (for review see Ref. 14). Only inhibition studies with B 512 dextran are considered here. Isomalto-oligosaccharides consisting of  $\alpha$ 1-6 linked glucosyl residues were found most effective. Their inhibitory power increased strikingly from isomaltose to isomaltopentaose with little further increase for isomalto-hexaose and -heptaose<sup>37</sup> (Fig. 4). These results were confirmed by the technique of 'indirect' single radial immunodiffusion<sup>38</sup>. In this way a dextran fragment of 6 glucose units (mol. wt 990) was found suitable as a monovalent hapten preparation for *in-vivo* experiments.

#### Animal models

Hapten inhibition has been shown to prevent lethal cytotoxic dextran anaphylaxis in guinea pigs. Dextran cross-reactive rabbit antipneumococcal type II sera<sup>39</sup> and rabbit antisera to B 512 dextran<sup>40</sup> were used for sensitization. The following information on the molecular mechanism was obtained, using B 512 dextran fractions of varying size for challenge. The amount of sensitizing antibody is critical: polyvalent dextran may elicit anaphylaxis in strongly sensitized animals, but not in weakly sensitized ones. Non-eliciting dextran fractions always exerted inhibition, when given together with eliciting fractions. The molecular weight of such protective isomalto-oligosaccharides or dextran fractions ranged from about 1,000-10,000 (Ref. 40,41). Inhibition of anaphylaxis was achieved by a moderate molar excess of non-eliciting/eliciting fractions (1.9-7.6). With maximal sensitization, the smallest dextran fragment with elicitor action in passive cutaneous anaphylaxis proved to be isomaltodecaose (mol. wt 1,600)<sup>41</sup>, see Table II. In contrast, isomaltohexaose (mol. wt 990) never elicited anaphylaxis, showing that it was truly a monovalent hapten.

It was also considered important to study immune complex anaphylaxis in animals, since ARs in man conform to this type. For this purpose, a special low molecular dextran product (Dextran I, 15% solution) comprising a selected mixture of isomalto-oligosaccharides of mol. wt ( $M_w$ ) 1,000 was developed (Ingelman *et al.*, unpublished); factors other than inhibitory power were also taken into account. A model was established in dogs made hypersensitive to

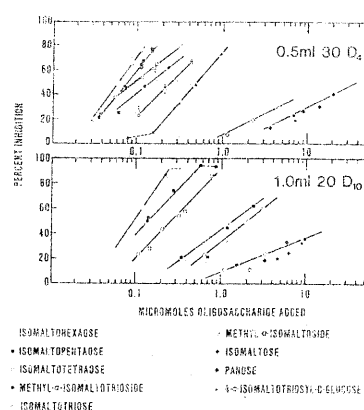


Fig. 4 Inhibition by various mono- and oligo-saccharides of precipitation of antidextran by dextran.

(From Ref. 3)

B 512 dextran by immunization with a protein-dextran conjugate<sup>42</sup>. Upon challenge of these dogs under anaesthesia with 1 ml of 'Macrodex' (mol. wt 60,000) 59% of animals showed anaphylactic reactions of varying severity. Among reactors, severe reactions occurred in 37%. They were characterized by decrease in cardiac output and of mean arterial pressure, whereas pulmonary arterial pressure and pulmonary resistance increased. Further, the number of circulating leukocytes and platelets fell, and a decrease in the titer of DRA was noted. The administration of Dextran 1 either as preinjection or as admixture to the challenging anaphylactogenic dextran, significantly reduced both the incidence and the severity of anaphylaxis. In the combined hapten-treated groups, only 16% of the dogs showed reactions. Among the reactors, 7% developed severe anaphylaxis<sup>42</sup>. Similar results were obtained in non-anaesthetized dogs by preinjection of Dextran 1 (Ref. 43).

#### Prevention of adverse reactions in man

Clinical trials with Dextran 1 (Promit<sup>®</sup>, 15%, Pharmacia AB) were now considered. Theoretically, a given dose should be more effective when administered as preinjection than when mixed with clinical dextran. Suitable doses, representing a molar excess of 50–200 times, were calculated from the number of antibody combining sites of DRA of IgG-class in sera of patients with severe DIAR.

Clinical studies were initiated in Sweden and Germany in 1978. In each patient, a preinjection of 10 or 20 ml of Dextran 1 or an admixture of 20 ml of Dextran 1–500 ml of clinical dextran is given. For each patient, a protocol containing information on sex, age, main diagnosis, type of operation performed etc., is completed. When an adverse reaction is observed or suspected, details about the reaction and the patient's history are obtained. Further, serum samples drawn before and after the reaction are analyzed for DRA. To achieve a uniform classification of reactions, clinical and immunological data are continuously

TABLE II. Monovalency of dextran fragments of six glucose residues indicated by incapability to elicit passive cutaneous anaphylaxis (PCA) in guinea pigs.

| µg antidextran per skin site | Challenging agent | Mol. wt (Mw) | PCA-lesion area (mm <sup>2</sup> ) |
|------------------------------|-------------------|--------------|------------------------------------|
| 0.3                          | IM-6              | 990          | 0                                  |
| 0.3                          | IM-10             | 1,638        | 0                                  |
| 0.3                          | Dx-fr.            | 3,100        | 121                                |
| 0.3                          | Dx-fr.            | 10,500       | 121                                |
| 0.3                          | Dx-fr.            | 71,000       | 289                                |
| 0.9                          | IM-6              | 990          | 0                                  |
| 0.9                          | IM-10             | 1,638        | 225                                |
| 0.9                          | Dx-fr.            | 3,100        | 196                                |
| 0.9                          | Dx-fr.            | 71,000       | 361                                |

From Ref. 41

TABLE III. Statistical comparison (Fisher's one-sided test) of the incidences of mild and severe ARs in patients receiving 10 or 20 ml of Dextran 1 before infusion of clinical dextran.

Status: September, 1981.

| Dose  | Incidence of                   |                                    |
|-------|--------------------------------|------------------------------------|
|       | Mild reactions (Grades I + II) | Severe reactions (Grades III + IV) |
| 10 ml | 65/35346 = 0.184%              | 9/35346 = 0.025%                   |
| 20 ml | 92/65948 = 0.141%              | 3/65948 = 0.005%                   |
|       | p = 0.06                       | p = 0.006                          |

Note: The reported incidence per patient of severe ARs without hapten prophylaxis is 0.037–0.050% (Ljungström, Renck *et al.*, to be published).

discussed between the physicians responsible and the study co-ordination centre.

At present, trials are going on in six countries and more than 100,000 patients have been investigated. Interim results from Scandinavia (Co-ordinators: H. Renck and K.-G. Ljungström) and Bavaria (Co-ordinators: K. Messmer, K. Peter and H. Laubenthal) are reported in Ref. 44 and in Table III. A dose-dependent prophylactic effect of preinjection of Dextran 1 is evident. The incidence of severe ARs is decreased by 50–50% with the 10 ml dose and by 90% with the 20 ml dose in comparison with controls (Ljungström, Renck *et al.*, to be published). The prophylactic effect of admixture of Dextran 1 to clinical dextran on severe ARs is insignificant. The clinical results are supported by immunological findings (DRA titer analysis), indicating attenuation of severe reactions into mild ones. The incidence of mild reactions is affected only slightly by hapten prophylaxis.

The series of investigations described here demonstrates the applicability of hapten inhibition to the elimination of adverse drug reactions – a principle that has also been applied to penicillin allergy<sup>45</sup>.

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## T-cell membrane antigens associated with cytotoxic function

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*In the past few years the first steps have been taken towards an understanding of the molecular basis of T-cell-mediated cytotoxicity. Particular attention has been paid to the part played in cytotoxicity by idiotype-bearing antigen-receptors and other molecules on the T-cell surface. This article reviews these studies and focuses on the information obtained from studies on the inhibition of cytotoxic T cells with antisera or monoclonal antibodies directed against molecules on their surface.*

Cytotoxic T lymphocytes (CTLs) are involved in allograft rejection *in vivo*<sup>1</sup> and the lysis of allogeneic<sup>2</sup> and virus- or hapten-modified syngeneic target cells *in vitro*<sup>3,4</sup>. Lysis takes place in three discrete steps<sup>5</sup>: (i) the binding of CTLs to target cells (a process probably involving T-cell receptor and target cell antigens); (ii) 'programming for lysis' (a  $Ca^{2+}$  and temperature-dependent process) and; (iii) the disintegration of the target cell (a step independent of the effector cell). In the initial event of CTL-mediated target cell lysis, effector lymphocytes interact with and bind to target cells.

Despite the recent advances in our understanding of the physiological requirements and cellular processes in CTL-mediated cytotoxicity, the molecular mechanism involved in target cell lysis remains to be resolved. Several models have been proposed. These include (1) interactions involving membrane-associated molecules of CTL other than the antigen-binding receptor; (2) the release from CTLs of soluble mediators and; (3) the role of the perturbation of the target cell membrane following an interaction between the CTL receptor and target cell antigen<sup>6</sup> which perturbs the target cell's membrane and so results in its lysis. There is