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Hexosaminidase Isozyme in Type 0 G_{M2} Gangliosidosis (Sandhoff-Jatzkewitz Disease)

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G_{M2} gangliosidoses are due to inherited deficiencies of hexosaminidase activity. In type B G_{M2} gangliosidosis (Tay-Sachs disease), only hexosaminidase (hex) A is missing, while the less acidic isozyme, hex B, is present in increased amounts. In type 0 G_{M2} gangliosidosis (Sandhoff-Jatzkewitz disease), both hex A and hex B are missing. There has been considerable speculation regarding the relationship between hex A and hex B. Earlier studies suggested that hex A could be converted to hex B by neuraminidase [1, 2], and it was suggested that hex B was merely the aneuraminyl derivative of hex A. However, it has been found that the observed conversion was, in fact, not due to neuraminidase but rather to merthiolate which had been used as a preservative [3–5]. Furthermore, the amino acid composition of hex B is different than that of hex A [6]. Based upon structural and immunological studies [6–8] and upon the conversion of hex A to hex B by merthiolate [3], we have proposed that hex A has a structure which may be designated as $(\alpha\beta)_3$ and that the structure of hex B is $(\beta)_6$. In this model type B G_{M2} gangliosidosis would be the α^- mutation, while the type 0 disorder is the β^- mutation.

We now report a new patient with type 0 G_{M2} gangliosidosis. As found in cases previously studied [9–11], the small amount of residual enzyme is more highly charged at neutral pH than is hex A. We find that it is identical with a minor fraction of enzyme which can be isolated from normal fibroblasts by repeated chromatography. In agreement with the proposed model of hexosaminidase structure, we are able to demonstrate by immunologic means that this enzyme is composed, at least in part, of α subunits and that it contains no β subunits.

CASE REPORT

The patient is a 20-month-old Mexican American female. She was well at birth and developed normally the first several months. At 4 months of age she was capable of turning over, but at 6 months she no longer tried to sit up and developed a series of lower respiratory infections. A cherry-red macula was noted bilaterally, and the diagnosis of type 0 G_{M2} gangliosidosis was established by demonstrating that both hex A and hex B activity were virtually absent from plasma.

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At the age of 6 months a complete blood count, urinalysis, blood sugar, cholesterol, BUN, uric acid, SGOT, urine amino acid pattern, and skull X-rays were normal. Serum aldolase was 43 U (normal = 11–22 U), and the cerebrospinal fluid showed lactate dehydrogenase activity of 310 U (normal = 13–80 U). At the age of 6½ months the patient was unable to roll over by herself, and by 9 months she showed decreased movements and was unable to hold her head up. There was a slight increase in deep tendon reflex in the lower extremities, but no clonus was present and there were no pathologic reflexes. From 1 year of age the patient followed a progressive downhill course characterized by spontaneous movements and frequent episodes of respiratory infections with fever. After 16 months of age she showed progressive loss of weight in muscle mass, generalized increase in deep tendon reflexes in the upper and lower extremities, and continued respiratory infections. Grand mal seizures were controlled with phenobarbitol, dilantin, and diazepan.

The family history revealed no similar illnesses in any family members. The propositus was the product of a consanguineous marriage, as shown in the pedigree (fig. 1).

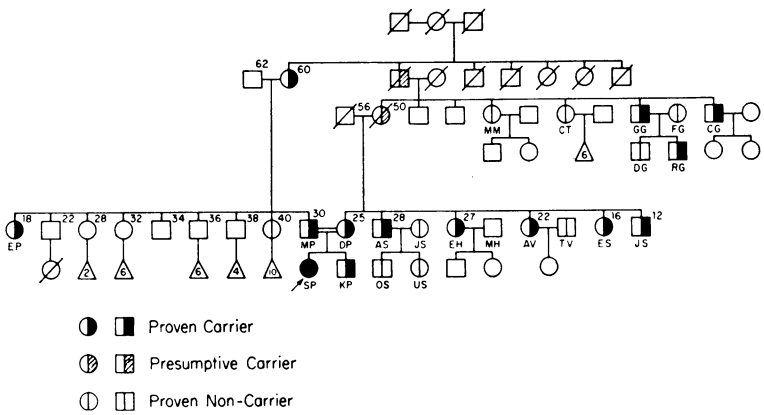


FIG. 1.—Pedigree of family with type 0 G_{M2} gangliosidosis

MATERIALS AND METHODS

Hexosaminidase assays were carried out as described previously [6] using the *β-N*-acetylglucosamine or *β-N*-acetylgalactosamine derivatives of 4-methylumbelliferone. Unless otherwise indicated, the glucosamine derivative was used. Thermostability studies were carried out in a system containing phosphate-citrate buffer (58 mM with respect to citrate and 85 mM with respect to phosphate, pH 4.4), 0.1% bovine serum albumin (hexosaminidase-free), and the enzyme fraction to be tested. The mixture was heated to 55°C; hexosaminidase activity was determined before heating and after 30, 60, and 90 min of heating.

To titrate enzyme with antiserum [8] (kindly provided by Dr. S. K. Srivastava), the sera were first heated at 56°C for 1 hr to destroy all remaining hexosaminidase activity. Various dilutions of antiserum were then made in control rabbit serum, and each of these dilutions was further diluted 1 to 4 in 0.154 M NaCl solution: in this way the final serum concentration in all tubes was the same. A 100-μl sample of enzyme solution containing between 50 and 170 μU of enzyme was mixed with 80 μl of 0.1 M KH_2PO_4/K_2HPO_4, pH 7.0. Then 20 μl of saline-diluted rabbit serum–antiserum mixture was added. Serum concentrations were expressed in terms of microliters of undiluted serum in each assay system. The mixtures were allowed to stand at 4°C for 18 hr, were diluted further by the

addition of 100 μl of .04 M KH_2PO_4/K_2HPO_4 buffer (pH 7.1) containing 0.1% bovine serum albumin (hexosaminidase-free), and were then centrifuged at 48,000 *g* for 1 hr at 4°C. Residual activity in the supernatant was measured in the usual manner. Control tubes which were not centrifuged and tubes to which only normal rabbit serum had been added were always assayed concurrently and showed no loss of activity. The pH activity curves were measured in systems containing 0.1 M citrate buffer, pH 3.0–6.5.

Starch gel electrophoresis was carried out in the system described by Okada and O'Brien [12], and Cellogel electrophoresis was carried out as described by Poenaru and Dreyfus [13].

Fibroblasts were grown in minimal essential medium [14] with 15% fetal calf serum using HEPES as a buffer. Washed trypsinized fibroblasts were suspended in 0.02 M potassium phosphate buffer (pH 8.0), frozen, and thawed. After centrifugation at 10,000 *g* for 20 min, the supernatant was used for chromatography. Chromatography was carried out at room temperature on a 5.5 × 68-mm column of DE-52 equilibrated with a 0.02 M potassium phosphate buffer, pH 8.0. The enzyme was eluted with a 200-ml linear gradient between the equilibrating buffer and a potassium phosphate buffer (0.04 M, pH 6.0) containing 0.4 M sodium chloride. Molecular weight determinations on Sephadex were carried out using a 9 × 530-mm Sephadex G-200 column calibrated with catalase (mol wt = 240,000), aldolase (mol wt = 158,000), ovalbumin (mol wt = 45,000), and cytochrome C (mol wt = 12,700).

RESULTS

Isolation of Hexosaminidase Fractions

Fibroblasts from the patient contained only 5 μU of enzyme/mg protein, approximately 1.6% of mean normal. Starch gel electrophoresis of fibroblast extracts from the patient showed that the residual enzyme moved further toward the anode than hexosaminidase A of normal fibroblasts. The same results were obtained using Cellogel electrophoresis, and in this system the fast moving band of the patient's fibroblasts had a mobility indistinguishable from the fast moving band of human brain, a band which has been designated as hexosaminidase C [13]. Chromatography of the residual enzyme revealed a double peak of activity eluting after the position of hexosaminidase A of normal fibroblasts. The major peak is designated hex S, the minor peak hex S′. In addition, there was a minimal but significant activity closely approximating the positions of hex A and hex B (fig. 2). No peak of hex S activity was seen in normal fibroblast extract or in extracts of fibroblasts from a patient with type B G_{M2} gangliosidosis. However, the quantity of hex A in normal fibroblasts and of hex B in type B G_{M2} gangliosidosis fibroblasts is enormously greater than the quantity of hex S in the patient's fibroblasts. Therefore, "trailing" of hex A and B could easily have obscured an amount of hex S equal to that found in the patient's fibroblasts. For this reason, the portion of the chromatogram corresponding to the position of hex S from normal and type B G_{M2} gangliosidosis fibroblasts was dialyzed against starting buffer and rechromatographed, redialyzed, and chromatographed a third time. The results are shown in figure 3. A peak of enzyme activity eluting in exactly the same position as the main peak of residual hexosaminidase in the fibroblasts from the patient with type 0 G_{M2} gangliosidosis, comprising only 0.1% of the total hexosaminidase activity, was identified in normal fibroblasts. Cellogel electrophoresis of this enzyme

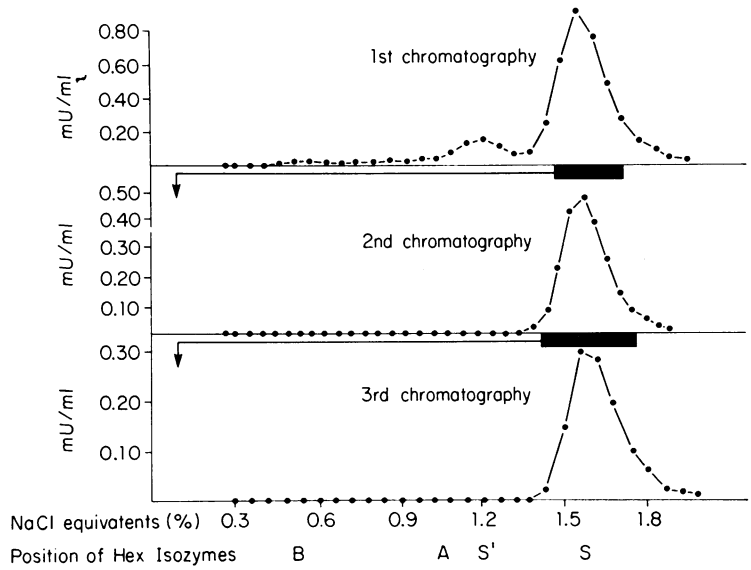


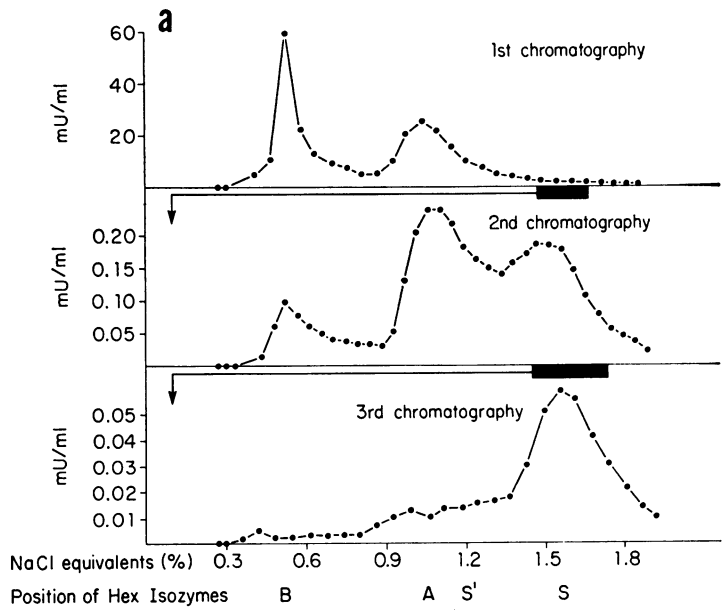
FIG. 2.—Chromatography of type 0 G_{M2} gangliosidosis fibroblast extract on DE 52 and subsequent rechromatography of area above solid bar. See text for conditions for chromatography. Hexosaminidase activity is plotted against concentration of NaCl as determined by conductivity. Approximate positions of hex A, hex B, hex S', and hex S are indicated.

confirmed that it had a band of activity with mobility identical with the hex S from type 0 G_{M2} gangliosidosis and that it contained, in addition, about an equal amount of hex A and a trace of hex B. The fibroblasts from the type B G_{M2} gangliosidosis patient contained no hex S peak.

Properties of Hexosaminidase S Peak

The reaction of hex S from normal and the type 0 G_{M2} gangliosidosis patient with anti–hex A and anti–hex B sera was studied. As shown in figure 4, the antiserum prepared against hex A was able to remove fibroblast hex A, hex B, and hex S from solution. The anti–hex B serum was able to remove both hex A and hex B from solution, but it had no effect on the hex S enzyme from the patient with type 0 G_{M2} gangliosidosis. In the case of the hex S from normal fibroblasts, which had been shown to be contaminated with about an equal amount of hex A, the results were intermediate between those obtained with the patient's hex S and hex A.

Some of the characteristics of hex A and hex B were compared with hex S and S' and are shown in table 1. Values from the literature [10] are included for hex C. The ratio of activity with the β-*N*-acetylglucosamine to the β-*N*-acetylgalactosamine derivatives of 4-methylumbelliferone of the S peak both of normal fibroblasts and fibroblasts from the patient was distinctly lowered as was the S' peak of the patient. The pH optima of all of the enzymes were the same, and the molecular weights did not differ significantly.



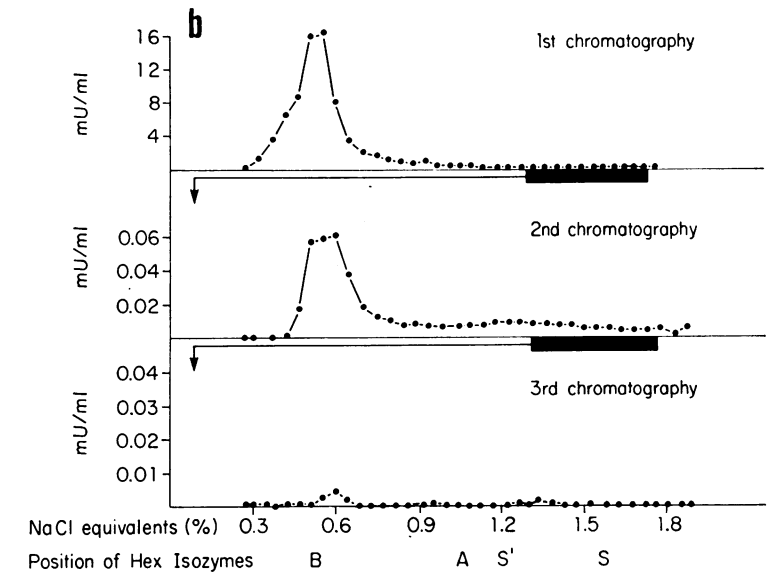


FIG. 3.—Chromatography of normal (*a*) and type B G_{M2} gangliosidosis (*b*) fibroblast extracts on DE 52 and subsequent rechromatography of the area above solid bar. General description as in fig. 2.

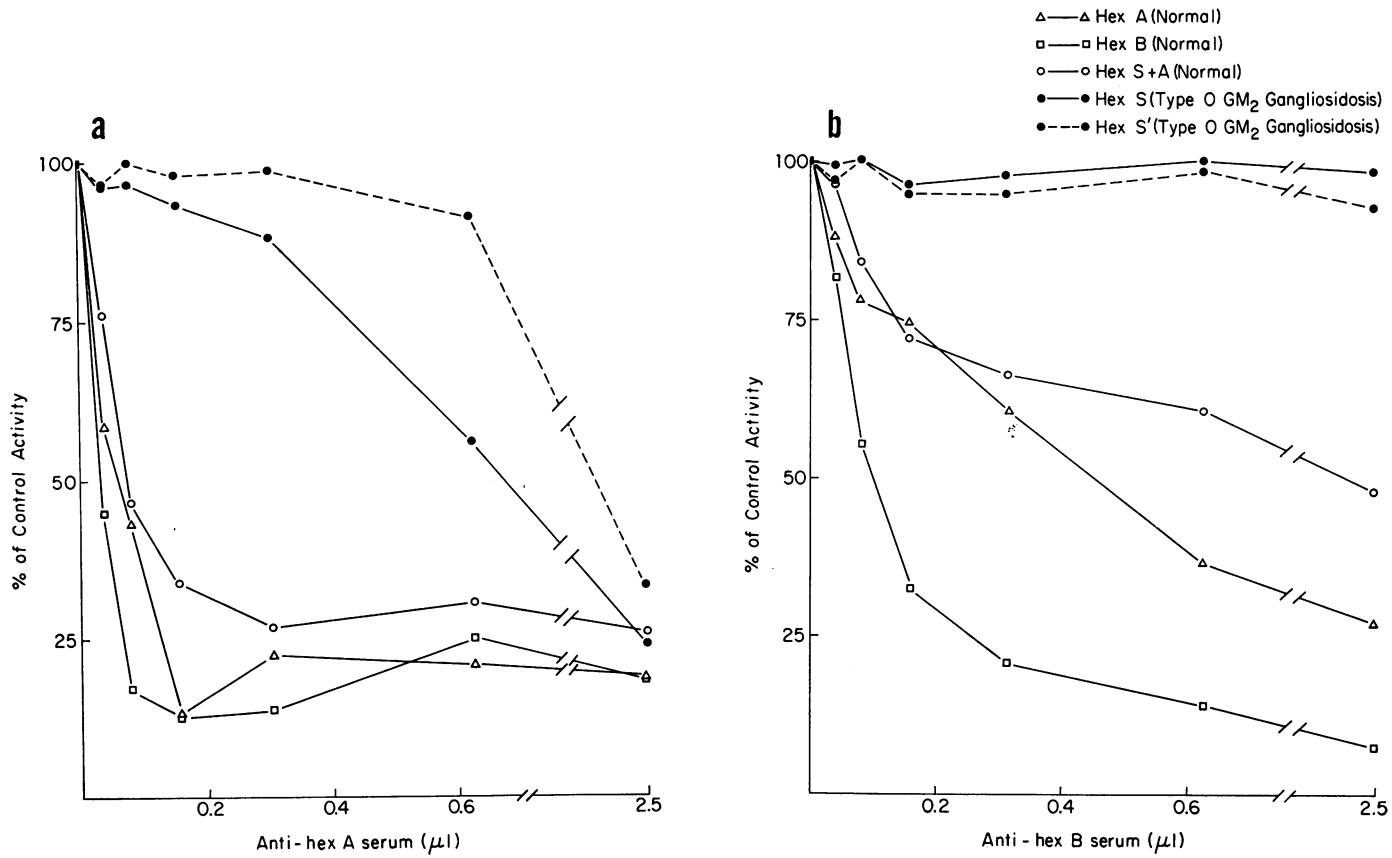


FIG. 4.—Titration of partially purified fibroblast hexosaminidases from normal and type 0 G_{M2} gangliosidosis with antiserum against hex A (*a*) and with antiserum against hex B (*b*). See text for conditions of titration.

TABLE 1

PROPERTIES OF HEXOSAMINIDASES

Property	Hex A	Hex B	Hex S	Hex S'	Hex C*
Thermostability	Labile	Stable	Labile	Labile	Labile
pH optimum	4.5	4.5	4.5	N.T.†	7
Ratio (*N*-acetylglucosamine/ *N*-acetylgalactosamine)	5.35	5.15	2.8	2.8	?
Precipitation with anti-hex A	+	+	+	+	0
Precipitation with anti-hex B	+	+	0	0	0
Molecular weight	140,000	140,000	158,000	N.T.†	?
Presence in normal fibroblasts	+	+	+	?	+‡
Presence in type A G_{M2} gangliosidosis	0	Increased	0	0	+‡
Presence in type 0 G_{M2} gangliosidosis	0	0	Increased	+	+§

* Data from [10].
† Not tested because of insufficient quantity.
‡ Brain.
§ "Tissues" and white blood cells.

DISCUSSION

The tissues of patients with type 0 G_{M2} gangliosidosis have small amounts of residual hexosaminidase activity. Sandhoff et al. [15] reported the residual liver enzyme to have an isoelectric point 0.3 pH units lower than hex A, and Braidman et al. [10] considered it to be identical with hex C, a more negatively charged isozyme found in various embryonic and adult tissues [16, 17]. Ikonne and Desnick [11], on the other hand, regarded the residual enzyme as being a species unique to type 0 G_{M2} gangliosidosis and have designated it hex S. We find that a minor component partially purified from normal fibroblasts is identical with the residual enzyme found in type 0 G_{M2} gangliosidosis. Although apparently similar in charge to hex C, this enzyme has characteristics which are quite different from those described for hex C by Braidman et al. [10]. Hex C has a pH optimum of approximately 7; the residual hexosaminidase in type 0 G_{M2} gangliosidosis has a pH optimum of 4.5. Hex C is apparently not removed from solution by anti-hex A serum; the residual hexosaminidase in type 0 G_{M2} gangliosidosis is readily removed by anti-hex A but not by anti-hex B. Hex C is apparently denatured on DEAE cellulose columns; the hexosaminidase in type 0 G_{M2} gangliosidosis is readily purified on DEAE cellulose columns. Finally, hex C was present in type B G_{M2} gangliosidosis tissues [10]; the isozyme which is found in type 0 G_{M2} gangliosidosis, while present in normal fibroblasts, is absent from fibroblasts of patients with type B G_{M2} gangliosidosis.

We have previously proposed that hex A has a subunit structure which might be designated as $(\alpha\beta)_3$ and that the structure of hex B is $(\beta)_6$. This model is supported not only by structural studies of the homogeneous enzyme but also by immunologic studies [8, 18–20] and by somatic cell hybridization studies [21,

22]. Furthermore, the conversion by merthiolate of hex A to what appears to be authentic hex B [3] indicates that hex A contains all of the subunits required for the formation of hex B. Other models which have been proposed to explain the relationship between hex A and hex B range from the suggestions that the two enzymes are the same [23] to their being unrelated proteins [24]. All of these models are clearly inconsistent with the experimental data now available. The suggestion that hex A and hex B differ only by virtue of their neuraminic acid content [1, 2] was not based upon the activity of neuraminidase, as originally thought, but rather on that of merthiolate [3–5]. This hypothesis and the suggestion of Tallman et al. [23] that the two enzymes are merely conformers are inconsistent with the different amino acid composition of the two enzymes [7] and with our finding that when hex A is converted to hex B by merthiolate, an additional protein subunit, the putative alkylated α chain, can easily be demonstrated [3, 5]. On the basis of cell hybridization studies, Gilbert et al. [24] recently proposed that there might be no structural relationship between hex A and hex B because it seemed that either of the two enzymes could be lost separately from human-mouse hybrids. Similar data were presented earlier by van Someren and van Henegouwen [25]. Tedesco et al. [26], however, reported that hex B could be lost without losing hex A but that hex A was not lost alone; Lalley et al. [27] reported opposite findings that hex B could not be lost without hex A. These contradictory studies demonstrate some of the difficulties in interpreting somatic cell hybridization techniques, particularly in the study of glycoproteins. Electrophoretic mobility of such proteins depends upon the tissue in which they are synthesized [28, 29], since their carbohydrate content may vary greatly. Human α galactosidase A, for example, was found to assume quite a different electrophoretic mobility in man-mouse hybrid cells than in human cells [30]. A number of observations are inconsistent with the suggestion that hex A and hex B are separate gene products. The two enzymes show marked immunologic cross-reactivity. It has been demonstrated clearly that hex A can be converted into an enzyme indistinguishable from hex B by immunologic, heat stability, electrophoretic, and chromatographic criteria. The intimate relationship between hex A and hex B is also emphasized by the finding that hex A is formed when type 0 and type B G_{M2} gangliosidosis cells are hybridized [21, 22].

Antiserum produced against hex A $(\alpha\beta)_3$ should contain antibodies both against the α and the β chains of hexosaminidase. In contrast, antisera raised against hex B $(\beta)_6$ should contain antibodies only against the β chain. Under these circumstances, it seems highly significant that hex S and hex S′ react only against the antiserum which contains antibodies against the α antigenic determinant: no reaction was found with the antiserum raised against only β chains. This suggests that hex S contains α subunits, a conclusion which is confirmed by the absence of this isozyme from fibroblasts of the α^- mutant, type B G_{M2} gangliosidosis. A much greater amount of anti-A antiserum was required to remove hex S from solution than was needed to remove an equal amount of hex A activity. It is quite possible

that the α subunits have much less catalytic activity than do the β subunits. Consistent with this view is the fact that homogeneous hex B $(\beta)_6$ has a higher specific activity than hex A $(\alpha\beta)_3$ [8].

Our studies do not definitively resolve the question of whether an additional unique subunit is also present in hex S. Thus, the present data could not permit us to distinguish between a $(\alpha)_6$ and a $(\alpha\gamma)_3$ structure for hex S. When α subunits are separated from β subunits by treatment with merthiolate or *p*-hydroxymercuribenzoic acid, the new catalytically inactive polypeptide which is formed has an electrophoretic mobility much faster than hex S on acrylamide disc electrophoresis. The rapidly moving polypeptide fragment appears to represent the alkylated α chains (E. Beutler and W. Kuhl, unpublished data). When treated with dithiothreitol, the alkylated hex A preparation develops activity which coincides with the position of purified placental hex S. This finding is consistent with the interpretation that hex S has, in point of fact, an $(\alpha)_6$ structure. The accumulation of hex B $(\beta)_6$ in type B G_{M2} gangliosidosis may be considered to be analogous to the accumulation of β hemoglobin chain polymers, Hb H, in patients with α thalassemia. Similarly, the accumulation of α chains (hex S) in type 0 G_{M2} gangliosidosis may be analogous to the circumstance in β thalassemia in which α hemoglobin chains accumulate. Whether the hexosaminidase α subunits found in patients with type 0 G_{M2} gangliosidosis represent an accumulation of a homopolymer of α subunits or whether they represent a heteropolymer of α with a non-β subunit will require further structural and immunologic studies of this minor hexosaminidase.

SUMMARY

The residual enzyme of the fibroblasts of a child with homozygous type 0 G_{M2} gangliosidosis (Sandhoff-Jatzkewitz disease) has been found to correspond with a minor fraction of enzyme which can be isolated from normal fibroblasts by repeated chromatography. This enzyme is designated as hexosaminidase (hex) S. It reacts with antiserum prepared against homogeneous hex A but not with serum prepared against homogeneous hex B.

These findings support our previously described model of the relationship between hex A and hex B: hex A has the structure $(\alpha\beta)_3$, while hex B is $(\beta)_6$. Type B G_{M2} gangliosidosis (Tay-Sachs disease) is the α^- mutation, while type 0 G_{M2} gangliosidosis (Sandhoff-Jatzkewitz disease) is the β^- mutation. In the absence of normal β subunits there is increased polymerization of α subunits forming hex S, which probably has a structure of $(\alpha)_6$. A parallel between the thalassemias and G_{M2} gangliosidosis is evident: deficiency of one of the chains of which the protein is composed leads to an excess of polymers comprised of the other chains. In type B G_{M2} gangliosidosis, the excess of β chains leads to increased amounts of hex B $(\beta)_6$; in type 0 G_{M2} gangliosidosis, the excess of α chains leads to formation of increased amounts of the α chain polymer, hex S.

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Conference on Tay-Sachs Disease

The First International Conference on Tay-Sachs Disease: Screening and Prevention will be held November 30–December 3, 1975, at the Riviera Resort Hotel, Palm Springs, California. Cosponsored by the National Tay-Sachs and Allied Diseases Association, Inc., and the National Foundation–March of Dimes, this conference is for both lay and professional people who are concerned with screening and prevention.

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