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STRUCTURAL REQUIREMENTS OF SUGARS AS ANTAGONISTS OF THE VASCULAR RESPONSE TO DEXTRAN IN RAT SKIN

BY

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The increase in vascular permeability induced by dextran in rat skin is inhibited by the simultaneous intradermal administration of glucose and certain other sugars (Beraldo, Dias Da Silva & Lemos Fernandes, 1962). These sugars also prevent the local vascular changes produced by other polysaccharides (Poyser & West, 1965 ; Harris, Luscombe & Poyser, 1967) and inhibit the release of histamine *in vitro* by dextran from tissue mast cells (Goth, 1961 ; Beraldo *et al.*, 1962 ; Dias Da Silva & Lemos Fernandes, 1965). In the present paper, an attempt has been made to determine the structural and stereospecific requirements of sugars for activity as antagonists of the dextran response. The mechanism of inhibition by these carbohydrates has also been investigated.

METHODS

Inhibition by sugars and other agents of the vascular response to dextran in rat skin was studied using the method of Poyser & West (1965). Each antagonist was dissolved in dextran (1 mg/ml.) and injected intradermally, in volumes of 0.1 ml., into the shaved ventral abdominal skin of male hooded Lister rats (body weight about 200 g). Each rat received eight to ten intradermal injections immediately after the intravenous injection of azovan blue dye (7 mg/kg). Thirty minutes later the rats were killed, and the reaction to each injection was assessed by measuring the mean diameter of the blue area on the inner surface of the skin. The response given by dextran (100 μg) in the presence of each sugar or other agent was then expressed as a percentage of that found in its absence. From the log dose/inhibition curves, doses producing 50% inhibition (termed the *ID*50 values) were obtained. Each value shown in the tables is the mean and standard error of three experiments, each using at least three rats.

The dextran used was Intradex (Glaxo) with an average molecular weight of 140,000. Sugars and other substances tested as antagonists included β-D-glucose, L-glucose, *n*-acetyl-D-glucosamine, methyl-β-D-glucopyranoside, 3-O-methyl-D-glucose, 2:3:4:6-tetra-O-methyl-D-glucose, D-tagatose, D-lyxose, D-glyceraldehyde (syrup), glycoaldehyde, cyclohexane-1:2-diol (*cis*/*trans* mixture) and cyclohexane-1:4-diol (cis) which were purchased from Koch-Light Laboratories Ltd. D-Talose, D-erythrose, and cyclohexane-1:3-diol (*cis*/*trans* mixture) were obtained from K. & K. Laboratories, Inc., Plainview, New York, U.S.A. L-Xylose, 6-deoxy-L-mannose (L-rhamnose), galactitol (dulcitol), trehalose, maltose, cellobiose, lactose and raffinose were purchased from Thomas Kerfoot & Co. Ltd.

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Cyclohexane-1:2-diol (*trans*) and cyclohexane-1:4-diol (*cis*/*trans* mixture) were obtained from the Aldrich Chemical Co., Inc., Milwaukee, Wisconsin, U.S.A. Isomaltose was kindly supplied by Dr. C. R. Ricketts, of the M.R.C. Industrial Injuries and Burns Research Unit, Birmingham. All other sugars and substances tested were purchased from British Drug Houses Ltd.

RESULTS

Inhibition by glucose and its derivatives

The β-form of D-glucose and the L-isomer were as effective as the more common α-D-isomer in antagonizing the vascular response to dextran in rat skin (see Table 1). Furthermore, the *ID*50 values for these isomers were not significantly different ($P<0.05$) from those of 2-deoxy-D-glucose and *n*-acetyl-D-glucosamine. Whereas the α- and β-methyl glucosides were also as effective as D-glucose, 3-*O*-methyl-D-glucose and 2:3:4:6-tetra-*O*-methyl-D-glucose were much less active.

TABLE 1

INHIBITION BY GLUCOSE AND ITS DERIVATIVES OF THE INCREASE IN VASCULAR PERMEABILITY IN RAT SKIN PRODUCED BY DEXTRAN (100 μg)

The antagonist and dextran were injected simultaneously into the skin. Inhibition was measured as the dose required to produce 50% reduction in response. *ID*50 values are the means and standard errors of three experiments. Inhibitory activities are also expressed relative to α-D-glucose (assigned a value of 100).

Glucose derivative	*ID*50 value (μg)	*ID*50 value (μ-moles)	Relative molar activity
α-D-Glucose	183±24	1·02±0·13	100
β-D-Glucose	166±13	0·92±0·07	111
L-Glucose	167± 2	0·93±0·01	110
2-Deoxy-D-glucose	172±16	1·05±0·10	97
N-Acetyl-D-glucosamine	186±13	0·84±0·06	121
Methyl-α-D-glucopyranoside	198±11	1·02±0·06	100
Methyl-β-D-glucopyranoside	173± 3	0·89±0·02	115
3-*O*-Methyl-D-glucose	1,233±59	6·35±0·30	16
2 : 3 : 4 : 6-Tetra-*O*-methyl-D-glucose	2,600±76	11·00±0·32	9

Inhibition by other monosaccharides

The relative activities of other monosaccharides as inhibitors of the dextran response are shown in Table 2. It was not possible to determine the *ID*50 value for D-talose because only a small amount of this agent was available, but it was, like D-galactose, much less active as an inhibitor than were the other hexoses tested. In the pentose group, D-ribose and L-arabinose had only weak inhibitory actions. D-Erythrose, a tetrose, was much less active than D-glucose.

The *ID*50 value for 2-deoxy-D-ribose was similar to that of the parent sugar but 6-deoxy-L-mannose was much less effective than D-mannose.

Inhibition by sugar alcohols and cyclohexanols

The sugar alcohols of D-glucose and D-mannose—namely sorbitol and D-mannitol, respectively—had much less inhibitory action than their corresponding sugars (see Table 3). Galactitol (dulcitol), however, had an activity similar to that of its corresponding sugar, D-galactose, and the inhibitory effect of erythritol (a tetritol) was not significantly different ($P<0.05$) from that of its parent sugar, D-erythose. Although *myo*-inositol, a

TABLE 2

INHIBITION BY DIFFERENT MONOSACCHARIDES OF THE INCREASE IN VASCULAR PERMEABILITY IN RAT SKIN PRODUCED BY DEXTRAN (100 μg)

The antagonist and dextran were injected simultaneously into the skin. Inhibition was measured as the dose required to produce 50% reduction in response. *ID*50 values are the means and standard errors of three experiments. Inhibitory activities are also expressed relative to α-D-glucose (assigned a value of 100).

Monosaccharide	*ID*50 value (μg)	*ID*50 value (μ-moles)	Relative molar activity
D-Glucose	183±24	1·02±0·13	100
D-Mannose	155± 3	0·86±0·02	119
D-Galactose	1,043±35	5·79±0·19	18
D-Talose	>500	>2·78	<37
D-Fructose	158±14	0·88±0·08	116
L-Sorbose	185±23	1·03±0·13	99
D-Tagatose	317± 7	1·76±0·04	58
D-Ribose	1,086±47	7·23±0·31	14
D-Arabinose	168± 9	1·12±0·06	91
L-Arabinose	554±60	3·69±0·40	28
D-Xylose	173± 9	1·15±0·06	89
L-Xylose	167±12	1·11±0·08	92
D-Lyxose	282± 4	1·88±0·03	54
D-Erythrose	461±23	3·84±0·19	27
6-Deoxy-L-mannose (L-Rhamnose)	2,817±44	17·20±0·27	6
2-Deoxy-D-ribose	1,080±49	8·05±0·37	13

TABLE 3

INHIBITION BY SUGAR ALCOHOLS AND CYCLOHEXANOLS OF THE INCREASE IN VASCULAR PERMEABILITY IN RAT SKIN PRODUCED BY DEXTRAN (100 μg)

The antagonist and dextran were injected simultaneously into the skin. Inhibition was measured as the dose required to produce 50% reduction in response. *ID*50 values are the means and standard errors of three experiments. Inhibitory activities are also expressed relative to α-D-glucose (assigned a value of 100).

Alcohol	*ID*50 value (μg)	*ID*50 value (μ-moles)	Relative molar activity
D-Glucitol (Sorbitol)	605± 50	3·32±0·28	31
D-Mannitol	2,833±317	15·60±1·74	7
Galactitol (Dulcitol)	1,015± 24	5·57±0·13	18
Erythritol	476± 20	3·90±0·16	26
myo-Inositol	158± 4	0·88±0·02	116
Cyclohexane-1 : 2-diol (*cis*/*trans* mixture)	307± 13	2·65±0·11	38
Cyclohexane-1 : 2-diol (*trans*)	280± 6	2·41±0·05	42
Cyclohexane-1 : 3-diol (*cis*/*trans* mixture)	1,373± 26	11·80±0·22	9
Cyclohexane-1 : 4-diol (*cis*)	1,397± 29	12·00±0·25	9
Cyclohexane-1 : 4-diol (*cis*/*trans* mixture)	1,607± 72	13·80±0·62	7

cyclohexanehexol, was as effective as D-glucose, all the cyclohexanediols tested were less active as inhibitors of the dextran response, although the 1:2-diols were more effective than the 1:3- and 1:4-diols.

Inhibition by trioses and related substances

DL-Glyceraldehyde was as active as α-D-glucose on a weight basis but only half as active on a molar basis (see Table 4). The D-isomer of glyceraldehyde was much less effective than the racemate, and dihydroxyacetone (the other triose tested) was even weaker as an inhibitor of the dextran response. When the glyceraldehyde structure was modified to yield other aldehydes, alcohols and ketones, greatly reduced inhibitory activities were found (see Table 4).

TABLE 4

INHIBITION BY TRIOSES AND RELATED SUBSTANCES OF THE INCREASE IN VASCULAR PERMEABILITY IN RAT SKIN PRODUCED BY DEXTRAN (100 μg)

The antagonist and dextran were injected simultaneously into the skin. Inhibition was measured as the dose required to produce 50% reduction in response. *ID*50 values are the means and standard errors of three experiments. Inhibitory activities are also expressed relative to α-D-glucose (assigned a value of 100).

Triose or other substance	*ID*50 value (μg)	*ID*50 value (μ-moles)	Relative molar activity
DL-Glyceraldehyde	194± 36	2·2±0·40	46
D-Glyceraldehyde (syrup)	660± 40	7·3±0·44	14
Dihydroxyacetone	1,973± 39	21·9±0·44	5
Glycerol	1,197± 74	13·0±0·80	8
Propane-1 : 3-diol	1,490± 74	19·6±0·97	5
Propane-1 : 2-diol	1,583± 33	20·8±0·44	5
n-Propyl alcohol	978±102	16·3±1·70	6
iso-Propyl alcohol	930±101	15·5±1·68	7
Acetone	2,017±159	34·7±2·74	3
Ethylene glycol	1,490± 59	24·0±0·94	4
Glycolaldehyde	943±113	15·6±1·88	7
Ethyl alcohol	2,073± 59	45·0±1·29	2

Inhibition by disaccharides and trisaccharides

The glucose disaccharides were about as active as glucose on a weight basis but nearly twice as effective on a molar basis (see Table 5). Turanose, containing glucose and fructose, was about as active as the diglucoses, but sucrose, which also consists of glucose and fructose, was less active. Disaccharides containing glucose and galactose were also

TABLE 5

INHIBITION BY DISACCHARIDES AND TRISACCHARIDES OF THE INCREASE IN VASCULAR PERMEABILITY IN RAT SKIN PRODUCED BY DEXTRAN (100 μg)

The antagonist and dextran were injected simultaneously into the skin. Inhibition was measured as the dose required to produce 50% reduction in response. *ID*50 values are the means and standard errors of three experiments. Inhibitory activities are also expressed relative to α-D-glucose (assigned a value of 100).

Di- or trisaccharide	*ID*50 value (μg)	*ID*50 value (μ-moles)	Relative molar activity
Trehalose (α-D-glucopyranosyl-α-D-glucopyranoside)	184± 12	0·54±0·03	189
Maltose (4-*O*-α-D-glucopyranosyl-D-glucose)	241± 42	0·70±0·12	146
Isomaltose (6-*O*-α-D-glucopyranosyl-D-glucose)	200± 6	0·59±0·02	173
Cellobiose (4-*O*-β-D-glucopyranosyl-D-glucose)	193± 3	0·57±0·01	179
Gentiobiose (6-*O*-β-D-glucopyranosyl-D-glucose)	193± 3	0·57±0·01	179
Turanose (3-*O*-α-D-glucopyranosyl-D-fructose)	218± 12	0·64±0·03	159
Sucrose (α-D-glucopyranosyl-β-D-fructofuranoside)	472± 15	1·38±0·04	74
Lactose (4-*O*-β-D-galactopyranosyl-D-glucose)	1,533±101	4·48±0·30	23
Melibiose (6-*O*-α-D-galactopyranosyl-D-glucose)	400± 58	1·17±0·17	87
Melezitose (*O*-α-D-glucopyranosyl-(1 : 3)-*O*-β-D-fructofuranosyl-(2 : 1)-α-D-glucopyranoside)	712± 15	1·41±0·03	72
Raffinose (*O*-α-D-galactopyranosyl-(1 : 6)-*O*-α-D-glucopyranosyl-(1 : 2)-β-D-fructofuranoside)	815± 28	1·62±0·06	63

TABLE 6

ACTIVITIES OF MONOSACCHARIDES AS ANTAGONISTS OF THE VASCULAR RESPONSE IN RAT SKIN PRODUCED BY DEXTRAN (100 μg)

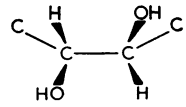
The values quoted are the molar inhibitory activities relative to α-D-glucose (assigned a value of 100).

Inhibitory activities of sugars which possess the D-*threo*-type of configuration in a cyclic form		Inhibitory activities of sugars which lack the D-*threo*-type of configuration	
α-D-Glucose	100	D-Galactose	18
β-D-Glucose	111	D-Talose	<37
L-Glucose	110		
2-Deoxy-D-glucose	97		
n-Acetyl-D-glucosamine	121		
D-Mannose	119	6-Deoxy-L-mannose	6
D-Fructose	116		
L-Sorbose	99		
D-Tagatose	58		
D-Xylose	89	D-Ribose	14
L-Xylose	92	2-Deoxy-D-ribose	13
D-Arabinose	91	L-Arabinose	28
D-Lyxose	54	D-Erythrose	27

less active than the diglucoses; lactose, in particular, was only 23% as active as α-D-glucose on a molar basis. The two trisaccharides, melezitose and raffinose, were both slightly less effective than glucose on a molar basis.

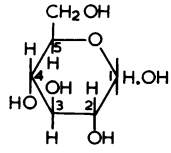
DISCUSSION

The results of the present work with antagonists of dextran throw light on the suggestion made by Poyser & West (1965) that the receptor for polysaccharides in rat skin may be stereospecific. Monosaccharides most active as inhibitors contain the D-*threo*-type of structure in their cyclic form as can be seen from the results in Table 6.



This structure seemed to confer on the monosaccharide maximum affinity for the receptor site. The simple tetrose, D-erythrose, lacks this type of structure and is much less effective than D-glucose. We have been unable to obtain the other aldotetrose, D-threose, but it would be expected that this would be more active than D-erythrose. Studies with cyclohexanediols indicate that, for compounds containing a 6-membered ring, two hydroxyl groups on adjacent carbon atoms are essential for inhibitory activity.

In D-glucose, the D-*threo*-configuration occurs at positions 3 and 4:



Studies with derivatives of this sugar reveal that free hydroxyl groups at positions 3 and 4 are essential for a potent inhibitory effect. The glycosidic hydroxyl group at position

1 and the hydroxyl group at position 2 seem to be less important because α- and β-methyl glucosides and 2-deoxy-D-glucose are all as active as D-glucose. Some pentoses such as xylose are also as effective as D-glucose, so it seems that the CH_2OH group at position 5 is also dispensable.

The acyclic sugar alcohols have low activities as antagonists of the dextran response, and this suggests that the ring form of a sugar is important for inhibitory activity. The oxygen in the ring is not essential, however, because *myo*-inositol, a cyclohexanehexol with a configuration similar to that of D-glucose, is as effective as D-glucose as an inhibitor. DL-Glyceraldehyde, like the sugar alcohols, is an acyclic structure but two molecules of this triose may combine to form a cyclic dimer (Wohl, 1898; Wohl & Neuberg, 1900; Baer & Fischer, 1943). Each mole of this cyclic dimer seems to have the same inhibitory activity as a mole of D-glucose. The D-isomer of glyceraldehyde is less active than the racemate but it may be that the combination of two molecules of this isomer does not form the required configuration for a potent antagonist. Glycoaldehyde and dihydroxyacetone also form cyclic dimers (Fenton & Jackson, 1899; Summerbell & Rochen, 1941) but these structures are weak antagonists and have no more activity than other simple alcohols and ketones.

The inhibitory activity of a disaccharide seems to depend on the activities of its constituent monosaccharide units. Galactose is a weak inhibitor of the dextran response and disaccharides containing this sugar—lactose and melibiose—are less effective than those composed only of glucose. The inhibitory activity of lactose per mole is similar to that of D-galactose and this may result from the absence of a free hydroxyl group on carbon 4 of the glucose constituent. The important hydroxyl groups at positions 3 and 4 of the glucose in melibiose are not involved in the linkage and this disaccharide is more active than lactose as an antagonist.

In the diglucoses, each monosaccharide constituent seems to retain its individual inhibitory activity. The type of linkage seems unimportant though in maltose and cellobiose the hydroxyl group in position 4 of one glucose unit is involved. It may be that in these disaccharides the second glucose unit combines with a receptor and so results in the first mentioned unit covering an adjacent site.

D-Glucose and D-fructose are both equiactive as inhibitors and turanose, which contains both these sugars, is a potent antagonist of the dextran response. Sucrose and the two trisaccharides, melezitose and raffinose, are less effective than turanose but this may be because the fructose in these sugars is present in the furanose form. This five-membered ring form of a sugar may have a lower affinity for the receptor than has the six-membered pyranose ring.

Regarding the mechanism of inhibition by glucose and other sugars of the dextran response in rat skin, it seems that factors concerning metabolism are unimportant because some of the sugars which are very active as inhibitors are not usually utilized whereas others are metabolized by the mammalian cell. Goth (1961) suggested that the receptor for dextran in rat mast cells was identical with some structure or carrier involved in sugar transport. In the present work, however, the structural requirements of sugars for antagonism of the dextran response do not correspond with those of any known transport system. The systems investigated include the penetration of sugars into muscle cells (Battaglia & Randle, 1959, 1960) and human erythrocytes (LeFevre & Marshall, 1958),

and active transport in the intestine (Cori, 1925; Crane, 1960; Rosenberg, 1961; Wilbrandt & Rosenberg, 1961). Some of the sugars which increase the potential or support fluid transfer across the intestinal wall (Barry, Dikstein, Matthews, Smyth & Wright, 1964) also differ from those which are potent antagonists of the dextran response.

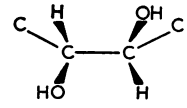
Penetration into the cell and utilization therefore seem unimportant for inhibition and it may be that glucose and other sugars compete with polysaccharides for receptor sites at, or close to, the exterior of the cellular membrane. These receptor sites may be present on some form of tissue-bound antibody, for Kabat (1957) has shown that different sugars exhibit different activities in inhibiting the precipitation reaction between dextran and human anti-dextran serum. The structural specificity varies with antibodies prepared to different dextrans (see Kabat & Mayer, 1964) and it is therefore of little value to compare the structural requirements observed in the present work with those of different dextran-anti-dextran systems as studied by Kabat and his various co-workers. No antibody to dextran has yet been found in the rat but Kabat & Mayer (1964) indicate that inhibition tests may be useful for studying the combination of antigen with antibody when no visible reaction occurs. Results with sugars as antagonists in the present study therefore suggest that there may be an antibody to polysaccharides in the skin of rats sensitive to these carbohydrate polymers.

Kabat (1954, 1956, 1957, 1960), Schlossman & Kabat (1962) and Kabat & Mayer (1964) observed that the size of the combining sites on antibodies to different dextrans, or on different antibodies to the same dextran, were complementary to different multiples of the glucose unit. When the combining site was directed against several glucose units, then the linkage was more important for combination than the stereochemistry of each sugar residue. Conversely, if the combining site was directed against a small number of monosaccharide units, then the stereochemistry of each sugar residue became of more importance. The receptor involved in the present work shows no specificity to a particular type of linkage and this suggests that the combining sites for sugars and polysaccharides in rat skin are complementary to a single monosaccharide unit.

SUMMARY

1. Different sugars have different activities as antagonists of the vascular response to dextran in rat skin.

2. Monosaccharides most active as inhibitors contain the D-*threo*-type of structure in their cyclic forms.



3. The six-membered ring structure of a sugar also seems to be a requisite for a potent antagonist, although the oxygen in the ring is probably not essential for combination with the dextran receptor because *myo*-inositol (a cyclohexanehexol) is as effective as D-glucose.

4. The inhibitory activity of a disaccharide depends on the activities of its constituent monosaccharide units; the type of linkage between the units, however, is not so important.

5. Inhibition by sugars probably does not involve metabolism or transport into cells. An antibody to polysaccharides may therefore exist in the skin of rats sensitive to carbohydrate polymers.

REFERENCES

BAER, E. & FISCHER, H. O. L. (1943). Glyceraldehyde 1,3-diphosphate (dimeric). *J. biol. Chem.*, **150**, 213–221.

BARRY, R. J. C., DIKSTEIN, S., MATTHEWS, J., SMYTH, D. H. & WRIGHT, E. M. (1964). Electric potentials associated with intestinal sugar transfer. *J. Physiol., Lond.*, **171**, 316–338.

BATTAGLIA, F. C. & RANDLE, P. J. (1959). Monosaccharide transport in rat diaphragm muscle. *Nature, Lond.*, **185**, 1713–1714.

BATTAGLIA, F. C. & RANDLE, P. J. (1960). Regulation of glucose uptake by muscle. IV. The specificity of monosaccharide transport systems in rat diaphragm muscle. *Biochem. J.*, **75**, 408–416.

BERALDO, W. T., DIAS DA SILVA, W. & LEMOS FERNANDES, A. D. (1962). Inhibitory effects of carbohydrates on histamine release and mast cell disruption by dextran. *Br. J. Pharmac. Chemother.*, **19**, 405–413.

CORI, C. F. (1925). The fate of sugar in the animal body. I. The rate of absorption of hexoses and pentoses from the intestinal tract. *J. biol. Chem.*, **66**, 691–715.

CRANE, R. K. (1960). Intestinal absorption of sugars. *Pharmac. Rev.*, **40**, 789–825.

DIAS DA SILVA, W. & LEMOS FERNANDES, A. D. (1965). Study of the mechanism of inhibition produced by hexoses on histamine release activity of dextran. *Experientia*, **21**, 96–97.

FENTON, H. J. H. & JACKSON, H. (1899). Crystalline glycollic aldehyde. *J. chem. Soc.*, **75**, 575–579.

GOTH, A. (1961). Probable mechanism of histamine release by dextran. *Fedn Proc.*, **20**, 257.

HARRIS, J. M., LUSCOMBE, D. K. & POYSER, R. H. (1967). The influence of molecular weight and structure on the vascular permeability responses induced by glucose polymers in rat skin. *Br. J. Pharmac. Chemother.*, **29**, 16–24.

KABAT, E. A. (1954). Some configurational requirements and dimensions of the combining site on an antibody to a naturally occurring antigen. *J. Am. chem. Soc.*, **76**, 3709–3713.

KABAT, E. A. (1956). Heterogeneity in extent of the combining regions of human antidextran. *J. Immun.* **77**, 377–385.

KABAT, E. A. (1957). Size and heterogeneity of the combining sites on an antibody molecule. *J. cell. comp. Physiol.*, **50**, 79–102.

KABAT, E. A. (1960). The upper limit for the size of the human antidextran combining site. *J. Immun.* **84**, 82–85.

KABAT, E. A. & MAYER, M. M. (1964). *Experimental Immunochemistry*, 2nd ed. Springfield, Illinois : Thomas.

LEFEVRE, P. G. & MARSHALL, J. K. (1958). Conformational specificity in a biological sugar transport system. *Am. J. Physiol.*, **194**, 333–337.

POYSER, R. H. & WEST, G. B. (1965). Changes in vascular permeability produced in rats by dextran, ovomucoid and yeast cell wall polysaccharides. *Br. J. Pharmac. Chemother.*, **25**, 602–609.

ROSENBERG, T. (1961). Membrane transport of sugars. A survey of kinetic and chemical approaches. *Path. Biol., Paris*, **9**, 795–802.

SCHLOSSMAN, S. F. & KABAT, E. A. (1962). Specific fractionation of a population of antidextran molecules with combining sites of various sizes. *J. exp. Med.*, **116**, 535–552.

SUMMERBELL, R. K. & ROCHEN, L. K. (1941). The structure of glycolaldehyde dimer. *J. Am. chem. Soc.*, **63**, 3241–3244.

WILBRANDT, W. & ROSENBERG, T. (1961). The concept of carrier transport and its corollaries in pharmacology. *Pharmac. Rev.*, **13**, 109–183.

WOHL, A. (1898). Synthese des r-glycerinaldehydes. *Ber. dtsch. chem. Ges.*, **31**, 2394–2395.

WOHL, A. & NEUBERG, C. (1900). Zur kenntniss des glycerinaldehydes. *Ber. dtsch. chem. Ges.*, **33**, 3095–3110.