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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 13-103374- -00014-0000
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Señor
SUPERINTENDENTE DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES
E. S. D.

Trámite: **11**
Evento: **378**
Actuación: **412**

Re: PI.-**ASHA NUTRITION SCIENCES, INC.**-Solicitud de Patente de Invención en Fase Nacional PCT para **"FORMULACIONES NUTRITIVAS OPTIMIZADAS, MÉTODOS PARA LA SELECCIÓN DE DIETAS ADAPTADAS A PARTIR DE LAS MISMAS, Y MÉTODOS PARA UTILIZAR LAS MISMAS"**.-Clase **A23L 1/29**.-Expediente número **13-103.374**.-

Yo, **ALICIA LLOREDA RICAURTE**, mayor, vecina de esta ciudad, identificada con la cédula de ciudadanía número 39.690.713 de Usaquén, Representante Legal en Bogotá para todos los asuntos relacionados con la Propiedad Industrial de la sociedad **ASHA NUTRITION SCIENCES, INC.,** organizada y existente de conformidad con las leyes del estado de California, Estados Unidos y domiciliada en Palo Alto, Estado de California, Estados Unidos de América, atentamente manifiesto a usted que interpongo **RECURSO DE REPOSICIÓN** contra la Resolución Número **79599** dictada por el señor Superintendente de Industria y Comercio el 30 de Septiembre de 2015 y notificada por fijación en lista el 6 de Octubre de 2015, por medio de la cual se niega el privilegio de patente solicitado para la invención contenida en el expediente de la referencia.

I. FUNDAMENTOS DE DERECHO

Comc fundamento de mi recurso, me permito manifestar ante ese Despacho que el contenido de la Resolución Número **79599** evidencia que durante el examen técnico realizado a la solicitud denegada se realizó una evaluación incorrecta del objeto de la invención allí reclamada, sin considerar su real alcance e importancia. En este sentido, no se consideró el verdadero y valioso aporte técnico que representa para el arte en cuestión el programa de manejo nutricional para un individuo que incluye una formulación nutritiva que comprende una fuente de fitoquímicos, de ácidos grasos oemga-6 y de antioxidantes revelado en la solicitud denegada.

Es así que, a pesar de los argumentos proporcionados por el solicitante en respuesta al Concepto Técnico correspondiente al Oficio No. 15196, emitido por ese Despacho el 4 de Diciembre de 2015, en la Resolución impugnada este Despacho traslada y mantiene las objeciones frente a la claridad, unidad de invención y novedad de la sclicitud, argumentando básicamente que:

"(...) no se acepta el nuevo capítulo reivindicatorio presentado (radicado bajo el No° 13-103374-00011-0000 el 16 de Abril de 2015), comoquiera no se ajusta a las prescripciones contenidas en el artículo 34 de la Decisión 486, debido que la definición de la invención como "un sistema de manejo nutricional para individuo" implica una ampliación de la protección correspondiente a la divulgación contenida en la solicitud inicial".

En este sentido, el señor Examinador reconoce que:

"(...) la solicitante mediante escrito radicado bajo el No° 13-103374-00011-0000 el 16 de Abril de 2015 respondió oportunamente el requerimiento formulado y presenta nuevas reivindicaciones 1 a 29 que reemplazan las originalmente presentada, atendiendo de esta manera las observaciones efectuadas en el examen de fondo".

Sin embargo, ese Despacho no acepta tales modificaciones y declara que:

"(...) se tendrá en cuenta el capítulo reivindicatorio presentado con el radicado No. 13-103374-00007-0000".

Entonces, es claro que el señor Examinador no tiene en cuenta los argumentos presentados en la respuesta al Concepto Técnico de Oficio No. 15196 y reitera que:

"las características esenciales de la formulación de la reivindicación 1 y 2 habían sido divulgadas previamente en los documentos D1 a D5, por lo tanto, la materia reivindicada no es nueva".

Aunado a lo anterior, el señor Examinador asegura que:

"(...) la fuente del documento D5 corresponde a una publicación de la Fundación del Consejo Internacional de Información (...) publicado el día 5 de junio de 2009. El documento D5 corresponde a la traducción a idioma español del documento publicado con anterioridad a la fecha de presentación de la solicitud de la cual se invoca prioridad, de manera que constituye una anterioridad válida, y que afecta la novedad del objeto de la reivindicación 2".

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Frente a las anteriores consideraciones, a continuación me permito brindar argumentos técnicos para no sólo demostrar ante ese Despacho que el nuevo capítulo reivindicatorio que se presenta junto con el presente recurso **cumple** a cabalidad con los requisitos de claridad, novedad y nivel inventivo exigidos por los artículos 16, 18 y 30 de la Decisión 486 de 2000, sino además para establecer que su alcance no representa ninguna ampliación a la materia originalmente presentada y tiene pleno sustento en la descripción de la solicitud.

1. CAPÍTULO REIVINDICATORIO DE LA SOLICITUD DENEGADA.

1.1. Modificaciones al Capítulo Reivindicatorio.

Inicialmente y en razón de defender la patentabilidad de la presente solicitud denegada, me permito manifestar que el solicitante ha decidido modificar el capítulo reivindicatorio de la invención actualmente presentada, con el fin de darle mayor claridad al objeto reclamado y demostrar que su alcance no representa en ningún momento una ampliación de la materia originalmente presentada.

Frente a lo anterior, me permito resaltar que el nuevo capítulo reivindicado presentado junto con este memorial encuentra pleno sustento en la descripción de la solicitud y en el capítulo reivindicatorio actualmente aceptado por ese Despacho (Radicado No. 13-103374-00007-0000), como se expone a continuación:

Nueva Reivindicación No.	Soporte (con base en el documento de Publicación Internacional WO 2012/051591)
1	Párrafos 13, 15, 25, 164 y 151.
2	Párrafos 13, 26, 153, 151, 161, 164 y 165.
3	Tabla 1, Párrafos 25, 27, 59 y 75.
4	Tabla 1, Párrafo 150.
5	Párrafos 21, 129 y 130, y reivindicación 19 actualmente presentada.
6	Párrafos 10 y 11.
7	Párrafos 11, 20, 36, 70, 120, 125, 126, 142 y 176.
8	Reivindicación 8 actualmente presentada y Párrafos 9, 12, 122, 129, 130, 139 y 171.
9	Párrafos 128 y 142.
10	Párrafos 153, 161 y 165.
11	Párrafos 154, 156, 160 a 162, 164 y 165.
12	Párrafos 150 a 152 y 163.
13	Párrafos 9, 13, 15, 16, 21, 25, 164 y 151.
14	Tabla 1 y Párrafos 27, 25, 59 y 75.
15	Tabla 1 y Párrafo 150.

16	Párrafos 20, 70 y 71.
17	Párrafo 150.
18	Párrafos 129 y 130 y reivindicación 19 actualmente presentada.
19	Párrafos 10 y 11.
20	Párrafos 11, 36, 120, 125, 126, 131, 142, 176 y 180.
21	Párrafos 9, 12, 38, 122, 129, 130, 139 y 171.
22	Párrafos 128 y 142
23	Párrafos 153, 161 y 165.
24	Párrafos 154, 156, 160 a 162, 164 y 165.
25	Párrafos 150 a 152 y 163.
26	Reivindicación 28 actualmente presentada y Párrafo 131.
27	Reivindicación 29 actualmente presentada.

En concordancia con lo anterior, me permito aclarar además que el orden de enumeración y dependencia de las nuevas reivindicaciones se ha reajustado de conformidad con las modificaciones previamente descritas.

De esta forma, el mencionado **capítulo reivindicatorio modificado queda constituido por 27 reivindicaciones**, las cuales no constituyen de ninguna manera una ampliación al alcance de la solicitud original y cuentan con pleno sustento en las enseñanzas de la descripción. A su vez, me permito señalar que dichas modificaciones cumplen con el propósito de precisar el alcance de la materia reclamada y así permitir una mayor diferenciación de la invención de la solicitud denegada con el estado del arte previo. Por lo tanto, me permito reiterar que dicho capítulo cumple a cabalidad con las disposiciones de patentabilidad establecidas en el Artículo 34 de la Decisión 486 de 2000

1.2. **Alcance del Nuevo Capítulo Reivindicatorio.**

a) En la Resolución aquí impugnada, el señor Examinador menciona que "*(...) el capítulo reivindicatorio modificado presentado mediante el Radicado N° 13-103374-00011-0000 el 16/abril/2015, no encuentra sustento en la descripción. <u>En particular,</u> el "sistema de manejo nutricional para un individuo" no se encuentra sustentado en la descripción del documento de Publicación Internacional o de la respectiva solicitud en idioma español, en los párrafos a los que la solicitante hace mención, ni en la totalidad del capítulo descriptivo. En este sentido, en virtud del artículo 34 de la Decisión 486, no es posible aceptar el nuevo capítulo reivindicatorio (...)*" (Resaltado fuera del texto).

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Frente a tal declaración, me permito señalar que la materia de las nuevas reivindicaciones independientes 1 y 2 (*y por lo tanto, la de las correspondientes reivindicaciones dependientes*) se define ahora como *"un programa nutricional para un individuo que incluye al menos una formulación nutricional"* (Resaltado fuera del texto), lo cual corresponde a previos modificaciones y encuentra pleno soporte en los párrafos mencionados, especialmente, en las líneas 20 a 29 de la página 7 de la memoria descriptiva (Párrafo 13 del documento de publicación internacional WO 2012/051591).

Dicho párrafo revela explícitamente *"uno o más (por ejemplo, de 2 a 10) formulaciones nutritivas que colectivamente constituyen un programa nutricional para un individuo (...) Al menos una formulación contiene uno o más de los fitoquímicos tales como fitosterol o polifenoles, los ejemplos no limitantes de los mismos incluye, curcumina, cumarinas y ácido rosemarínico (...)"* (Resaltado fuera del texto).

De lo anterior, es claro que la descripción sí revela un programa nutricional (*el cual, a la luz de la descripción, es sinónimo de un sistema de manejo nutricional, como se había reivindicado*) constituido por una o más formulaciones nutricionales para un individuo. Entonces, la definición del objeto reclamado en el nuevo capítulo reivindicatorio, como *"programa nutricional"*, encuentra explícito y pleno sustento en la memoria descriptiva de la solicitud denegada y en ningún momento implica una ampliación de la protección correspondiente a la divulgación contenida en la solicitud inicial.

Aunado a lo anterior, me permito presentar como soporte adicional las declaraciones de los doctores Undurti N. Das y Kent L. Erickson, quienes dan su opinión científica en favor de la claridad del objeto reivindicado y en su debido soporte por la descripción de la solicitud. En este sentido, los Drs. Erickson y Das declaran en el párrafo [005] de las declaraciones que:

> *"El objeto de las reivindicaciones 1, 2, y 13 (y reivindicaciones dependientes) es claramente, sin ambigüedades, y directamente obtenido a partir de la especificación. Por ejemplo, el párrafo 13 recita de manera explícita, "uno o más (por ejemplo, del 2 al 10) formulaciones nutricionales que colectivamente constituyen un programa nutricional para un individuo". A la luz de la descripción, "programa nutricional" significa una o más formulaciones nutricionales (véanse los párrafos 11, 13, 15 y 38, por ejemplo). Además, a la luz de la descripción "sistema de manejo nutricional" es sinónimo de "programa nutricional" (véanse los párrafos 5, 15, 17 y 20, por ejemplo). El resto de los elementos en las reivindicaciones 1, 2 y 13 están claramente, sin ambigüedades, y directamente obtenidos de los párrafos 9, 21, 25, 26, 151, 153, 161, 164 y 165, por ejemplo".*

De esta manera, **me permito manifestar que el nuevo capítulo reivindicatorio cumple con las prescripciones contenidas en el Artículo 34 de la Decisión Andina 486 de 2000,** superando así la objeción del señor Examinador a éste respecto.

1.3. **Claridad del Nuevo Capítulo Reivindicatorio.**

b) Ahora bien, habiendo rechazado el capítulo reivindicatorio presentado con la respuesta al Concepto Técnico de Oficio No. 15196, ese Despacho mantiene las objeciones de claridad del capítulo reivindicatorio presentado bajo el radicado No. 13-103374-00007-0000, desconociendo los cambios y comentarios técnicos que resaltaban y soportaban la claridad del capítulo reivindicatorio modificado.

De esta forma y en primer lugar, el señor Examinador vuelve a mencionar en la Resolución aquí impugnada que el capítulo reivindicatorio no es claro ni conciso porque incluye cinco reivindicaciones independientes: dos de proceso, dos de producto y una referida a un sistema computarizado. Asimismo declara que se incluyen frases que van dirigidas a resultados a alcanzar, mediante un método o plan nutricional requerido por el consumidor, diseñado con diferentes fuentes nutricionales, durante una o más semanas.

Frente a tales objeciones, me permito destacar que, en vista de las modificaciones realizadas sobre el capítulo reivindicatorio, el número de reivindicaciones independientes se ha disminuido a tres, las cuales se refieren de manera clara y concisa a los programas nutricionales y a los métodos para seleccionar un programa nutricional como el reclamado, por lo que claramente esta objeción ha sido superada.

De otra parte, respecto a la objeción frente a las partes caracterizantes de la reivindicación 1 y a la mención de frases consideradas como resultados a alcanzar, amablemente me permito indicar que, como parte del capítulo reivindicatorio modificado, se han reducido las partes caracterizantes, y además se han eliminado las frases que fueron consideradas por el señor Examinador como resultados a alcanzar.

c) En segundo lugar, el señor Examinador aleja que la formulación reclamada podría contener uno solo de los componentes listados y que no define ninguna proporción de sus componentes. Además, agrega que las reivindicaciones 5-12 y 14, aunque estén encabezadas por una formulación, no definen específicamente los componentes de dicha formulación, ni mucho menos sus proporciones de combinación. En este sentido, el señor Examinador aduce que lo realmente reivindicado es un plan de dieta que pertenece claramente a un esquema de método de tratamiento dirigido a mejorar la salud de un consumidor y no una formulación caracterizada por sus componentes y proporciones.

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Frente a los antericres señalamientos, me permito manifestar que, de acuerdo con las modificaciones del numeral 1.1 del presente memorial, el nuevo capítulo reivindicatorio efectivamente incluye los componentes y las proporciones de las formulaciones nutricionales que constituyen el programa nutricional reivindicado. Así entonces, a lo largo de las reivindicaciones independientes y dependientes se definen porcentajes en peso o proporciones directas de los componentes de las formulaciones, con lo cual se logra un caracterización adecuada del objeto reclamado y se evidencia claramente la diferenciación de la invención frente a programas y/o formulaciones nutricionales del arte previo.

Ahora, me permito aclarar ante ese Despacho que ninguna reivindicación del nuevo capítulo reivindicatorio que se presenta junto con este memorial está dirigida a un método de tratamiento. El señor Examinador basa su objeción en una supuesta violación al alcance del Artículo 20, literal d) de la Decisión Andina 486 de 2000, el cual establece que no serán patentables: *"d) los métodos terapéuticos o quirúrgicos para el tratamiento humano o animal, así como los métodos de diagnóstico aplicados a los seres humanos o a animales"* (resaltado fuera de texto).

No obstante, me permito resaltar que el capítulo reivindicatorio modificado está explícitamente dirigido a reclamar un programa nutricional para un individuo que incluye una formulación nutricional que comprende una fuente de fitoquímicos, de ácidos grasos oemga-6 y de antioxidantes y los métodos correspondientes para seleccionar el mismo. La descripción divulga las posibles aplicaciones de dicho programa y el alcance para *"mejorar la salud del consumidor"*: sin embargo, la materia que es reclamada no hace referencia a un método de tratamiento.

En realidad, la caracterización del programa nutricional se hace directamente a través de sus componentes –*las formulaciones nutricionales que lo constituyen*- y de la relación proporcional o caracterización cuantitativa de los mismos. Entonces, es evidente que el tipo de formulaciones del plan nutricional y métodos que aquí se reclaman no caen dentro del alcance del mencionado Artículo 20, literal d) de la Decisión Andina 486 de 2000, y por lo tanto el capítulo reivindicatorio modificado que se presenta junto con este memorial no está de ninguna manera dirigido a materia no patentable.

En consecuencia, me permito señalar que el capítulo reivindicatorio modificado se ajusta completamente a los requerimientos del Artículo 20 de la Decisión Andina 486 de 2000.

d) Continuando con las objeciones, el señor Examinador menciona que, en cuanto a la reivindicación 14, no es aceptable que una formulación se caracterice por el uso de un kit. Frente a esto, ese Despacho aclara que la definición de un kit-de-partes no puede darse en términos exclusivos de la forma de ingesta o administración, el uso clínico, el

metabolismo de los fármacos combinados o de los parámetros farmacocinéticos o farmacodinámicos de los compuestos combinados y, tampoco podrá incluir las instrucciones de preparación ni la forma de administración de cada una de las preparaciones.

Sobre este particular, me permito señalar que, siguiendo las sugerencias del señor Examinador, las reivindicaciones 13 y 27 – *referentes al empleo de un kit que comprende las formulaciones nutricionales de la invención*- han sido eliminadas del nuevo capítulo reivindicatorio. Consecuentemente, se considera que la objeción del señor Examinador a este respecto queda completamente superada.

e) El señor Examinador manifiesta en la Resolución aquí impugnada que las reivindicaciones comprenden términos y expresiones imprecisas que no permiten definir especificamente el objeto de invención.

Frente a tal señalamiento, inicialmente me permito destacar ante ese Despacho que los términos empleados en las nuevas reivindicaciones han sido modificados para hacerlos más precisos. Sin embargo, respetuosamente me permito manifestar que no siempre es posible eliminar términos como *"al menos"* y *"menor que"*, debido a que las reivindicaciones deben permitir su adaptación a diferentes aplicaciones de producto.

Sobre lo anterior, me permito agregar que tales términos, generalmente usados para describir las proporciones o porcentajes de peso de los componentes de las formulaciones que constituyen el programa nutricional, no son imprecisos dado que su alcance es claramente conocido por la persona normalmente versada en la materia y es ampliamente utilizado en el campo técnico de la invención.

En este punto, considero importante resaltar que dichos términos no pueden sacarse de contexto y considerarse como "aislados", sino que deben interpretarse en el contexto de la reivindicación en el que se encuentran y deben ser entendidos por el experto en la materia a quien se dirigen a la luz del alcance de la memoria descriptiva. De acuerdo con el numeral 2.6.5.1 de la Guía para el examen de patentes de invención y modelo de utilidad de la Superintendencia de Industria y Comercio, *"el significado y alcance de las palabras de las reivindicaciones debe ser el que normalmente se les da en el área técnica de la solicitud"*. En este sentido, al experto en la materia se le puede hablar con la terminología habitual en su campo técnico, y no hay necesidad de explicar detalles de la invención que son completamente obvios para él.

Como prueba de lo anterior, en el testimonio adjunto de los Drs. Erickson y Das, quienes son expertos en la materia y conocen con detalle la terminología del campo de la invención, confirman que las reivindicaciones son claras y se encuentran plenamente soportadas por la descripción (Párrafo [0006]). En sus palabras:

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"Todos los elementos y limitaciones en las reclamaciones 1-27 son perfectamente claros a la luz de la descripción. Los términos utilizados en las reivindicaciones 1-27 son términos estándar utilizados en la técnica, y un experto puede entender, sin duda, su significado. Por ejemplo, los términos, "menor que, al menos, cantidades, productos alimenticios" se utilizan rutinariamente en la técnica. Además, los términos y rangos de medida utilizados en las reivindicaciones son claros. Por ejemplo, se ha dado a conocer en toda la descripción que el requisito de los nutrientes citados puede verse afectado por la presencia de otros nutrientes. Además, se ha descrito que las formulaciones pueden estar en forma de suplementos o dieta entera (por ejemplo, véanse los párrafos 25, 26, 131, y reivindicaciones modificadas 8 y 21). Por lo tanto, la presencia de los rangos alternativos es razonable y el experto en la materia ha sido bien instruido sobre cómo practicar aquellos rangos".

Aunado a lo anterior, muy amablemente me permito señalar que, en la práctica de patentes, la determinación de intervalos puntuales o concretos en lugar de "términos relativos" no es un aspecto mandatorio. En realidad, lo que sí es exigible es la utilización de términos relativos que sean comparables y, por tanto, perfectamente claros y entendibles para un experto en la materia. Tal es el caso de los términos *"al menos"* o *"menor que"*, los cuales tiene que interpretarse dentro del contexto de la invención, y de la misma reivindicación, para poder entender su alcance comparativo.

Cabe resaltar que el objetivo de la invención es equilibrar diversos nutrientes y mantenerlos en un rango seguro dentro del programa nutricional definido. Ahora bien, dado que el requerimiento de un nutriente depende de la presencia de otros nutrientes, es más efectivo mencionar el límite superior del nutriente. Entonces, ese Despacho debe tener en cuenta que, en dosis nutricionales, un límite superior de nutrientes es significativo, y puede ser interpretado fácilmente por una persona versada en el área técnica a la luz de las enseñanzas de la descripción. Además, no siempre es conveniente proporcionar todos estos nutrientes a través de una formulación, por lo tanto, los programas están creados de manera que las formulaciones se diseñen para adaptarse entre sí.

Por otra parte, también me permito manifestar a ese Despacho que resultaría una restricción injusta delimitar las proporciones o porcentajes de comparación en peso a una única manera de realización (*un único valor*), toda vez que, modificando el número de elementos, un tercero podría aprovechar impunemente el desarrollo realizado por el solicitante.

A la luz de lo anterior, me permito señalar que todos los términos de caracterización y definición de las reivindicaciones son claros y permiten la fácil identificación y directa comparación del objeto de la materia reclamada con lo divulgado en el estado de la técnica anterior. En este sentido, dichos términos resultan la mejor manera de describir la

invención, y de ninguna manera restan claridad a la reclamación. Por lo tanto, se considera que se supera completamente la objeción del señor Examinador a este respecto.

f) Finalmente, me permito traer a colación que, tal y como se explicó en la respuesta al Concepto Técnico de Oficio No. 15196, la materia reclamada en la presente invención en efecto se encuentra divulgada con mucha claridad y en los términos técnicos adecuados a lo largo de toda la descripción de la solicitud.

En este sentido, vale la pena señalar que toda la información que está incluida en la descripción enseña a la persona versada en la materia el por qué y cómo formular los nuevos productos nutricionales en el programa nutricional reclamado. Así, debe tenerse presente que el objetivo de los documentos de patente es enseñarle a la persona versada en la materia la manera en que puede llevar a cabo la invención después de que expire la patente. Es por esta razón, que el inventor de la presente solicitud ha dado instrucciones detalladas en la descripción.

A la luz de lo anterior y con el fin de orientar al señor Examinador, me permito presentar a continuación un resumen de la disposición de la información dentro de la descripción:

- Desde la pág. 1, línea 18 hasta la pág. 2 línea 21, y desde la pág. 12, línea 24 hasta la pág. 14, línea 7, se revela que los requerimientos de micronutrientes para la salud son sensibles, y que demasiada cantidad puede ser nocivos para la salud.

- Desde la pág. 2, línea 22 hasta la pág. 4 línea 26, se describe que hay una necesidad de programas nutricionales adaptados nuevos diseñados para adaptarse entre sí y mantener el consumo global de micronutrientes bajo control.

- Desde la pág. 5, línea 1 hasta la pág. 12 línea 22, se resume la forma de desarrollar este tipo de sistemas/programas de componentes y cómo usarlos.

- Desde la pág. 15, línea 12 hasta la pág. 21 línea 15, se proporcionan definiciones de los términos científicos utilizados.

- Desde la pág. 21, línea 16 hasta la pág. 77 línea 3, se divulgan los factores científicos que influyen en la selección de nutrientes y la forma de seleccionar los mismos.

- Desde la pág. 77, línea 5 hasta la pág. 88 línea 12, se proporcionan instrucciones detalladas para desarrollar los sistemas/programas nutricionales.

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- Desde la pág. 88, línea 13 hasta la pág. 89 línea 2, se da a conocer que existen ventajas de la fabricación y producción de la invención descrita.

- Desde la pág. 89, línea 3 hasta la pág. 96 línea 28, se divulgan los componentes de las formulaciones nutricionales y limitaciones alternas.

- Desde la pág. 97, línea 1 hasta la pág. 100 línea 5, se dan ejemplos concretos sobre cómo seleccionar nutrientes para diferentes grupos.

- Desde la pág. 100, línea 6 hasta la pág. 101 línea 20, se describen que las nuevas formulaciones pueden ser aplicadas en un método de profilaxis.

- Desde la pág. 101, línea 21 hasta la pág. 103 línea 3, se da a conocer un sistema computarizado novedoso para implementar computacionalmente los métodos reclamados.

- Desde la pág. 104, línea 26 hasta la pág. 149 línea 15, se divulgan 14 ejemplos concretos de las nuevas formulaciones y sus beneficios.

Consecuentemente, es evidente que la descripción de la presente solicitud permite que la persona del oficio normalmente versada en la materia pueda comprender el problema técnico y la solución aportada por la invención y además pueda reproducirla.

Frente a todas las anteriores consideraciones, me permito manifestar que el nuevo capítulo reivindicatorio cumple a cabalidad con las disposiciones de patentabilidad establecidas en el artículo 30 de la Decisión 486 de 2000, toda vez que es claro, conciso y encuentra pleno sustento en la descripción de la solicitud.

1.4. **Unidad de Invención del Nuevo Capítulo Reivindicatorio.**

De acuerdo con el señor Examinador en la Resolución aquí impugnada, la solicitud denegada en cuestión no cumple con el requisito de unidad de invención porque, sus reivindicaciones se refieren a por lo menos 2 grupos inventivos:

- Grupo Inventivo I: Una formulación nutricional.

- Grupo Inventivo II: Un sistema computarizado.

Frente a tales grupos, el señor Examinador señala que, al mencionar que la formulación se caracteriza porque comprende al menos un módulo y uno o más nutrientes en cada módulo, la invención da origen a infinitas formulaciones distintas y así mismo a un número indefinido de grupos inventivos.

En respuesta a lo anterior y de conformidad con las modificaciones señaladas en el numeral 1.1 del presente memorial, me permito señalar ante ese Despacho que el nuevo capítulo reivindicatorio se encuentra dirigido a proteger materia que comparte **un único concepto inventivo** y que por lo tanto cumple a cabalidad con las disposiciones de patentabilidad establecidas en el artículo 25 de la Decisión 486 de 2000.

En efecto, lo que se busca reivindicar con la presente solicitud (*a partir de las nuevas reivindicaciones 1 y 2*) es un programa nutricional para un individuo que incluye formulaciones nutricionales formadas por una fuente de fitoquímicos, una fuente de ácidos grasos omega-6 y una fuente de anti-oxidantes.

En tal capítulo reivindicatorio, las nuevas reivindicaciones independientes 1 y 2 definen correctamente los elementos y las proporciones de los componentes de la formulación nutricional, y por lo tanto, del programa nutritivo que se reclama y las nuevas reivindicaciones dependientes 3 a 12 no sólo agregan características técnicas esenciales que delimitan el programa reclamado sino que también incluyen las todas las limitaciones de las nuevas reivindicaciones 1 y 2 de la que son dependientes (*características técnicas esenciales*).

Por su parte, la nueva reivindicación 13 define correctamente los elementos y las condiciones técnicas del método que es útil para seleccionar un programa nutricional, y las nuevas reivindicaciones dependientes 14 a 27 sólo las agregan características técnicas esenciales que delimitan el método reclamado.

Consecuentemente, todas las reivindicaciones independientes 1, 2 y 13 incluyen las siguientes características comunes:

- Un programa nutricional para un individuo y/o el método para proveer nutrición a un individuo;
- Una fuente de fitoquímicos, de ácidos omega-6 y de antioxidantes;
- Una dosis diaria de omega-6; y
- Una dosis diaria de 25 mg a 10 g de antioxidantes.

En ese orden de ideas, también cabe destacar que la nueva reivindicación 27 es una reivindicación dependiente de la nueva reivindicación 13 (*método para proveer nutrición*), y por lo tanto el sistema computarizado reclamado en dicha reivindicación está diseñado para llevar a cabo el método de la reivindicación 13 para desarrollar los programas nutricionales. Teniendo en cuenta lo anterior, es evidente que el sistema computarizado que se reclama

pertenece al mismo grupo inventivo, único y común, dado que incluye todas las características técnicas de la nueva reivindicación independiente 13.

En consecuencia, es evidente que el capítulo reivindicatorio modificado se encuentra cobijado bajo el mismo concepto inventivo y por lo tanto dicho capítulo cumple a cabalidad con lo exigido por el Artículo 25 de la Decisión Andina 486 de 2000.

2. CONSIDERACIONES TÉCNICAS FRENTE A LAS ENSEÑANZAS DEL ARTE PREVIO

Ahora, teniendo en cuenta el alcance del nuevo capítulo reivindicatorio de la invención en cuestión, me permito manifestar ante ese Despacho que el programa nutricional para un individuo que incluye una formulación nutricional que comprende una fuente de fitoquímicos, de ácidos grasos omega-6 y de antioxidantes y el correspondiente método de selección revelados en la solicitud de patente denegada presentan un inequívoco carácter novedoso frente a los documentos **US 2004/001874 (D1), US 2006/280840 (D2), US 2009/220649(D3), US 2003/225731 (D4) e International Food Information Council Foundation, "*Ácidos grasos Omega 6 más que una moda, una cuestión de salud*" (D5).**

En la Resolución aquí impugnada, el señor Examinador considera que todas las características esenciales del programa nutricional de las reivindicaciones 1 y 2 son anticipadas por las revelaciones de los documentos D1, D2, D3, D4 y D5.

A este respecto, el Señor examinador señala que las características técnicas de las reivindicaciones independientes del capítulo reivindicatorio actualmente presentado "*(...) ya había sido divulgadas previamente los documentos (...)*" del arte previo. Es así como el señor Examinador concluye que "*(...) los argumentos de la solicitante no desvirtúan de manera alguna las objeciones a la patentabilidad ya sustentada*".

Frente a tales consideraciones, **me permito aseverar que los mencionados documentos D1, D2, D3, D4 y D5 de ninguna manera sugieren o enseñan una formulación nutricional que posea todas y cada una de las características técnicas estructurales y funcionales del programa nutricional que es objeto de la presente invención, tal como es reclamado dentro del capítulo reivindicatorio modificado que se presenta junto con este memorial.**

Ahora bien, con el ánimo de demostrar ante ese Despacho que la anterior afirmación es completamente correcta, a continuación me permito realizar un análisis comparativo detallado entre la información revelada en la presente solicitud y las enseñanzas brindadas por el documento D1:

2.1. **Los documentos D1, D2, D3, D4 y D5 enseñan formulaciones nutricionales con características técnicas estructurales diferentes a las del programa nutricional de la presente invención.**

Antes de entrar a discutir las diferencias más relevantes con cada documento del arte previo, es importante señalar que las reivindicaciones 1, 2 y 13 definen dos sets de condiciones/características principales que debe cumplir el programa y las formulaciones nutricionales allí revelados:

- ✓ Comprender una fuente de fitoquímicos, una fuente de ácidos grasos omega-6 y una fuente de antioxidantes (...) en donde la formulación o formulaciones del programa nutricional en conjunto comprenden una dosis diaria de 1 a 40 gramos de ácidos grasos omega-6 y de 25 mg – 10 gramos de antioxidantes; o

- ✓ Comprender una mezcla de lípidos de diferentes fuentes, (...) en donde las formulaciones proporcionan a un individuo una dosis de ácidos grasos omega-6 y omega-3 en una relación de omega-6 a omega-3 de 5:1 o mayor y una dosis diaria de 25 mg a 10 g de antioxidantes, en donde:

    (i) los ácidos grasos omega-6 son mayores que el 20% en peso de los lípidos totales; o,
    (ii) la dosis de ácidos grasos de omega-6 es menor que 40 gramos, y la dosis de ácidos grasos omega-3 es menor que 2 gramos.

Documento D1.

Teniendo en cuenta lo anterior, al revisar las enseñanzas de dicha anterioridad, el documento D1 no hace mención de formulaciones que comprendan ácidos grasos de omega-6, lo cual es la caracteristica técnica esencial de las nuevas reivindicaciones 1, 2 y 13.

Además, D1 no enseña la característica de una **dosis diaria de antioxidantes**, en el sentido de "antioxidantes" como se describe en la descripción de la solicitud (véanse los párrafos 25, 59 y 75). Por ejemplo, el párrafo 75 da a conocer que *"(...) los antioxidantes son moléculas capaces de retardar o prevenir la oxidación de otras moléculas"*, y que ciertos fitoquímicos como los carotenoides, flavonoides, polifenoles, licopeno, luteína, lignanos, etc., tienen propiedades anticxidantes. En contraste, D1 sólo enseña la acción antioxidante de la coenzima Q10 y no hace mención alguna de la dosis diaria atribuida. Por lo tanto, la definición de los antioxidantes en la descripción de la solicitud es diferente a la del documento D1. De este modo, es claro que D1 no revela el rango de dosis diaria de 25 mg a 10g de antioxidantes en el programa nutricional reclamado.

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Junto a lo anterior, me permito señalar que D1 no divulga todos y cada una de las características estructurales mencionadas en las nuevas reivindicaciones 1, 2 y 13 de la presente invención, ni tampoco **enseña ninguna de los dos sets de condiciones técnicas definidos anteriormente. Por lo tanto, D1 no sirve para desvirtuar la novedad de la invención denegada.**

Documento D2.

Ahora bien, el documento D2 tampoco hace mención alguna sobre la dosis diaria de omega-6, la cual es una característica técnica esencial de las nuevas reivindicaciones 1, 2 y 13, ni tampoco de la proporción de omega-6 a omega-3, la cual es una característica crucial de la nueva reivindicación 2.

Adicionalmente, D2 no tiene información alguna de la dosis diaria de antioxidantes, en un rango de 25 mg a 10 g, la cual es una característica técnica esencial de las nuevas reivindicaciones 1, 2 y 13. Como ya se describió para D1, el significado y definición del término *"antioxidante"* en la presente invención es diferente al que se le da en el documento D2.

Así las cosas, es claro que **el documento D2 tampoco enseña alguno de los dos sets de condiciones técnicas definidos en las nuevas reivindicaciones 1, 2 y 13 de la presente invención, y por lo tanto, tampoco sirve para desvirtuar la novedad de la presente solicitud.**

Documentos D3 y D4.

En primer lugar, los documentos D3 y D4 no hacen mención alguna sobre los ácidos grasos omega-6, los cuales son elementos imprescindibles en las formulaciones del programa nutricional reclamado. En segundo lugar, ni D3 ni D4 divulgan información específica sobre los antioxidantes, tal y como se reclaman en la presente invención.

Por lo tanto, es claro que **los documentos D3 y D4 no enseñan alguno de los dos sets de condiciones técnicas definidos en las nuevas reivindicaciones 1, 2 y 13 de la presente invención, y por lo tanto, tampoco sirve para desvirtuar la novedad de la presente solicitud.**

Documento D5.

Frente a las enseñanzas concretas del documento D5 *–las cuales el señor Examinador señala que afectan la materia de la nueva reivindicación 2-*, cabe resaltar que tal anterioridad no anticipa la materia reclamada en la presente invención dado que:

- El documento D5 **no** divulga *"una fuente de fitoquímicos, una fuente de ácidos grasos omega-6, y una fuente de antioxidantes"* como se reclama en las nuevas reivindicaciones 1, 2 y 13 que se presentan junto con este memorial.

- El documento D5 **no** revela una dosis **total** de ácidos grasos omega-6, tal y como se reivindica en las nuevas reivindicaciones 1, 2 y 13. La tabla de la página 3 de D5 simplemente enseña una dosis diaria de *"ácidos grasos esenciales omega-6 y omega-3: Recomendado y tomas habituales"*. Tales ácidos omega-6 y omega-3 esenciales se refieren al ácido linoleico (LA) y al ácido alfa-linolénico (ALA) (*Columna 1 de la tabla 3 y "Una cartilla sobre Grasas" en la página 1 de D5*), pero no se refieren a la totalidad de ácidos grasos omega-6 y omega-3. Cuando LA es 17g/día total, el omega-6 puede ser 50 g/día y, cuando ALA es 1,6 g/día total, el omega- 3 puede ser 3g/día, rangos que claramente no solapan con los reclamados en la presente invención.

- El documento D5 **no** da a conocer una dosis de antioxidantes, como se reclama en las nuevas reivindicaciones 1, 2 y 13 que se presentan junto con este memorial.

- El documento D5 **no** enseña una *"mezcla de lípidos de diferentes fuentes, (...) proporcionan a un individuo una dosis de ácidos grasos omega-6 y omega-3 en una relación de omega-6 a omega-3 de **5:1 o mayor**"*, como en la nueva reivindicación 2. En realidad, el documento D5 enseña que la relación de omega-6 a omega-3 está entre 2: 1 a 5: 1, mientras que la nueva reivindicación 2 indica que la *"relación de omega-6 a omega-3 de **5:1 o mayor**"*.

- A partir de la tabla de la página 2 del documento D5, no se llegaría inevitablemente a una *"mezcla de lípidos de diferentes fuentes"* en donde *"los ácidos grasos omega-6 son mayores que el 20% en peso de los lípidos totales*, porque el aceite de lino contiene sólo 13% de omega-6 en peso y una composición que comprende una alta cantidad de aceite de lino no contendría inevitablemente una cantidad de ácidos grasos omega-6 que sea mayor al 20% en peso de los lípidos totales.

Es preciso resaltar que las anteriores consideraciones son confirmadas por las declaraciones de los científicos que se adjuntan, específicamente en el párrafo [007]. Ahora, ese Despacho debe tener en presente que, para que se vea afectada la novedad de la invención, cada elemento de la reivindicación debe ser mencionado en el documento citado como arte previo exactamente como se menciona en la reivindicación que está siendo objeto de análisis. Una divulgación o anticipación no puede basarse en posibilidades y probabilidades *-o en una comparación utilizando las mismas palabras para cada anterioridad-*, sino que es una cuestión de carácter inevitable, tal y como aparece plenamente establecido en el numeral 2.12 de la Guía para el examen de patentes de invención y modelos de utilidad de la Superintendencia de Industria y Comercio.

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En vista de los argumentos anteriores, es claro que las características estructurales y funcionales del programa nutricional de la solicitud denegada no han sido exactamente divulgadas en su totalidad por los documentos D1 a D5. En consecuencia, me permito manifestar que la materia revelada en la presente invención es novedosa frente a las enseñanzas de tales documentos, cumpliendo por lo tanto a cabalidad con las disposiciones de patentabilidad establecidas en el artículo 16 de la Decisión 486 de 2000.

2.2. **En el estado de la técnica anterior también se encuentran fórmulas nutricionales que también difieren significativamente con el programa nutricional que es objeto de la presente invención.**

Aunado a los argumentos brindados en el anterior numeral, también me permito manifestar ante ese Despacho que en el estado de la técnica se encuentran enseñanzas radicalmente opuestas a la materia reclamada en el capítulo reivindicatorio modificado que se presenta anexo a este memorial, creando una serie de vacíos técnicos por los cuales para la persona medianamente versada en la materia no sería posible obtener la solución técnica brindada por el solicitante partiendo del arte previo.

En efecto, una vez más me permito llamar la atención de ese Despacho sobre los siguientes aspectos:

i. El arte previo enseña enfáticamente relaciones entre ácidos grasos omega-6 y omega-3 menores que 4:1, y adicionalmente no menciona las condiciones en las cuales pueden emplearse relaciones menores.

ii. El arte previo enseña enfáticamente la necesidad de consumir cantidades relativamente altas de EPA y DHA.

iii. El arte previo no menciona y tampoco considera la concentración de omega-6 y omega-3 con respecto a la totalidad de lípidos, incluyendo antioxidantes y fitoquímicos. En este sentido, tan sólo hace alusión a porcentajes de ácidos grasos, de grasas o de calorías (*Ver párrafo [0010] de la declaración de los científicos*).

iv. El arte previo divulga enfáticamente la disminución en el consumo de omega-6, recomendando que corresponda a menos del 4% e incluso menos del 1% de las calorías.

v. El arte previo no presenta la importancia de la dosificación de omega-6 total y omega-3 total, lo que lleva a que en todas las anterioridades se haga referencia a relaciones indeterminadas (*Ver párrafo [0007] de la declaración de los científicos*).

vi. En el arte previo, se recomienda el consumo de nutrientes que suprimen la actividad y el metabolismo del omega-6 como agente anti-inflamatorio, lo anterior sin que ni siquiera se haga alusión a las consecuencias de una supresión o deficiencia durante tiempos prolongados de dicho omega-6 (*Ver párrafo [0009] de la declaración de los científicos*).

vii. El arte previo no enseña que los antioxidantes y los fitoquímicos (los cuales también tienden a ser lípidos) pueden reducir la tolerancia y/o el requerimiento de ácidos grasos omega-3 (*Ver párrafo [0008] de la declaración de los científicos*).

En relación con lo anterior, en la siguiente Tabla se resumen algunas enseñanzas de dichas publicaciones:

Número	**Documento**	**Fecha de publicación**	**Enseñanza**
E1	US5780451 *"Producto nutricional para una persona que padece colitis ulcerativa"*	Abril 1, 1994	Relación de omega-6 a omega-3: 0,32, aunque el rango preferido es 0,25-4,0. Rango de EPA preferido: 16-19,5% Rango de DHA preferido: 5,7-8,3% Tabla 10
E2	Noticia de la US-FDA	Septiembre de 2004	3 gramos diarios de EPA y DHA
E3	EP 1510133A1 *"Composición grasa balanceada"*	2003	Relación de omega-6 a omega-3 1:1, el omega-6 representando <10% de la composición (Resumen y párrafos 2 y 6), y los ácidos grasos mono insaturados > 70% (párrafo 2)
E4	Dubnov G. *"Ácidos grasos omega-6 y enfermedad arterial coronaria: Pros y contras"*. Current Atherosclerosis reports, 2004, 6:441-446.	Noviembre de 2004	Relación de omega-6 a omega-3 ~1:1 (página 441, columna 1, párrafo 1)
E5	Hulbert A. *"Grasas dietarias y función de membrana: Implicaciones para el metabolismo y la enfermedad"*. Biol. Rev. (2005), 80, pp. 155-169.	Febrero de 2005	Relación de omega-6 a omega-3 ~1:1 (página 163, columna 2, párrafo 1)

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E6	Hamazaki et. al. *"La sociedad japonesa de nutrición de lípidos recomienda reducir el consumo de ácido linoleico. Una revisión y crítica a la evidencia científica". World Rev Nutr Diet. 2003; 92: 109-32.*	2003	El consumo de omega-6 (AL) debe corresponder a entre 3-4% de porcentaje de energía (página 130 - Conclusiones)
E7	Lands WE. *"Grasa dietaria y salud: La evidencia y la política de prevención". Lands, Ann. N.Y. Acad. Sci. 1055: 179-192 (2005)*	2005	El consumo de omega-6 (AL) debe corresponder a menos de 0,5% de las calorías (página 183)

*__Nota:__ *E* se refiere a un documento del arte previo diferente a D1 a D5.

Con respecto a lo anterior, me permito dirigir la atención del señor Examinador a lo siguiente:

- El documento E7 enseña la inclusión diaria de ácido graso omega-6 del 0.5% o menos como un porcentaje del total de calorías. Para una dieta calórica de 1800, un 0.5% o menos significa una dosis de menos de 1 gramo de omega-6 (0,5x1800= 9 calorías o 1 gramo). Esta es una enseñanza totalmente opuesta a lo que se reclama en las nuevas reivindicaciones 1 y 13, las cuales mencionan *"una dosis de 1 a 40 gramos de ácidos grasos de omega-6".*

- Los documentos E1, E3, E4 y E5 enseñan una relación de omega-6 a omega-3 menor a 5: 1. Esta enseñanza es opuesta a lo que se reclama en la nueva reivindicación 2, la cual indica *"una* dosis de ácidos grasos omega-6 y omega-3 en una relación de omega-6 a omega-3 de 5:1 o mayor".

- Entre un 3-4% de omega-6 como porcentaje de calorías totales (de acuerdo con E6) es igual a menos de 11,4% de la grasa total sobre la base de 35% de calorías provenientes de la grasa que generalmente se recomienda (4%/35% = 11,4%), mientras que el 0,5% de omega-6 como porcentaje de calorías totales (de acuerdo con E7) equivale a ~1,42% de grasa total (0,5%/35% = 1,42%). Esta enseñanza es opuesta a lo que se reclama en la nueva reivindicación 2 literal (i), la cual indica que *"los ácidos grasos omega-6 son mayores que el 20% en peso de los lípidos totales".*

- Adicionalmente, en la reivindicación 2 literal (ii) se enseña que la dosis de ácidos grasos omega-6 es de hasta 40 gramos, lo que es opuesto a la enseñanza de menos de 1 gramo que enseña E7. Además, la reivindicación 2 literal (ii) indica que la dosis de ácidos grasos omega-3 es menor a 2 gramos, lo que es opuesto a la altas cantidades que son enseñadas en el arte previo, particularmente en los documentos E1 y E2.

En vista de los argumentos anteriores, me permito manifestar que también es evidente que las nuevas reivindicaciones independientes 1, 2 y 13, así como sus reivindicaciones dependientes, de ninguna manera son anticipadas ni son obvias a partir de las enseñanzas encontradas en los documentos del arte previo (*Documentos D1 a D5 y E1 a E7*), y por lo tanto es innegable que la presente invención, cumple a cabalidad con las disposiciones de patentabilidad establecidas en el artículo 16 de la Decisión 486 de 2000.

2.3. **Consideraciones técnicas finales.**

Aparte de lo mencionado hasta el momento en el presente memoria, considero relevante destacar ante ese Despacho que los ácidos grasos, tales como omega-3, omega-6 y ácidos grasos mono-insaturados, poli-insaturados y saturados, corresponden simplemente a un subgrupo dentro de los lípidos, mientras que el término *'grasa'* hace referencia a triglicéridos (los cuales son otro subgrupo dentro de los lípidos). En este sentido, los lípidos comprenden ácidos grasos libres, mono-glicéridos, di-glicéridos, tri-glicéridos, vitaminas A, E, D, K, carotenoides, esteroles, ceras y otros tantos compuestos fenólicos (Ver documentos anexos a mi memorial del 14 de octubre de 2014: *Fany et al. J. Lipid Res. 2005. 46:839-861 and The Nomenclature of Lipids, J Lipid Res. 1978 Jan;19(1):114-28*).

Además, como se mencionó previamente, los lípidos hacen parte de un grupo denominado fitoquímicos, y por lo tanto, es claro que la existencia de una referencia particular a un constituyente específico que cae dentro del grupo general de nutrientes (*tal como lo divulgan los documentos D1 a D4*) de ninguna manera implica la inexistencia de novedad frente a las enseñanzas de tales anterioridades.

Ahora, sumado a lo anterior, atentamente me permito resaltar una vez más que los documentos D1, D2, D3 y D4 citados por el señor Examinador también fueron mencionados en el Reporte de Búsqueda Internacional realizado por la Oficina Coreana de Propiedad Intelectual. Sin embargo, tal y como lo podrá corroborar el señor Examinador, dicha Oficina internacional catalogó tales documentos D1 a D4 como categoría "A", esto es, como documentos que definen el estado general de la técnica, pero que no son de relevancia particular.

Ante todo es preciso señalar que con la información mencionada anteriormente de ninguna manera pretendo desconocer la independencia de la que goza la Superintendencia de Industria y Comercio al momento de analizar los méritos de patentabilidad de una solicitud, de acuerdo con las disposiciones del Convenio de París para la protección de la propiedad industrial.

Sin embargo, sí considero de gran importancia resaltar el hecho de que la materia técnica revelada en la solicitud de patente en cuestión ha sido catalogada como novedosa por los Examinadores de la Oficina Coreana de patentes (actuando como Oficina internacional), hecho que evidentemente representa un claro indicio de que la solic tud de patente en cuestión cumple a cabalidad con los requisitos de patentabilidad establecidos en la Decisión 486 de 2000.

II. CONCLUSIONES

Con base en los argumentos técnicos mostrados previamente, me permito manifestar ante ese Despacho que la materia revelada en la solicitud de patente en cuestión presenta un inequívoco carácter novedoso frente a las enseñanzas de los documentos citados en la Resolución Número **79599** aquí impugnada, cumpliendo de esta manera con las disposiciones establecidas en el artículo 16 de la Decisión 486 de 2000, y por lo tanto demostrando ser merecedora del privilegio de patente requerido.

Así mismo me permito manifestar que el nuevo capítulo reivindicatorio cumple a cabalidad con las disposiciones de claridad exigidas por los artículos 30 y 34 de la Decisión 486 de 2000, respectivamente.

III. PETICIÓN

En vista de todo lo anterior, ruego a usted proceder a estudiar nuevamente la solicitud a la luz de las argumentaciones presentadas y proceder a revocar la Resolución Número **79599**, con el fin de que se conceda el privilegio de patente a la presente invención.

IV. PODER

En este punto, me permito mencionar ante ese Despacho que el documento que acredita mi calidad de Representante Legal en Bogotá para asuntos relativos a la Propiedad Industrial de la sociedad peticionaria fue allegado junto con mi memorial del 5 de Agosto de 2014.

V. ANEXOS

Anexo al presente recurso me permito presentar:

i) Recibo número 15-112280, expedido por la Superintendencia de Industria y Comercio, que acredita el pago de las modificaciones mencionadas; y

ii) Copia de las páginas **1** a **13** que corresponden al nuevo capítulo reivindicatorio modificado, compuesto por **27 reivindicaciones**, tal y como se describe en el numeral 1.1 del presente memorial;

iii) Copia de las Declaraciones de los Drs. Kent L. Erickson y Undurti N. Das;

iv) Copia del documento: Fahy et al. J. Lipid Res. 2005. 46:839–861;

v) Copia del documento: The Nomenclature of Lipids, J Lipic Res. 1978 Jan; 19(1):114-23; y,

vi) Copia del documento: Lands. Ann. N.Y. Acad. Sci. 1055: 179–192 (2005).

VI. DOMICILIO

Mi dirección es Calle 72 No. 5-83, Piso 6º, Bogotá D.C.

Del Señor Superintendente,

ALICIA LLOREDA RICAURTE
T. P. 53.215

REIVINDICACIONES

1. Un programa nutricional para un individuo, que incluye al menos una formulación nutricional que comprende una fuente de fitoquímicos, una fuente de ácidos grasos omega-6 y una fuente de antioxidantes, en donde la formulación o formulaciones del programa nutricional en conjunto comprenden una dosis diaria de 1 a 40 gramos de ácidos grasos omega-6 y de 25 mg – 10 gramos de antioxidantes.

2. El programa nutricional para un individuo, que incluye al menos una formulación nutricional que comprende una mezcla de lípidos de diferentes fuentes, por lo que la formulación o formulaciones del programa nutricional en conjunto proporcionan una dosis diaria de ácidos grasos omega-6 y omega-3 en una relación de omega-6 a omega-3 de 5:1 o mayor y una dosis diaria de 25 mg – 10 gramos de antioxidantes a el individuo, en donde:

   (i) los ácidos grasos omega-6 son mayores que el 20% en peso de los lípidos totales; o,

   (ii) la dosis de ácidos grasos de omega-6 es menor que 40 gramos, y la dosis de ácidos grasos omega-3 es menor que 2 gramos.

3. El programa nutricional de acuerdo con la reivindicación 1 o 2, en donde:

   (i) el fitoquímico se selecciona de un grupo que consiste en monofenoles, polifenoles, carotenoides, monoterpenos, saponinas, lípidos, triterpenoides, betalaínas, organosulfurados, índoles, glucosinolatos y compuestos de azufre; y/o

   (ii) los ácidos grasos de omega-6 comprenden uno o más ácidos grasos seleccionados de un grupo que consiste en ácido linoleico (C18:2), ácido linoleico conjugado (C18:2), ácido gamma-linolénico (C18:3), ácido eicosadienoico (C20:2), ácido di-homo-gamma-linolénico (C20:3) y ácido araquidónico (C20:4); y/o

(iii) el antioxidante se selecciona de un grupo que consiste en flavonoides, flavonas, isoflavonas, catequinas, antocianidinas, isotiocianatos, carotenoides, sulfuros alílicos, polifenoles, terpenos, limonoides, fitosteroles, beta-caroteno, licopeno, luteína, lignano, ácido ascórbico (vitamina C), ácido fólico, selenio, super-óxido dismutasa (SOD), catalasa y glutatión peroxidasa (GSHpx), coenzima Q10 (CoQ10), glutatión y vitamina E; y/o

(iv) las formulación o formulaciones nutricionales comprenden ácidos grasos de omega-3 y los ácidos grasos de omega-3 comprenden uno o más ácidos grasos seleccionados de un grupo que consiste en ácido alfa-linolénico (C18:3), ácido estearidónico (C18:4), ácido eicosapentaenoico (C20:5), ácido docosapentaenoico (C22:5) y ácido docosahexaenoico (C22:6).

4. El programa nutricional de acuerdo con la reivindicación 3, en donde:

(i) uno o más polifenoles se seleccionan de un grupo que consiste en flavonoides, ácidos fenólicos, lignanos, estilbenos, punicalaginas, ácidos hidroxicinámicos y tirosoles; y/o

(ii) la dosis de polifenoles es mayor que 5 mg; y/o

(iii) uno o más fitosteroles se seleccionan de un grupo que consiste en campesterol, sitosterol, gama-sitosterol y estigmasterol.

5. El programa nutricional de acuerdo con cualquiera de las reivindicaciones 1 a 4, en donde el individuo pertenece a un grupo seleccionado de los siguientes:

(i) un grupo con base en los ingredientes dietéticos primarios de la dieta diaria o semanal del individuo, que se determina al comparar los niveles de uno o más antioxidantes, fitoquímicos, vitaminas, minerales, lípidos, carbohidratos, y proteínas provenientes de los alimentos de la dieta del individuo con los niveles en un conjunto de grupos predeterminados;

(ii) un grupo con base en el consumo diario promedio de uno o más granos, vegetales, frutas, legumbres, lácteos, carnes, mariscos, hierbas, edulcorantes y bebidas; y/o

(iii) un grupo con base en un factor demográfico.

6. El programa nutricional de acuerdo con cualquiera de las reivindicaciones 1 a 5, en donde la determinación del programa nutricional comprende seleccionar un grupo de dieta entre los basados en vegetales, los basados en carne y los basados en mariscos.

7. El programa nutricional de acuerdo con cualquiera de las reivindicaciones 1 a 6, en donde la formulación o formulaciones nutricionales comprenden:

(i) menos de 500 calorías o menos del 25% de calorías diarias; y/o

(ii) envases de vegetales o jugo de vegetales, envases de fruta o jugo de fruta, envases de granos deshidratados, envases de cereales, envases de legumbres, granos, nueces, semillas, envases de carne y/o mariscos, hierbas, lípidos, comidas, bocadillos, guarnición, ensalada, postres, lácteos, polvo, puré y/o yogur; y/o

(iii) nutrientes seleccionados de fitoquímicos, lípidos, antioxidantes, vitaminas, minerales, simbióticos, probióticos, prebióticos, microorganismos y fibras; y/o

(iv) artículos alimenticios enteros provenientes de fuentes naturales; y/o

(v) fuentes naturales de lípidos seleccionados de aceites, mantequillas, margarinas, nueces y semillas; y/o

(vi) micronutrientes derivados total o parcialmente de fuentes naturales; y/o

(vii) líquidos, crema o parche para uso tópico.

8. El programa nutricional de acuerdo con cualquiera de las reivindicaciones 1 a 7, en donde la formulación o formulaciones nutricionales proporcionan:

(i) una ingesta dietética diaria parcial o completa de nutrientes para el individuo; y/o

(ii) suplementos, equilibrios o reemplazos del consumo de alimentos diarios del individuo con base en el grupo del individuo o el consumo de lípidos del individuo; y/o

(iii) al menos 25%, preferiblemente al menos 50% o más preferiblemente al menos 80% de una ingesta total de calorías diaria o semanal para el individuo; y/

(iv) la saciedad y preferencia dietética del individuo.

9. El programa nutricional de acuerdo con cualquiera de las reivindicaciones 1 a 8, en donde:

(i) la formulación o formulaciones nutricionales comprenden artículos alimenticios que se seleccionan con base en los métodos de procesamiento empleados para preparar la formulación o artículo alimenticio, y en donde el procesamiento no se selecciona o se selecciona de descascarar, retirar una capa, deshidratar, proporcionar en fresco, asar y asar a la parrilla; y/o

(ii) los nutrientes de los alimentos se extraen, y se incorporan en una formulación para la administración como líquido, polvo seco, crema o parche tópico.

10. El programa nutricional de acuerdo con cualquiera de las reivindicaciones 1 o 3 a 9, en donde:

(i) la formulación o formulaciones nutricionales comprenden ácidos grasos omega-3, en donde la proporción de ácidos grasos omega-6 a omega-3 es de 1:1 a 10:1, 10:1 a 20:1 o de 20:1 a 50:1; y/o

(ii) los ácidos grasos omega-6 son del 20-70% en peso de los lípidos totales; y/o.

(iii) la formulación o formulaciones nutricionales comprenden ácidos grasos omega-3, en donde la dosis de ácidos grasos omega-3 es de menos de 2 gramos.

11. El programa nutricional de acuerdo con cualquiera de las reivindicaciones 1 a 10, en donde:

(i) la formulación o formulaciones nutricionales comprenden ácidos grasos omega-9, en donde la proporción de ácidos grasos omega-9 a omega-6 es menor de 4:1; y /o

(ii) la formulación o formulaciones nutricionales comprenden ácidos grasos mono insaturados y poliinsaturados, en donde la proporción de ácidos grasos mono insaturados a poliinsaturados es menor de 4:1; y/o

(iii) la formulación o formulaciones nutricionales comprenden ácidos grasos omega-9, en donde los ácidos grasos omega-9 son de 10-30% o 30-60% en peso de los lípidos totales; y/o

(iv) los ácidos grasos omega-6 son de 30-70% en peso de los lípidos totales; y/o

(v) la formulación o formulaciones nutricionales comprenden ácidos grasos omega-3, en donde los ácidos grasos omega-3 son menores del 20% o menores del 10% en peso de los lípidos totales; y/o

(vi) la dosis de los ácidos grasos omega-6 es menor de 35 g, o menor de 25 g, o menor de 10 g; y/o

(vii) la formulación o formulaciones nutricionales comprenden ácidos grasos omega-3, en donde la dosis de los ácidos grasos omega-3 es menor de 1 g o menor de 0.5 g.

12. El programa nutricional de acuerdo con cualquiera de las reivindicaciones 1 a 11, en donde la formulación o formulaciones nutricionales comprenden:

(i) uno o más polifenoles, cuya dosis es de 5-140 mg o de 140-300 mg; y/o

(ii) folato, cuya dosis es de 100-500 mcg o 500-1000 mcg; y/o

(iii) uno o más fitosteroles, cuya dosis es de 150-550 mg o de 550-1000 mg; y/o

(iv) uno o más carotenoides, cuya dosis es de 100-1000 mcg o de 1000-5000 mcg, o de 5000-14000 mcg; y/o

(v) betaina y/o colina, cuya dosis es de 25-100 mg, o de 100-400 mg, o de 400-600 mg; y/o

(vi) antioxidantes, cuya dosis es de 100-500 mg, o de 500 mg - 4 g, o de 4-10 g; y/o

(vii) selenio, cuya dosis es de 5-55 mcg, o de 55-95 mcg, o de 95-135 mcg; y/o

(viii) una o más fibras, cuya dosis es de 1-10 g, o de 10-30 g, o 30-50 g; y/o

(ix) vitamina E alfa/gama de 0 001-0.01%, o de 0.01-0.15%, o de 0.15-0.30% en peso de los lípidos totales.

13. Un método para proveer nutrición a un individuo, donde el método comprende las etapas de:

(a) determinar para el individuo un grupo con base en las preferencias alimentarias y/o un factor demográfico; y

(b) sobre la base del grupo dietario, seleccionar un programa nutricional para el individuo, incluyendo al menos una formulación nutricional que comprende una fuente de fitoquímicos, una fuente de ácidos grasos omega-6, y una fuente de antioxidante,

en donde la formulación o formulaciones del programaa nutricional comprenden en conjunto una dosis diaria de 1 a 40 g de ácidos grasos omega-6, y de 25 mg a 10 g de antioxidantes.

14. El método de acuerdo con la reivindicación 13, en donde:

(i) el fitoquímico se selecciona de un grupo que consiste en monofenoles, polifenoles, carotenoides, monoterpenos, saponinas, lípidos, triterpenoides, betalaínas, organosulfurados, índoles, glucosinolatos y compuestos de azufre; y/o

(ii) los ácidos grasos de omega-6 comprenden uno o más ácidos grasos seleccionados de un grupo que consiste en ácido linoleico (C18:2), ácido linoleico conjugado (C18:2), ácido gamma-linolénico (C18:3), ácido eicosadienoico (C20:2), ácido di-homo-gamma-linolénico (C20:3) y ácido araquidónico (C20:4); y/o

(iii) el antioxidante se selecciona de un grupo que consiste en flavonoides, flavonas, isoflavonas, catequinas, antocianidinas, isotiocianatos, carotenoides, sulfuros alílicos, polifenoles, terpenos, limonoides, fitosteroles, beta-caroteno, ácido ascórbico (vitamina C), ácido fólico, selenio, super-óxido dismutasa (SOD), catalasa y glutatión peroxidasa (GSHpx), coenzima Q10 (CoQ10), glutatión y vitamina E.

15. El método de acuerdo con la reivindicación 14, en donde:

(i) uno o más polifenoles se seleccionan de un grupo que consiste en flavonoides, ácidos fenólicos, lignanos, estilbenos, punicalaginas, ácidos hidroxicinámicos y tirosoles; y/o

(ii) uno o más fitosteroles se seleccionan de un grupo que consiste en campesterol, sitosterol, gama-sitosterol y estigmasterol.

16. El método de acuerdo con la reivindicación 13, en donde el programa nutricional comprende una pluralidad de artículos alimenticios y/o suplementos que comprenden fitoquímicos, lípidos, antioxidantes, vitaminas, minerales, simbióticos, probióticos, prebióticos, microorganismos y fibras o combinaciones de los mismos.

17. El método de acuerdo con cualquiera de las reivindicaciones 13 a 16, en donde el programa nutricional proporciona una dosis de polifenoles mayor de 5 mg

18. El método de acuerdo con cualquiera de las reivindicaciones 13 a 17, en donde el individuo pertenece a un grupo seleccionado de los siguientes:

(i) un grupo con base en los ingredientes dietéticos primarios de la dieta diaria o semanal del individuo, que se determina al comparar los niveles de uno o más antioxidantes, fitoquímicos, vitaminas, minerales, lípidos, carbohidratos, y proteínas provenientes de los alimentos de la dieta del individuo con los niveles en un conjunto de grupos predeterminados;

(ii) un grupo con base en el consumo diario promedio de uno o más granos, vegetales, frutas, legumbres, lácteos, carnes, mariscos, hierbas, edulcorantes y bebidas.

19. El método de acuerdo con cualquiera o varias de las reivindicaciones 13 a 18, en donde la determinación del programa nutricional comprende seleccionar un grupo de dieta entre los basados en vegetales, los basados en carne y los basados en marisco.

20. El método de acuerdo con cualquiera de las reivindicaciones 13 a 19, en donde la formulación o formulaciones nutricionales, artículos alimenticios y/o suplementos comprenden:

(i) menos de 500 calorías o menos del 25% de calorías diarias; y/o

(ii) envases de vegetales o jugo de vegetales, envases de fruta o jugo de fruta, envases de granos deshidratados, envases de cereales, envases de legumbres, granos, nueces, semillas, envases de carne y/o mariscos, hierbas, lípidos, comidas, bocadillos, guarnición, ensalada, postres, lácteos, polvo, puré y/o yogur; y/o

(iii) artículos alimenticios enteros provenientes de fuentes naturales; y/o

(iv) fuentes naturales de lípidos seleccionados de aceites, mantequillas, margarinas, nueces y semillas; y/o

(v) micronutrientes derivados total o parcialmente de fuentes naturales; y/o

(vi) artículos alimenticios suficientes para suplementar la dieta del consumidor y/o uno o más nutrientes seleccionados para suplementar un grupo; y/o

(vii) líquidos, crema o parche para uso tópico.

21. El método de acuerdo con cualquiera de las reivindicaciones 13 a 20, en donde la formulación o formulaciones nutricionales, artículos alimenticios y/o suplementos proveen:

(i) una ingesta dietética diaria parcial o completa de nutrientes para el individuo; y/o

(ii) suplementos, equilibrios o reemplazos del consumo de alimentos diarios del individuo con base en el grupo del individuo o el consumo de lípidos del individuo; y/o

(iii) al menos 25%, preferiblemente al menos 50% o más preferiblemente al menos 80% de una ingesta total de calorías diaria o semanal para el individuo; y/o

(iv) la saciedad y preferencia dietética del individuo.

22. El método de acuerdo con cualquiera de las reivindicaciones 13 a 21, en donde:

(i) la formulación o formulaciones nutricionales o artículos alimenticios se seleccionan con base en los métodos de procesamiento empleados para preparar la formulación o artículo alimenticio, y en donde el procesamiento no se selecciona o se selecciona de descascarar, retirar una capa, deshidratar, proporcionar en fresco, asar y asar a la parrilla; y/o

(ii) los nutrientes de los alimentos se extraen, y se incorporan en una formulación para la administración como líquido, polvo seco, crema o parche tópico.

23. El método de acuerdo con cualquiera de las reivindicaciones 13 a 22, en donde la formulación o formulaciones nutricionales, artículos alimenticios y/o suplementos comprenden:

(i) ácidos grasos omega-3, en donde la proporción de ácidos grasos omega-6 a omega-3 es de 1:1 a 10:1, 10:1 a 20:1 o de 20:1 a 50:1; y/o

(ii) ácidos grasos omega-6 son mayores que el 20% en peso del total de lípidos; y/o

(iii) ácidos grasos omega-3, en donde la dosis de los ácidos grasos omega-3 es menor que 2 gramos.

24. El método de acuerdo con cualquiera o varias de las reivindicaciones 13 a 23, en donde la formulación o formulaciones nutricionales, artículos alimenticios y/o suplementos comprenden:

(i) ácidos grasos omega-9, en donde la proporción de ácidos grasos omega-9 a omega-6 es menor de 4:1; y /o

(ii) ácidos grasos mono insaturados y poliinsaturados, en donde la proporción de ácidos grasos mono insaturados a poliinsaturados es menor de 4:1; y/o

(iii) ácidos grasos omega-9, en donde los ácidos grasos omega-9 son de 10-30% o 30-60% en peso de los lípidos totales; y/o

(iv) ácidos grasos omega-6 de 30-70% en peso de los lípidos totales; y/o

(v) ácidos grasos omega-3, en donde los ácidos grasos omega-3 son menores del 20% o menores del 10% en peso de los lípidos totales; y/o

(vi) ácidos grasos omega-6 en una dosis menor de 35 g, o menor de 25 g, o menor de 10 g; y/o

(vii) ácidos grasos omega-3, en donde la dosis de los ácidos grasos omega-3 es menor de 1 g o menor de 0.5 g.

25. El método de acuerdo con cualquiera de las reivindicaciones 13 a 24, en donde la formulación o formulaciones nutricionales, artículos alimenticios y/o suplementos comprenden:

(i) uno o más polifenoles, cuya dosis es de 5-140 mg o de 140-300 mg; y/o

(ii) folato, cuya dosis es de 100-500 mcg o 500-1000 mcg; y/o

(iii) uno o más fitosteroles, cuya dosis es de 150-550 mg o de 550-1000 mg; y /o

(iv) uno o más carctenoides, cuya dosis es de 100-1000 mcg o de 1000-5000 mcg, o de 5000-14000 mcg; y/o

(v) betaina y/o colina, cuya dosis es de 25-100 mg, o de 100-400 mg, o de 400-600 mg; y/o

(vi) antioxidantes, cuya dosis es de 25-500 mg, o de 500 mg - 4 g, o de 4-10 g; y/o

(vii) selenio, cuya dosis es de 5-55 mcg, o de 55-95 mcg, o de 95-135 mcg; y/o

(viii) una o más fibras, cuya dosis es de 1-10 g, o de 10-30 g, o 30-50 g; y/

(ix) vitamina E alfa/gama de 0.001-0.01%, o de 0.01-0.15%, o de 0.15-0.30% en peso de los lípidos totales.

26. El método de acuerdo con cualquiera de las reivindicaciones 13 a 25, en donde se prepara una lista para el individuo, la cual proporciona:

(i) fuentes naturales predeterminadas de lípidos, las fuentes se seleccionan de aceites, mantequilla, margarinas, nueces y semillas, y uno o más nutrientes seleccionados de antioxidantes, fitoquímicos, vitaminas y minerales en cantidades que optimicen los nutrientes dietéticos de tal forma que la ingesta de lípidos del individuo proporcione un efecto benéfico al individuo; y/o

(ii) una recomendación para el consumo de artículos alimenticios durante al menos una semana; y/o

(iii) los artículos alimenticios que no deberán estar incluidos en la dieta diaria del individuo; artículos alimenticios que deberán estar limitados en la dieta diaria del individuo; o artículos alimenticios que se deberán agregar a la dieta diaria del individuo.

27. Un sistema computarizado para implementar computacionalmente el método de acuerdo con cualquiera de las reivindicaciones 13 a 26, caracterizado porque comprende:

(a) un dispositivo de computadora que tenga una memoria;

(b) un dispositivo de entrada para ingresar la información que se relacione con la ingesta dietética actual del individuo en la memoria;

(c) una base de datos en la memoria para almacenar la información;

(d) un primer módulo de programa, para la ejecución en el dispositivo de computadora, para determinar un grupo de dieta del individuo correspondiente a la ingesta dietética actual del individuo; en donde el grupo de dieta del individuo se:

(i) predetermina e ingresa directamente en el dispositivo de computadora; y/o

(ii) determina ya sea manual o computacionalmente; y/o

(iii) selecciona de basado en vegetales, basado en mariscos y basado en carnes;

(e) una base de datos de nutrientes para almacenar los lineamientos dietéticos con relación a los grupos de dieta de individuos; en donde la base de datos de nutrientes comprende las variaciones adecuadas para el consumo dietético diario promedio de nutrientes correspondiente a cada grupo de dieta, y/o las variaciones adecuadas para un consumo dietético diario de carbohidratos, proteína, vitaminas, minerales y fitoquímicos;

(f) una base de conocimientos en la memoria que tenga reglas para manipular la información en la base de datos para proporcionar un programa dietético futuro recomendado para el individuo, el programa dietético comprende uno o más nutrientes seleccionados de antioxidantes, fitoquímicos, fitosteroles, vitaminas y minerales en cantidades que optimicen los nutrientes dietéticos para proporcionar un efecto benéfico al individuo, cuando se obtienen a

partir de los alimentos listados en el programa al menos el 25% u opcionalmente al menos el 70% de las calorías diarias promedio del individuo;

(g) un segundo módulo de aplicación, para ejecución en el dispositivo de computadora, para aplicar las reglas en la base de conocimientos para la información en la base de datos y a los lineamientos en la base de nutrientes y para generar un programa de nutrición para el usuario en una base de datos de resultados; y

(h) medios para transferir el contenido de la base de datos de resultados, bajo la dirección del segundo módulo de programa,

en donde el programa de nutrición comprende un listado de formulación o formulaciones y opcionalmente artículos alimenticios para el consumo diario por el individuo.

REPUBLIC OF COLOMBIA
SUPERINTENDENCE OF INDUSTRY AND TRADE

In re the Application of:

Asha Nutrition Sciences, Inc.

Application No. 13-103.374

Filed: April 23, 2013

For: OPTIMIZED NUTRITIONAL FORMULATIONS, METHODS FOR SELECTION OF TAILORED DIETS THEREFROM, AND METHODS OF USE THEREOF

DECLARATION

Mr.
SUPERINTENDENT OF INDUSTRY AND COMMERCE
DIVISION OF NEW CREATIONS

Sir:

I, Kent L. Erickson, hereby declare:

[001] I received a Ph.D. in Anatomy from Oregon Health and Sciences University, Portland, OR, and I performed post-doctoral work at Oregon Regional Primate Research Center in the field of Dermatology. I served as a Scientist in the Cancer Metastasis and Treatment Laboratory at the National Cancer Research Institute, National Institutes of Health, Frederick, MD. I also served as a Researcher at the National Institute of Arthritis, Musculoskeletal and Skin Diseases of the National Institutes of Health, Bethesda, MD. I was an Underwood Fellow of the Biotechnology and Biological Sciences Council-UK and worked in the Centre for Stem Cell Biology at the University of Sheffield, UK. I served as Chair of the Department of Cell Biology & Human Anatomy at the University of California, Davis, School of Medicine for 17 years. I also served as a member of the editorial board of the Journal of Nutrition for 4 years; the American Journal of Clinical Nutrition for 6 years and the Journal of Food Science and Nutrition for 16 years. I am currently one of the Editors of the British Journal of Nutrition as well as the

Journal of Nutritional Sciences. From 1975 to 2013, I was employed as a professor by The University of California, Davis, School of Medicine; I currently hold the position of Professor and Chairman Emeritus.

[002] I am not an inventor, applicant, owner, or assignee of the above-referenced patent application. I serve on the Scientific Advisory Board (SAB) of Asha Nutrition Sciences, the assignee of the subject application. I have been allotted a modest amount of stock option grant as compensation for my SAB role. I have not received any compensation specifically for preparing this declaration.

[003] I have read the international publication document WO 2012/051591, which corresponds to the above-referenced patent application. Throughout this declaration the paragraph numbers mentioned in reference to the current patent application correspond to the international publication document WO 2012/051591. I have also read the amended claims 1-27 being filed with the Office in November 2015. Further, I have read all the other documents referenced in this declaration.

[004] I interact with many professionals in my career who possess ordinary skills in the art, such as doctors, scientists, nurses, dieticians, nutritionists, and the like ("skilled artisans"). These professionals typically have advanced degrees such as masters, Ph Ds., and/or M.Ds. I am closely aware of the knowledge and skill levels of such professionals. I am confident in declaring that the following matters are clear to me and would be clear to other skilled artisans.

[005] The amended independent claims 1, 2, and 13 are as follows:

1. A nutritional program for an individual, including at least one nutritional formulation comprising a source of phytochemical, a source of omega-6 fatty acids, and a source of antioxidant, wherein formulation(s) of the nutritional program collectively comprise a daily dosage of 1 to 40g of omega-6 fatty acids and 25mg-10g of antioxidants.

2. A nutritional program for an individual, including at least one nutritional formulation comprising mixture of lipids from different sources, whereby the formulation(s) of the program collectively provide a daily dosage of omega-6 and omega-3 fatty acids at an omega-6 to omega-3 ratio of 5:1 or greater and a daily dosage of 25mg-10g of antioxidants to the individual, wherein:
   (i) the omega-6 fatty acids are greater than 20% by weight of total lipids; or
   (ii) the dosage of omega-6 fatty acids is less than 40g and the dosage of omega-3 fatty acids is less than 2g.

13. A method for providing nutrition to an individual, the method comprising the steps of:
   (a) determining for the individual a cohort based on dietary preferences and/or a demographic factor; and

(b) on the basis of the cohort selecting a nutritional program for the individual, including at least one nutritional formulation comprising a source of phytochemical, a source of omega-6 fatty acids, and a source of antioxidant, wherein formulation(s) of the nutritional program collectively comprise a daily dosage of 1 to 40g of omega-6 fatty acids and 25mg-10g of antioxidants.

The subject matter of claims 1, 2, and 13 (and dependent claims) is clearly, unambiguously, and directly obtained from the specification. For example, paragraph 13 explicitly recites, "one or more (e.g., from 2 to 10) nutritional formulations that collectively make up a nutritional program for an individual." In light of the specification "nutritional program" means one or more nutritional formulations (see paragraphs 11, 13, 15, and 38, for example). Further, in light of the specification "nutritional management system" is synonymous with "nutritional program" (see paragraphs 5, 15, 17, and 20, for example). Rest of the elements in claims 1, 2, and 13 are clearly, unambiguously, and directly obtained from paragraphs 9, 21, 25, 26, 151, 153, 161, 164, and 165, for example.

[006] All the elements and limitations in claims 1-27 are perfectly clear in light of the disclosure. The terms used in claims 1-27 are standard terms used in the art, a skilled person can undoubtedly understand their meaning. For example, the terms, *"less than, at least, amounts, food items"* are routinely used in the art. Further, the terms and the ranges used in the claims are clear. For example, it has been disclosed throughout the specification that the requirement for the recited nutrients can be affected by presence of other nutrients, additionally it has been disclosed that the formulations may be in form of supplements or entire diet (for example, see paragraphs 25, 26, 131, amended claim 8 and 21). Therefore, presence of alternate ranges is reasonable and the skilled person has been well directed how to practice the ranges.

[007] The reference D5, "Omega-6 Fatty Acids and Health Fact Sheet" published by International Food Information Council Foundation on June 5, 2009, teaches omega-6 to omega-3 ratio of 2:1-5:1 (page 3 paragraph 2), which is outside the range of 5:1 or greater claimed in instant claim 2. Further, there is no teaching of daily dosage of antioxidants in D5. Furthermore, there is no teaching of daily dosage of total omega-6 or omega-3 in D5. The table on page 3 of D5 merely teaches daily dosage of "Essential Omega-6 and Omega-3 Fatty Acids: Recommended and Usual Intakes" (see title of the Table). Essential omega-6 and omega-3 refers to linoleic acid and alpha-linoleic acid, confirmed in column 1 of the table, not total omega-6 and omega-3. Furthermore, D5 does not teach "mixture of lipids from different

sources" "wherein, omega-6 fatty acids are greater than 20% by weight of total lipids." The table at page 2 of D5 merely lists some sources of omega-6 fatty acids. There is no teaching anywhere in the document regarding which sources to choose. For example, if one selects canola oil and flaxseed oil in equal parts the resulting omega-6 to omega-3 ratio would be 1:1.88. Therefore, D5 does not meet the limitations recited in any of the instant claims 1, 2, or 15.

[008] The subject patent application has disclosed important factors that were neither common-knowledge nor well known or routine in the prior art regarding omega-6, omega-3 fatty acids, antioxidants, and phytochemicals in general. The disclosure explains at great length that phytochemicals have strong properties including antioxidant and oxidant actions, and that antioxidants and phytochemicals can reduce the tolerance for omega-3 fatty acids and increase the requirement of omega-6 fatty acids, and that such actions are not just attributable to antioxidant actions of phytochemicals (see paragraphs 58, 59 and 78). The disclosure also explains that antioxidants have a narrow window of healthful effects (paragraphs 79-81). The disclosure further explains that phytochemicals and antioxidants can suppress a number of inflammatory pathways and that excessive suppression may be problematic (see paragraph 4, 101 and 102). The disclosure also teaches omega-6 dosage to be critical for health (see paragraph 69, 73, 164, examples 6-14). Therefore, the disclosure specifically teaches upper limits on daily dosage of omega-6, antioxidants, and various phytochemicals

[009] In contrast, prior art widely-held the belief that omega-6 is inflammatory and omega-3 is anti-inflammatory, in the prior art, when in-vitro and/or in-vivo omega-6 levels or the metabolites of omega-6 are found to be suppressed by certain nutrient(s) or omega-3 uptake or metabolism is enhanced by a certain nutrient(s), the nutrient(s) is (are) recommended as anti-inflammatory and its use is encouraged. For example, prior art has recommended use of vitamin E, curcumin, flavonoids, and other phytochemicals for suppression of PGE2 an arachidonic acid (omega-6) metabolite, assumed to be inflammatory, or inhibition of cycloxygenases (COX-1 and -2), enzymes responsible for formation of PGE2 (*Wu D. et al. Am J Physiol. 1998 Sep;275(3 Pt 1):C661-8*; *Shah et al., Biochemical Pharmacology, Vol. 58, pp. 1167–1172, 1999; O'Leary et al. Mutat Res. 2004 Jul 13;551(1-2):245-54*). Prior to the filing of the subject application, one of ordinary skill in the art would have thought that it was beneficial to suppress omega-6 activity

(and the activity of cyclooxygenases). However, the current patent application teaches that long-term deficiency and/or suppression of omega-6 activity is harmful (see para 101-104).

[0010] Further, the significance of "total lipids" as a category is not well understood in the art, even though the definition/classification of lipids is very well known (see *Fahy et al. J. Lipid Res. 2005. 46:839–861,* and *The Nomenclature of Lipids, J Lipid Res. 1978 Jan;19(1):114-28*). The effect of important lipid components, such as various phytochemicals in health and physical and chemical properties of formulations is not well understood. Food labeling practices routinely ignore important lipid components. Further, various authoritative nutrient databases (such as USDA databases) miss to report several important lipids and significance of "total lipids" as a category. Even authoritative guidelines do not recognize the significance of "total lipids" as a category as evidenced by FDA Nutrition Facts Labeling requirements (http://www.fda.gov/Food/ IngredientsPackagingLabeling/ LabelingNutrition/ucm274593. htm#sec3) and Dietary Guidelines for Americans http://www.cnpp.usda.gov/sites/default/files/dietary_guidelines_ for_ americans/ PolicyDoc.pdf. Typical disclosure is of total fat and omega-6/omega-3 as percent of fat, percent of fatty acids or percent of calories. For these reasons, unless a reference expressly teaches the effect of various lipid components on omega-6/omega-3 requirements and/or specifically teaches to obtain omega-6/omega-3 as a ratio of total lipids, one cannot presume that skilled artisans will be know to obtain omega-6/omega-3 as a ratio of total lipids.

[0011] I further declare that all statements made herein of my own knowledge are true and that statements made of information and belief are believed to be true. I further acknowledge that any willful false statements and the like so made are punishable by fine or imprisonment, or both, and may jeopardize the validity of the application or any patent issuing therefrom.

Kent L Erickson Date: November 17, 2015

Kent L. Erickson, Ph.D.

REPUBLIC OF COLOMBIA
SUPERINTENDENCE OF INDUSTRY AND TRADE

In re the Application of:

Asha Nutrition Sciences, Inc.

Application No. 13-103.374

Filed: April 23, 2013

For: OPTIMIZED NUTRITIONAL FORMULATIONS, METHODS FOR SELECTION OF TAILORED DIETS THEREFROM, AND METHODS OF USE THEREOF

DECLARATION

Mr.
SUPERINTENDENT OF INDUSTRY AND COMMERCE
DIVISION OF NEW CREATIONS

Sir:

I, Undurti N. Das, hereby declare:

[001] I received M.B.B.S. in Medicine (surgery and Obstetrics and Gynecology) from Andhra Medical College, MD from Osmania Medical College in Internal Medicine and FAMS from the National Academy of Medical Sciences in India and I am also a Fellow of the Royal Society of Chemistry (FRSC). For past 30 years I have been investigating the role of polyunsaturated fatty acids, particularly omega-6 and omega-3, in various diseases, and understand their molecular mechanism of action. The results obtained in my investigation have been published in more than 400 publications in international journals. I have also written three books on the subject. I serve on editorial boards of several nutrition science journals.

[002] I am not an inventor, applicant, owner, or assignee of the above-referenced patent application. I have not received compensation, financial or otherwise, for preparing this declaration. I serve as Chief Medical Officer and Chairman of the Scientific Advisory Board of

Asha Nutrition Sciences, the assignee of the subject application. I have been allotted a modest amount of stock option grant as compensation for these roles.

[003] I have read the international publication document WO 2012/051591, which corresponds to the above-referenced patent application. Throughout this declaration the paragraph numbers mentioned in reference to the current patent application, correspond to the international publication document WO 2012/051591. I have also read the amended claims 1-27 being filed with the Office in November 2015. Further, I have read all the other documents referenced in this declaration.

[004] I interact with many professionals in my career who possess ordinary skills in the art, such as doctors, scientists, nurses, dieticians, nutritionists, and the like ("skilled artisans"). These professionals typically have advanced degrees such as masters, Ph.Ds., and/or M.Ds. I am closely aware of the knowledge and skill levels of such professionals. I am confident in declaring that the following matters are clear to me and would be clear to other skilled artisans.

[005] The amended independent claims 1, 2, and 13 are as follows:

1. A nutritional program for an individual, including at least one nutritional formulation comprising a source of phytochemical, a source of omega-6 fatty acids, and a source of antioxidant, wherein formulation(s) of the nutritional program collectively comprise a daily dosage of 1 to 40g of omega-6 fatty acids and 25mg-10g of antioxidants

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[0011] I further declare that all statements made herein of my own knowledge are true and that statements made of information and belief are believed to be true. I further acknowledge that any willful false statements and the like so made are punishable by fine or imprisonment, or both, and may jeopardize the validity of the application or any patent issuing therefrom.

U. Naveen Das

Undurti N. Das M.D., FAMS, FRSC

Date: November 17, 2015

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A comprehensive classification system for lipids[1]

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Abstract **Lipids are produced, transported, and recognized by the concerted actions of numerous enzymes, binding proteins, and receptors. A comprehensive analysis of lipid molecules, "lipidomics," in the context of genomics and proteomics is crucial to understanding cellular physiology and pathology; consequently, lipid biology has become a major research target of the postgenomic revolution and systems biology. To facilitate international communication about lipids, a comprehensive classification of lipids with a common platform that is compatible with informatics requirements has been developed to deal with the massive amounts of data that will be generated by our lipid community. As an initial step in this development, we divide lipids into eight categories (fatty acyls, glycerolipids, glycerophospholipids, sphingolipids, sterol lipids, prenol lipids, saccharolipids, and polyketides) containing distinct classes and subclasses of molecules, devise a common manner of representing the chemical structures of individual lipids and their derivatives, and provide a 12 digit identifier for each unique lipid molecule. The lipid classification scheme is chemically based and driven by the distinct hydrophobic and hydrophilic elements that compose the lipid. This structured vocabulary will facilitate the systematization of lipid biology and enable the cataloging of lipids and their properties in a way that is compatible with other macromolecular databases.**—Fahy, E., S. Subramaniam, H. A. Brown, C. K. Glass, A. H. Merrill, Jr., R. C. Murphy, C. R. H. Raetz, D. W. Russell, Y. Seyama, W. Shaw, T. Shimizu, F. Spener, G. van Meer, M. S. VanNieuwenhze, S. H. White, J. L. Witztum, and E. A. Dennis. **A comprehensive classification system for lipids.** *J. Lipid Res.* **2005.** 46: **839–861.**

Supplementary key words lipidomics • informatics • nomenclature • chemical representation • fatty acyls • glycerolipids • glycerophospholipids • sphingolipids • sterol lipids • prenol lipids • saccharolipids • polyketides

The goal of collecting data on lipids using a "systems biology" approach to lipidomics requires the development of a comprehensive classification, nomenclature, and chemical representation system to accommodate the myriad lipids that exist in nature. Lipids have been loosely defined as biological substances that are generally hydrophobic in nature and in many cases soluble in organic solvents (1). These chemical properties cover a broad range of mole-

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[1] The evaluation of this manuscript was handled by the former Editor-in-Chief Trudy Forte.

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cules, such as fatty acids, phospholipids, sterols, sphingolipids, terpenes, and others (2). The LIPID MAPS (LIPID Metabolites And Pathways Strategy; http://www.lipidmaps.org), Lipid Library (http://lipidlibrary.co.uk), Lipid Bank (http://lipidbank.jp), LIPIDAT (http://www.lipidat.chemistry.ohio-state.edu), and Cyberlipids (http://www.cyberlipid.org) websites provide useful online resources for an overview of these molecules and their structures. More accurate definitions are possible when lipids are considered from a structural and biosynthetic perspective, and many different classification schemes have been used over the years. However, for the purpose of comprehensive classification, we define lipids as hydrophobic or amphipathic small molecules that may originate entirely or in part by carbanion-based condensations of thioesters (fatty acids, polyketides, etc.) and/or by carbocation-based condensations of isoprene units (prenols sterols, etc.). Additionally, lipids have been broadly subdivided into "simple" and "complex" groups, with simple lipids being those yielding at most two types of products on hydrolysis (e.g., fatty acids, sterols, and acylglycerols) and complex lipids (e.g., glycerophospholipids and glycosphingolipids) yielding three or more products on hydrolysis. The classification scheme presented here organizes lipids into well-defined categories that cover eukaryotic and prokaryotic sources and that is equally applicable to archaea and synthetic (man-made) lipids.

Lipids may be categorized based on their chemically functional backbone as polyketides, acylglycerols, sphingolipids, prenols, or saccharolipids. However, for historical and bioinformatics advantages, we chose to separate fatty acyls from other polyketides, the glycerophospholipids from the other glycerolipids, and sterol lipids from other prenols, resulting in a total of eight primary categories. An important aspect of this scheme is that it allows for subdivision of the main categories into classes and subclasses to handle the existing and emerging arrays of lipid structures. Although any classification scheme is in part subjective as a result of the structural and biosynthetic complexity of lipids, it is an essential prerequisite for the organization of lipid research and the development of systematic methods of data management. The classification scheme presented here is chemically based and driven by the distinct hydrophobic and hydrophilic elements that constitute the lipid. Biosynthetically related compounds that are not technically lipids because of their water solubility are included for completeness in this classification scheme.

The proposed lipid categories listed in **Table 1** have names that are, for the most part, well accepted in the literature. The fatty acyls (FA) are a diverse group of molecules synthesized by chain elongation of an acetyl-CoA primer with malonyl-CoA (or methylmalonyl-CoA) groups that may contain a cyclic functionality and/or are substituted with heteroatoms. Structures with a glycerol group are represented by two distinct categories: the glycerolipids (GL), which include acylglycerols but also encompass alkyl and 1*Z*-alkenyl variants, and the glycerophospholipids (GP), which are defined by the presence of a phosphate (or phosphonate) group esterified to one of the glycerol hydroxyl groups. The sterol lipids (ST) and prenol lipids (PR) share a common biosynthetic pathway via the polymerization of dimethylallyl pyrophosphate/isopentenyl pyrophosphate but have obvious differences in terms of their eventual structure and function. Another well-defined category is the sphingolipids (SP), which contain a long-chain base as their core structure. This classification does not have a glycolipids category per se but rather places glycosylated lipids in appropriate categories based on the identity of their core lipids. It also was necessary to define a category with the term "saccharolipids" (SL) to account for lipids in which fatty acyl groups are linked directly to a sugar backbone. This SL group is distinct from the term "glycolipid" that was defined by the International Union of Pure and Applied Chemists (IUPAC) as a lipid in which the fatty acyl portion of the molecule is present in a glycosidic linkage. The final category is the polyketides (PK), which are a diverse group of metabolites from plant and microbial sources. Protein modification by lipids (e.g., fatty acyl, prenyl, cholesterol) occurs in nature; however, these proteins are not included in this database but are listed in protein databases such as GenBank (http://www.ncbi.nlm.nih.gov) and SwissProt (http://www.ebi.ac.uk/swissprot/).

LIPID NOMENCLATURE

A naming scheme must unambiguously define a lipid structure in a manner that is amenable to chemists, biologists, and biomedical researchers. The issue of lipid nomenclature was last addressed in detail by the International Union of Pure and Applied Chemists and the International Union of Biochemistry and Molecular Biology (IUPAC-IUBMB) Commission on Biochemical Nomenclature in 1976, which subsequently published its recommendations (3). Since then, a number of additional documents relating to the naming of glycolipids (4), prenols (5), and sterols (6) have been released by this commission and placed on the IUPAC website (http://www.chem.qmul.ac.uk/iupac/). A large number of novel lipid classes have been discovered during the last three decades that have not yet been systematically named. The present classification includes these new lipids and incorporates a consistent nomenclature.

In conjunction with our proposed classification scheme, we provide examples of systematic (or semisystematic) names for the various classes and subclasses of lipids. The nomenclature proposal follows existing IUPAC-IUBMB rules closely and should not be viewed as a competing format. The main differences involve *a*) clarification of the use of core structures to simplify systematic naming of some of the more complex lipids, and *b*) provision of systematic names for recently discovered lipid classes.

Key features of our lipid nomenclature scheme are as follows:

a) The use of the stereospecific numbering (*sn*) method to describe glycerolipids and glycerophospholipids (3) The glycerol group is typically acylated or alkylated at the *sn*-1 and/or *sn*-2 position, with the exception of some lipids

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TABLE 1. Lipid categories and examples

Category	Abbreviation	Example
Fatty acyls	FA	dodecanoic acid
Glycerolipids	GL	1-hexadecanoyl-2-(9*Z*-octadecenoyl)-*sn*-glycerol
Glycerophospholipids	GP	1-hexadecanoyl-2-(9*Z*-octadecenoyl)-*sn*-glycero-3-phosphocholine
Sphingolipids	SP	*N*-(tetradecanoyl)-sphing-4-enine
Sterol lipids	ST	cholest-5-en-3β-ol
Prenol lipids	PR	2*E*,6*E*-farnesol
Saccharolipids	SL	UDP-3-*O*-(3*R*-hydroxy-tetradecanoyl)-α-D-*N*-acetylglucosamine
Polyketides	PK	aflatoxin B_1

that contain more than one glycerol group and archaebacterial lipids in which *sn*-2 and/or *sn*-3 modification occurs.

b) Definition of sphinganine and sphing-4-enine as core structures for the sphingolipid category, where the D-*erythro* or 2*S*,3*R* configuration and 4*E* geometry (in the case of sphing-4-enine) are implied. In molecules containing stereochemistries other than the 2*S*,3*R* configuration, the full systematic names are to be used instead (e.g., 2*R*-amino-1,3*R*-octadecanediol).

c) The use of core names such as cholestane, androstane, and estrane for sterols.

d) Adherence to the names for fatty acids and acyl chains (formyl, acetyl, propionyl, butyryl, etc.) defined in Appendices A and B of the IUPAC-IUBMB recommendations (3).

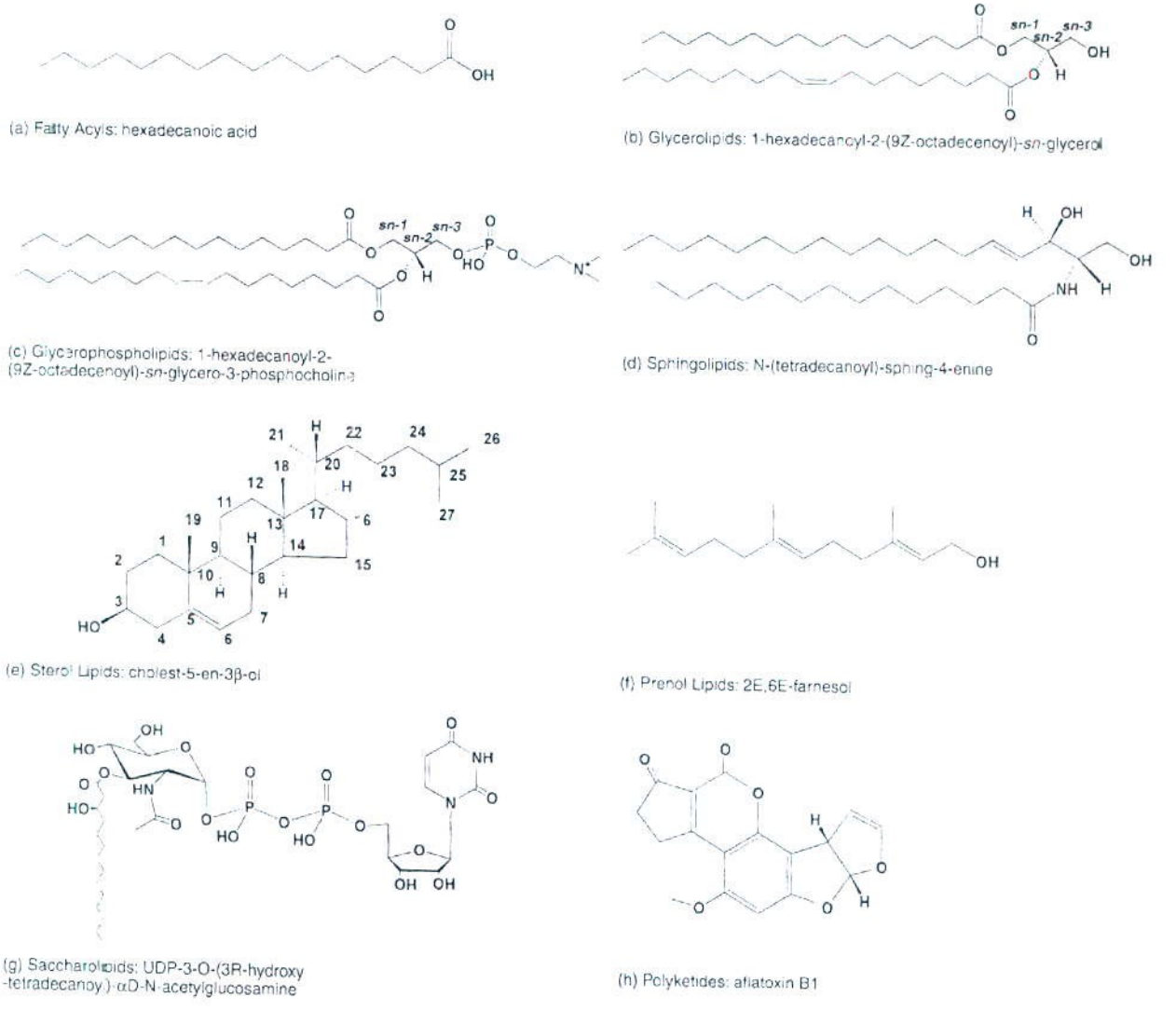


Fig. 1. Representative structures for each lipid category.

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TABLE 2. Format of 12 character LIPID ID

Characters	Description	Example
1–2	Fixed database designation	LM
3–4	Two letter category code	FA
5–6	Two digit class code	03
7–8	Two digit subclass code	02
9–12	Unique four character identifier within subclass	7812

e) The adoption of a condensed text nomenclature for the glycan portions of lipids, where sugar residues are represented by standard IUPAC abbreviations and where the anomeric carbon locants and stereochemistry are included but the parentheses are omitted. This system has also been proposed by the Consortium for Functional Glycomics (http://web.mit.edu/glycomics/consortium/main.shtml).

f) The use of *E*/*Z* designations (as opposed to *trans*/*cis*) to define double bond geometry.

g) The use of *R*/*S* designations (as opposed to α/β or D/L) to define stereochemistries. The exceptions are those describing substituents on glycerol (*sn*) and sterol core structures and anomeric carbons on sugar residues. In these latter special cases, the α/β format is firmly established.

h) The common term "lyso," denoting the position lacking a racyl group in glycerolipids and glycerophospholipids, will not be used in systematic names but will be included as a synonym.

i) The proposal for a single nomenclature scheme to cover the prostaglandins, isoprostanes, neuroprostanes, and related compounds, where the carbons participating in the cyclopentane ring closure are defined and where a consistent chain-numbering scheme is used.

j) The "d" and "t" designations used in shorthand notation of sphingolipids refer to 1,3-dihydroxy and 1,3,4-trihydroxy long-chain bases, respectively.

LIPID STRUCTURE REPRESENTATION

In addition to having rules for lipid classification and nomenclature, it is important to establish clear guidelines for drawing lipid structures. Large and complex lipids are difficult to draw, which leads to the use of shorthand and unique formats that often generate more confusion than clarity among lipidologists. We propose a more consistent format for representing lipid structures in which, in the simplest case of the fatty acid derivatives, the acid group (or equivalent) is drawn on the right and the hydrophobic hydrocarbon chain is on the left (**Fig. 1**). Notable exceptions are found in the eicosanoid class, in which the hydrocarbon chain wraps around in a counterclockwise direction to produce a more condensed structure. Similarly, with regard to the glycerolipids and glycerophospholipids, the radyl chains are drawn with the hydrocarbon chains to the left and the glycerol group depicted horizontally with stereochemistry at the *sn* carbons defined (if known). The general term "radyl" is used to denote either acyl, alkyl, or 1-alkenyl substituents (http://www.chem.qmul.ac.uk/iupac/lipid/lip1n2.html), allowing for coverage of alkyl and 1*Z*-alkenylglycerols. The sphingolipids, although they do not contain a glycerol group, have a similar structural relationship to the glycerophospholipids in many cases and may be drawn with the C1 hydroxyl group of the long-chain base to the right and the alkyl portion to the left. This methodology places the head groups of both sphingolipids and glycerophospho-

TABLE 3. Shorthand notation for selected lipid categories

Category	Abbreviation	Class or Subclass	Example[a]
GP	GPCho	Glycerophosphocholines	GPCho (16:0/9*Z*,12*Z*-18:2)
GP	GPnCho	Glycerophosphonocholines	
GP	GPEtn	Glycerophosphoethanolamines	
GP	GPnEtn	Glycerophosphonoethanolamines	
GP	GPSer	Glycerophosphoserines	
GP	GPGro	Glycerophosphoglycerols	
GP	GPGroP	Glycerophosphoglycerophosphates	
GP	GPIns	Glycerophosphoinositols	
GP	GPInsP	Glycerophosphoinositol monophosphates	
GP	$GPInsP_2$	Glycerophosphoinositol bis-phosphates	
GP	$GPInsP_3$	Glycerophosphoinositol tris-phosphates	
GP	GPA	Glycerophosphates	
GP	GPP	Glyceropyrophosphates	
GP	CL	Glycerophosphoglycerophosphoglycerols	
GP	CDP-DG	CDP-glycerols	
GP	[glycan]GP	Glycerophosphoglucose lipids	
GP	[glycan]GPIns	Glycerophosphoinositolglycans	EtN-P-6Manα1−2Manα1−6 Manα1−4GlcNα1-6CPIns (14:0/14:0)
SP	Cer	Ceramides	Cer (d18:1/9*E*-16:1)
SP	SM	Phosphosphingolipids	SM (d18:1/24:0)
SP	[glycan]Cer	Glycosphingolipids	NeuAcα2−3Galβ1−4Glcβ-Cer (d18:1/16:0)
GL	MG	Monoradyl glycerols	MG (16:0/0:0/0:0)
GL	DG	Diradyl glycerols	DG (18:0/16:0/0:0)
GL	TG	Triradyl glycerols	TG (12:0/14:0/18:0)

[a] Shorthand notation for radyl substituents in categories GP and GL are presented in the order of *sn*-1 to *sn*-3. Shorthand notation for category SP is presented in the order of long-chain base and *N*-acyl substituent. Numbers separated by colons refer to carbon chain length and number of double bonds, respectively.

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TABLE 4. Fatty acyls [FA] classes and subclasses

- Fatty acids and conjugates [FA01]
  - Straight-chain fatty acids [FA0101]
  - Methyl branched fatty acids [FA0102]
  - Unsaturated fatty acids [FA0103]
  - Hydroperoxy fatty acids [FA0104]
  - Hydroxy fatty acids [FA0105]
  - Oxo fatty acids [FA0106]
  - Epoxy fatty acids [FA0107]
  - Methoxy fatty acids [FA0108]
  - Halogenated fatty acids [FA0109]
  - Amino fatty acids [FA0110]
  - Cyano fatty acids [FA0111]
  - Nitro fatty acids [FA0112]
  - Thia fatty acids [FA0113]
  - Carbocyclic fatty acids [FA0114]
  - Heterocyclic fatty acids [FA0115]
  - Mycolic acids [FA0116]
  - Dicarboxylic acids [FA0117]
- Octadecanoids [FA02]
  - 12-Oxophytodienoic acid metabolites [FA0201]
  - Jasmonic acids [FA0202]
- Eicosanoids [FA03]
  - Prostaglandins [FA0301]
  - Leukotrienes [FA0302]
  - Thromboxanes [FA0303]
  - Lipoxins [FA0304]
  - Hydroxyeicosatrienoic acids [FA0305]
  - Hydroxyeicosatetraenoic acids [FA0306]
  - Hydroxyeicosapentaenoic acids [FA0307]
  - Epoxyeicosatrienoic acids [FA0308]
  - Hepoxilins [FA0309]
  - Levuglandins [FA0310]
  - Isoprostanes [FA0311]
  - Clavulones [FA0312]
- Docosanoids [FA04]
- Fatty alcohols [FA05]
- Fatty aldehydes [FA06]
- Fatty esters [FA07]
  - Wax monoesters [FA0701]
  - Wax diesters [FA0702]
  - Cyano esters [FA0703]
  - Lactones [FA0704]
  - Fatty acyl-CoAs [FA0705]
  - Fatty acyl-acyl carrier proteins (ACPs) [FA0706]
  - Fatty acyl carnitines [FA0707]
  - Fatty acyl adenylates [FA0708]
- Fatty amides [FA08]
  - Primary amides [FA0801]
  - *N*-Acyl amides [FA0802]
  - Fatty acyl homoserine lactones [FA0803]
  - *N*-Acyl ethanolamides (endocannabinoids) [FA0804]
- Fatty nitriles [FA09]
- Fatty ethers [FA10]
- Hydrocarbons [FA11]
- Oxygenated hydrocarbons [FA12]
- Other [FA00]

TABLE 5. Glycerolipids [GL] classes and subclasses

- Monoradylglycerols [GL01]
  - Monoacylglycerols [GL0101]
  - Monoalkylglycerols [GL0102]
  - Mono-(1Z-alkenyl)-glycerols [GL0103]
  - Monoacylglycerolglycosides [GL0104]
  - Monoalkylglycerolglycosides [GL0105]
- Diradylglycerols [GL02]
  - Diacylglycerols [GL0201]
  - Alkylacylglycerols [GL0202]
  - Dialkylglycerols [GL0203]
  - 1Z-Alkenylacylglycerols [GL0204]
  - Diacylglycerolglycosides [GL0205]
  - Alkylacylglycerolglycosides [GL0206]
  - Dialkylglycerolglycosides [GL0207]
  - Di-glycerol tetraethers [GL0208]
  - Di-glycerol tetraether glycans [GL0209]
- Triradylglycerols [GL03]
  - Triacylglycerols [GL0301]
  - Alkyldiacylglycerols [GL0302]
  - Dialkylmonoacylglycerols [GL0303]
  - 1Z-Alkenyldiacylglycerols [GL0304]
  - Estolides [GL0305]
- Other [GL00]

lipids on the right side. Although the structures of sterols do not conform to these general rules of representation, the sterol esters may conveniently be drawn with the acyl group oriented according to these guidelines. In addition, the linear prenols or isoprenoids are drawn in a manner analogous to the fatty acids, with the terminal functional group on the right side. Inevitably, a number of structurally complex lipids, such as acylaminosugar glycans polycyclic isoprenoids, and polyketides, do not lend themselves to these simplified drawing rules. Nevertheless, we believe that the adoption of the guidelines proposed here will unify chemical representation and make it more comprehensible.

DATABASING LIPIDS, ANNOTATION, AND FUNCTION

A number of repositories, such as GenBank, SwissProt, and ENSEMBL (http://www.ensembl.org), support nucleic acid and protein databases; however, there are only a few specialized databases [e.g., LIPIDAT (7) and Lipid Bank (8)] that provide a catalog, annotation, and functional classification of lipids. Given the importance of these molecules in cellular function and pathology, there is an imminent need for the creation of a well-organized database of lipids. The first step toward this goal is the establishment of an ontology of lipids that is extensible, flexible, and scalable. Before establishing an ontology, a structured vocabulary is needed, and the IUPAC nomenclature of the 1970s was an initial step in this direction.

The ontology of lipids must contain definitions, meanings, and interrelationships of all objects stored in the database. This ontology is then transformed into a well-defined schema that forms the foundation for a relational database of lipids. The LIPID MAPS project is building a robust database of lipids based on the proposed ontology.

Our database will provide structural and functional annotations and have links to relevant protein and gene data. In addition, a universal data format (XML) will be provided to facilitate exportation of the data into other repositories. This database will enable the storage of curated information on lipids in a web-accessible format and will provide a community standard for lipids.

An important database field will be the LIPID ID, a unique 12 character identifier based on the classification scheme described here. The format of the LIPID ID, outlined in **Table 2**, provides a systematic means of assigning unique IDs to lipid molecules and allows for the addition of large numbers of new categories, classes, and subclasses in the future, because a maximum of 100 classes/subclasses (00 to 99) may be specified. The last four characters of the

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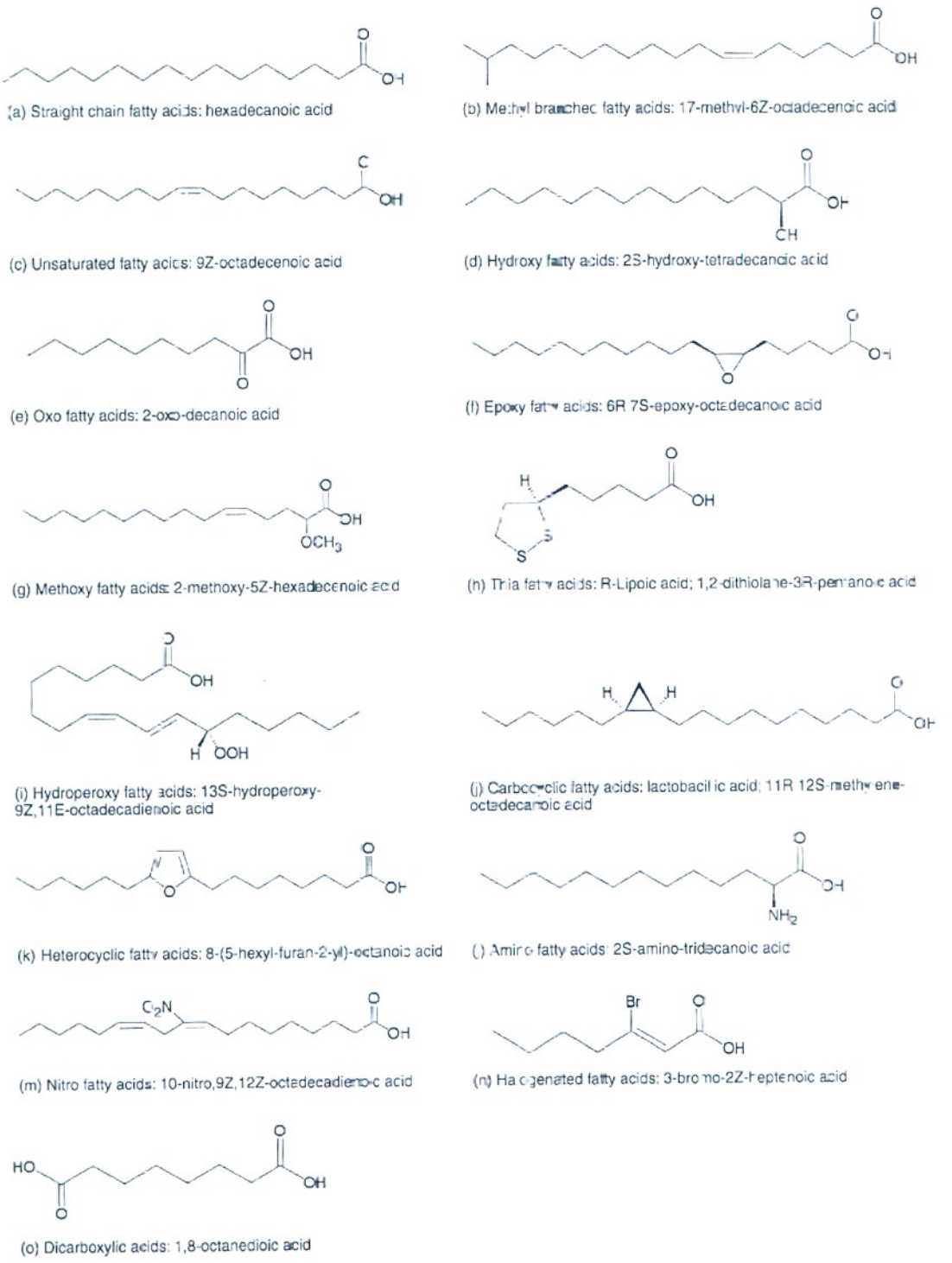


Fig. 2. Representative structures for fatty acyls.

ID constitute a unique identifier within a particular subclass and are randomly assigned. By initially using numeric characters, this allows 9,999 unique IDs per subclass, but with the additional use of 26 uppercase alphabetic characters, a total of 1.68 million possible combinations can be generated, providing ample scalability within each subclass. In cases in which lipid structures are obtained from other sources such as LipidBank or LIPIDAT, the corresponding IDs for those databases will be included to enable cross-referencing. The first two characters of the ID contain the database identifier (e.g., LM for LIPID MAPS), although other databases may choose to use their own two character identifier (at present, LB for Lipid Bank and LD for LIPIDAT) and assign the last four or more characters uniquely while retaining characters 5 to 8, which pertain to classification. The corresponding IDs of the other data-

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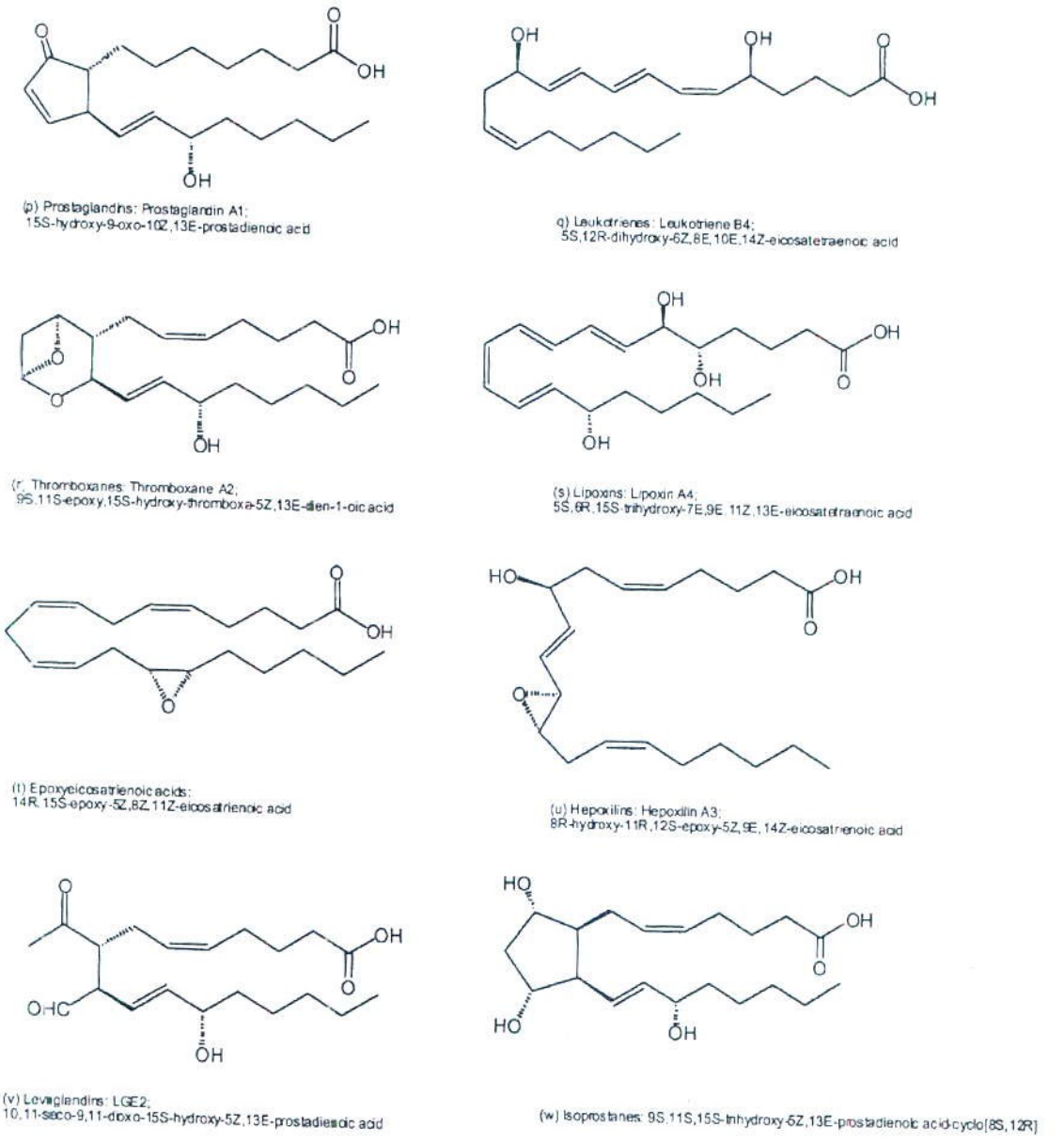


Fig. 2. Continued.

bases will always be included to enable cross-referencing. Further details regarding the numbering system will be decided by the International Lipids Classification and Nomenclature Committee (see below). In addition to the LIPID ID, each lipid in the database will be searchable by classification (category, class, subclass), systematic name, synonym(s), molecular formula, molecular weight, and many other parameters that are part of its ontology. An important feature will be the databasing of molecular structures, allowing the user to perform web-based substructure searches and structure retrieval across the database. This aim will be accomplished with a chemistry cartridge software component that will enable structures in formats such as MDL molfile and Chemdraw CDX to be imported directly into Oracle database tables.

Furthermore, many lipids, in particular the glycerolipids, glycerophospholipids, and sphingolipids, may be conveniently described in terms of a shorthand name in which abbreviations are used to define backbones, head groups, and sugar units and the radyl substituents are defined by a descriptor indicating carbon chain length and number of double bonds. These shorthand names lend themselves to fast, efficient text-based searches and are used widely in lipid research as compact alternatives to systematic names. The glycerophospholipids in the LIPIDAT database, for example, may be conveniently searched with a shorthand notation that has been extended to handle side chains with acyl, ether, branched-chain, and other functional groups (7). We propose the use of a shorthand notation for selected lipid categories (**Table 3**) that incorporates a

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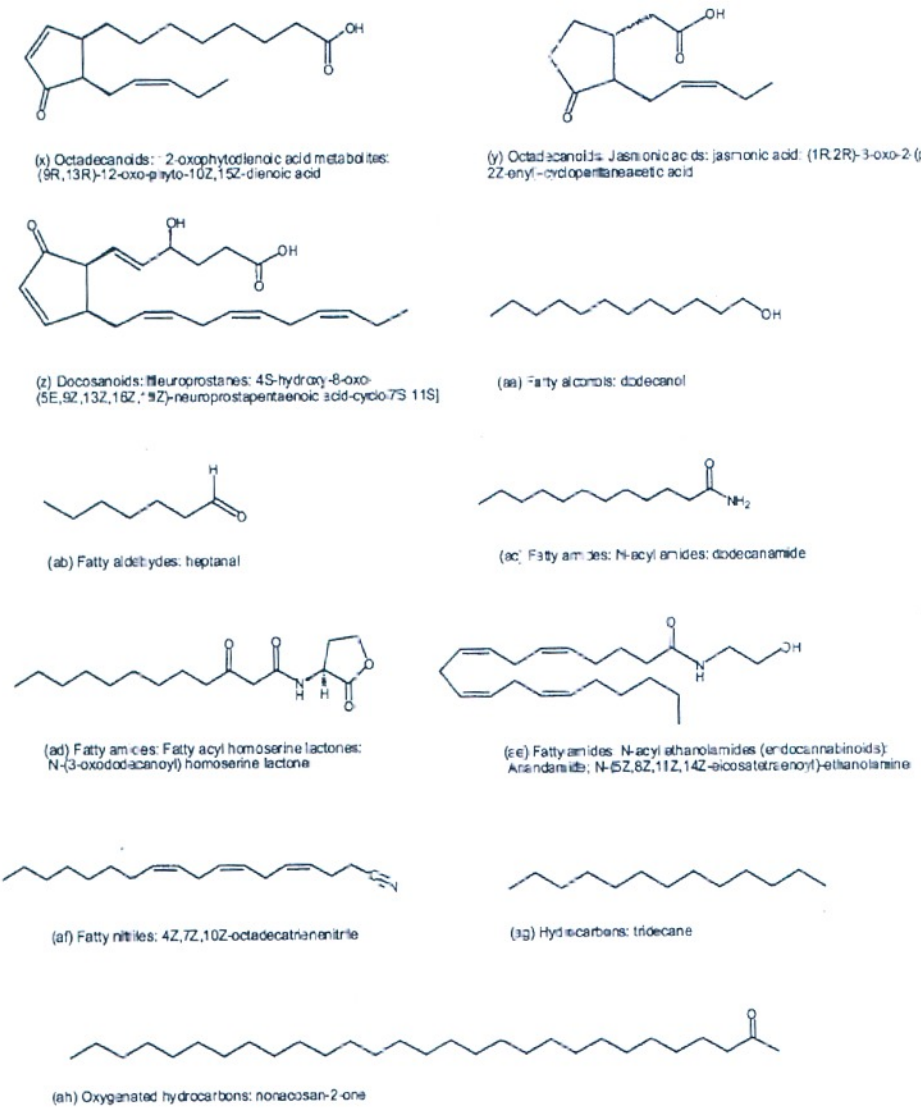


Fig. 2. Continued.

condensed text nomenclature for glycan substituents. The abbreviations for the sugar units follow the current IUPAC-IUBMB recommendations (4).

LIPID CLASSES AND SUBCLASSES

Fatty acyls [FA]

The fatty acyl structure represents the major lipid building blocks of complex lipids and therefore is one of the most fundamental categories of biological lipids. The fatty acyl group in the fatty acids and conjugates class (**Table 4**) is characterized by a repeating series of methylene groups that impart hydrophobic character to this category of lipids. The first subclass includes the straight-chain saturated fatty acids containing a terminal carboxylic acid. It could also be considered the most reduced end product of the polyketide pathway. Variants of this structure have one or more methyl substituents and encompass quite complex branched-chain fatty acids, such as the mycolic acids. The longest chain in branched-chain fatty acids defines the chain length of these compounds. A considerable number of variations on this basic structure occur in all kingdoms of life (9–12), including fatty acids with one or more double bonds and even acetylenic (triple) bonds. Heteroatoms of oxygen, halogen, nitrogen, and sulfur are also linked to the carbon chains in specific subclasses. Cyclic fatty acids containing three to six carbon atoms as well as heterocyclic rings containing oxygen or nitrogen are found in nature. The cyclopentenyl fatty acids are an example of this latter subclass. The thia fatty acid subclass contains sulfur atom(s) in the fatty acid structure and is exemplified by lipoic acid and biotin. Thiols and thioethers are in this class, but the thioesters are placed in the ester class because of the involvement of these and similar esters in fatty acid metabolism and synthesis.

Separate classes for more complex fatty acids with mul-

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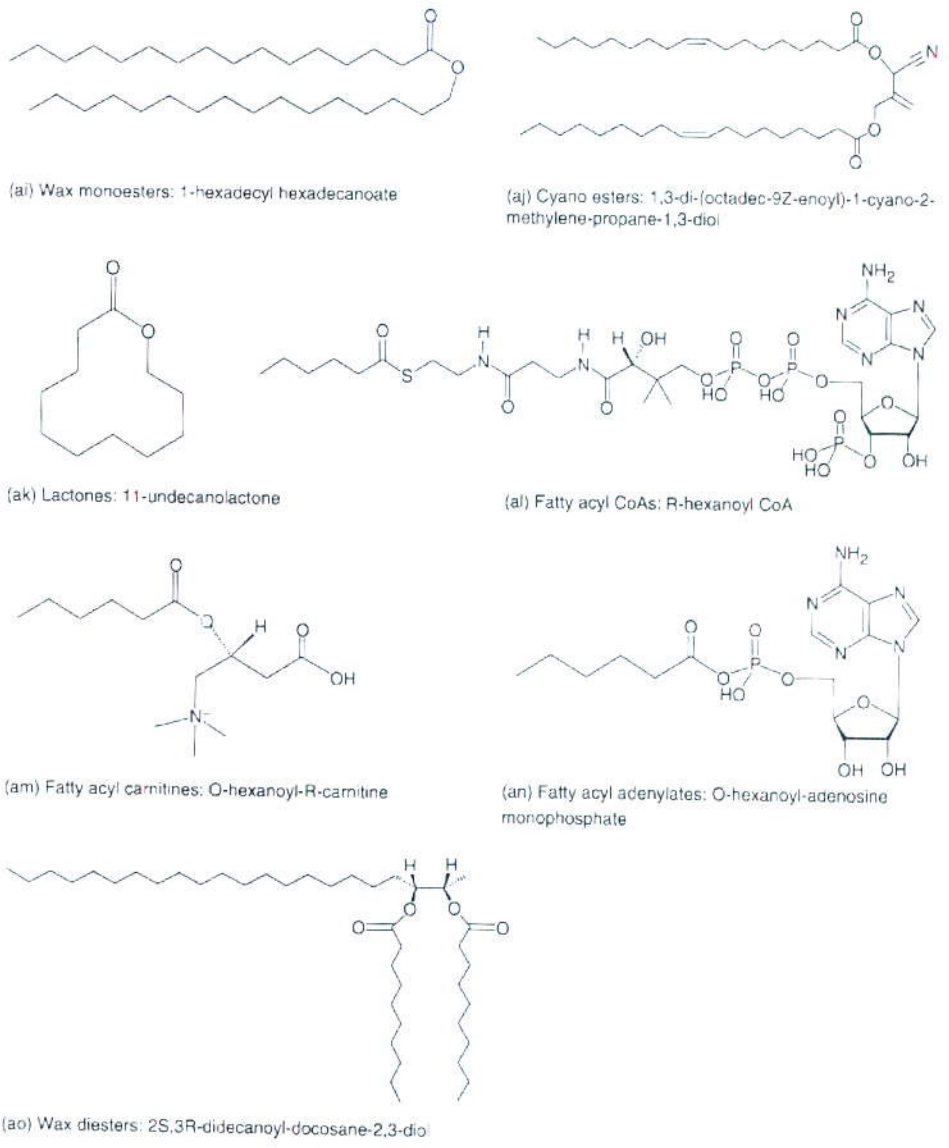


Fig. 2. Continued.

tiple functional groups (but nonbranched) are designated by the total number of carbon atoms found in the critical biosynthetic precursor. These include octadecanoids and lipids in the jasmonic acid pathway of plant hormone biosynthesis, even though jasmonic acids have lost some of their carbon atoms from the biochemical precursor, 12-oxophytodienoic acid (13). Eicosanoids derived from arachidonic acid include prostaglandins, leukotrienes, and other structural derivatives (14). The docosanoids contain 22 carbon atoms and derive from a common precursor, docosahexaenoic acid (15). Many members of these separate subclasses of more complex fatty acids have distinct biological activities.

Other major lipid classes in the fatty acyl category include fatty acid esters such as wax monoesters and diesters and the lactones. The fatty ester class also has subclasses that include important biochemical intermediates such as fatty acyl thioester-CoA derivatives, fatty acyl thioester-acyl carrier protein (ACP) derivatives, fatty acyl carnitines (esters of carnitine), and fatty adenylates, which are mixed anhydrides. The fatty alcohols and fatty aldehydes are typified by terminal hydroxy and oxo groups, respectively. The fatty amides are also *N*-fatty acylated amines and unsubstituted amides, and many simple amides have interesting biological activities in various organisms. Fatty acyl homoserine lactones are fatty amides involved in bacterial quorum sensing (16).

Hydrocarbons are included as a class of fatty acid derivatives because they correspond to six electron reduction products of fatty acids that may have been generated by loss of the carboxylic acid from a fatty acid or fatty acyl moiety during the process of diagenesis in geological samples. Long-chain ethers also have been observed in nature. Chemical structures of the fatty acyls are shown in **Fig. 2**.

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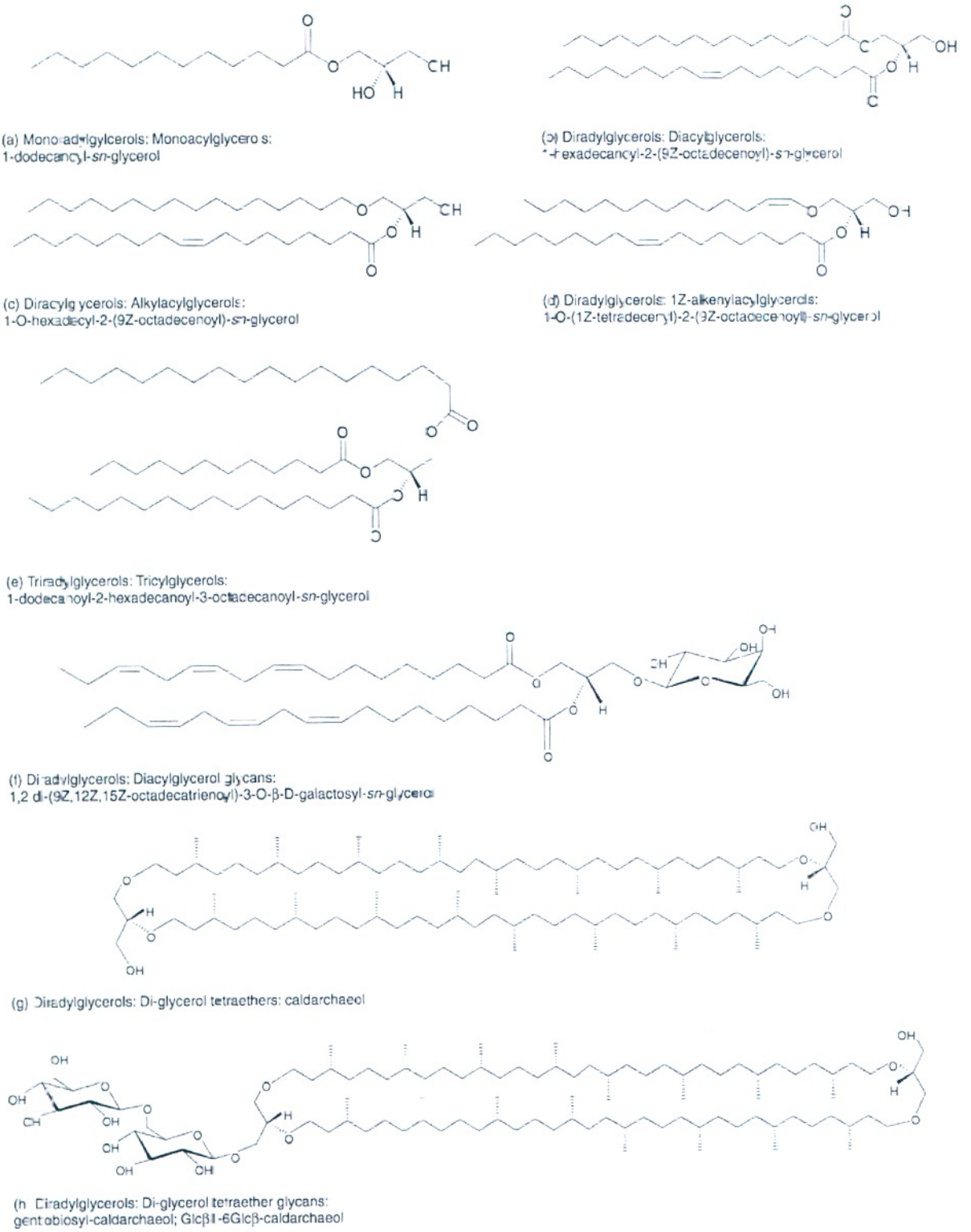


Fig. 3. Representative structures for glycerolipids.

Glycerolipids [GL]

The glycerolipids essentially encompass all glycerol-containing lipids. We have purposely made glycerophospholipids a separate category because of their abundance and importance as membrane constituents, metabolic fuels, and signaling molecules. The glycerolipid category (**Table 5**) is dominated by the mono-, di- and tri-substituted glycerols, the most well-known being the fatty acid esters of glycerol (acylglycerols) (17, 18). Additional subclasses are represented by the glycerolglycans, which are character-

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TABLE 6. Glycerophospholipids [GP] classes and subclasses

- Glycerophosphocholines [GP01]
  - Diacylglycerophosphocholines [GP0101]
  - 1-Alkyl,2-acylglycerophosphocholines [GP0102]
  - 1Z-Alkenyl,2-acylglycerophosphocholines [GP0103]
  - Dialkylglycerophosphocholines [GP0104]
  - Monoacylglycerophosphocholines [GP0105]
  - 1-Alkyl glycerophosphocholines [GP0106]
  - 1Z-Alkenylglycerophosphocholines [GP0107]
- Glycerophosphoethanolamines [GP02]
  - Diacylglycerophosphoethanolamines [GP0201]
  - 1-Alkyl,2-acylglycerophosphoethanolamines [GP0202]
  - 1Z-Alkenyl,2-acylglycerophosphoethanolamines [GP0203]
  - Dialkylglycerophosphoethanolamines [GP0204]
  - Monoacylglycerophosphoethanolamines [GP0205]
  - 1-Alkyl glycerophosphoethanolamines [GP0206]
  - 1Z-Alkenylglycerophosphoethanolamines [GP0207]
- Glycerophosphoserines [GP03]
  - Diacylglycerophosphoserines [GP0301]
  - 1-Alkyl,2-acylglycerophosphoserines [GP0302]
  - 1Z-Alkenyl,2-acylglycerophosphoserines [GP0303]
  - Dialkylglycerophosphoserines [GP0304]
  - Monoacylglycerophosphoserines [GP0305]
  - 1-Alkyl glycerophosphoserines [GP0306]
  - 1Z-Alkenylglycerophosphoserines [GP0307]
- Glycerophosphoglycerols [GP04]
  - Diacylglycerophosphoglycerols [GP0401]
  - 1-Alkyl,2-acylglycerophosphoglycerols [GP0402]
  - 1Z-Alkenyl,2-acylglycerophosphoglycerols [GP0403]
  - Dialkylglycerophosphoglycerols [GP0404]
  - Monoacylglycerophosphoglycerols [GP0405]
  - 1-Alkyl glycerophosphoglycerols [GP0406]
  - 1Z-Alkenylglycerophosphoglycerols [GP0407]
  - Diacylglycerophosphodiradylglycerols [GP0408]
  - Diacylglycerophosphomonoradylglycerols [GP0409]
  - Monoacylglycerophosphomonoradylglycerols [GP0410]
- Glycerophosphoglycerophosphates [GP05]
  - Diacylglycerophosphoglycerophosphates [GP0501]
  - 1-Alkyl,2-acylglycerophosphoglycerophosphates [GP0502]
  - 1Z-Alkenyl,2-acylglycerophosphoglycerophosphates [GP0503]
  - Dialkylglycerophosphoglycerophosphates [GP0504]
  - Monoacylglycerophosphoglycerophosphates [GP0505]
  - 1-Alkyl glycerophosphoglycerophosphates [GP0506]
  - 1Z-Alkenylglycerophosphoglycerophosphates [GP0507]
- Glycerophosphoinositols [GP06]
  - Diacylglycerophosphoinositols [GP0601]
  - 1-Alkyl,2-acylglycerophosphoinositols [GP0602]
  - 1Z-Alkenyl,2-acylglycerophosphoinositols [GP0603]
  - Dialkylglycerophosphoinositols [GP0604]
  - Monoacylglycerophosphoinositols [GP0605]
  - 1-Alkyl glycerophosphoinositols [GP0606]
  - 1Z-Alkenylglycerophosphoinositols [GP0607]
- Glycerophosphoinositol monophosphates [GP07]
  - Diacylglycerophosphoinositol monophosphates [GP0701]
  - 1-Alkyl,2-acylglycerophosphoinositol monophosphates [GP0702]
  - 1Z-Alkenyl,2-acylglycerophosphoinositol monophosphates [GP0703]
  - Dialkylglycerophosphoinositol monophosphates [GP0704]
  - Monoacylglycerophosphoinositol monophosphates [GP0705]
  - 1-Alkyl glycerophosphoinositol monophosphates [GP0706]
  - 1Z-Alkenylglycerophosphoinositol monophosphates [GP0707]
- Glycerophosphoinositol bisphosphates [GP08]
  - Diacylglycerophosphoinositol bisphosphates [GP0801]
  - 1-Alkyl,2-acylglycerophosphoinositol bisphosphates [GP0802]
  - 1Z-Alkenyl,2-acylglycerophosphoinositol bisphosphates [GP0803]
  - Monoacylglycerophosphoinositol bisphosphates [GP0804]
  - 1-Alkyl glycerophosphoinositol bisphosphates [GP0805]
  - 1Z-Alkenylglycerophosphoinositol bisphosphates [GP0806]
- Glycerophosphoinositol trisphosphates [GP09]
  - Diacylglycerophosphoinositol trisphosphates [GP0901]
  - 1-Alkyl,2-acylglycerophosphoinositol trisphosphates [GP0902]
  - 1Z-Alkenyl,2-acylglycerophosphoinositol trisphosphates [GP0903]
  - Monoacylglycerophosphoinositol trisphosphates [GP0904]
  - 1-Alkyl glycerophosphoinositol trisphosphates [GP0905]
  - 1Z-Alkenylglycerophosphoinositol trisphosphates [GP0906]

TABLE 6. (*Continued*)

- Glycerophosphates [GP10]
  - Diacylglycerophosphates [GP1001]
  - 1-Alkyl,2-acylglycerophosphates [GP1002]
  - 1Z-Alkenyl,2-acylglycerophosphates [GP1003]
  - Dialkylglycerophosphates [GP1004]
  - Monoacylglycerophosphates [GP1005]
  - 1-Alkyl glycerophosphates [GP1006]
  - 1Z-Alkenylglycerophosphates [GP1007]
- Glyceropyrophosphates [GP11]
  - Diacylglyceropyrophosphates [GP1101]
  - Monoacylglyceropyrophosphates [GP1102]
- Glycerophosphoglycerophosphoglycerols (cardiolipins) [GP12]
  - Diacylglycerophosphoglycerophosphodiradylglycerols [GP1201]
  - Diacylglycerophosphoglycerophosphomonoradylglycerols [GP1202]
  - 1-Alkyl,2-acylglycerophosphoglycerophosphodiradylglycerols [GP1203]
  - 1-Alkyl,2-acylglycerophosphoglycerophosphomonoradylglycerols [GP1204]
  - 1Z-Alkenyl,2-acylglycerophosphoglycerophosphodiradylglycerols [GP1205]
  - 1Z-Alkenyl,2-acylglycerophosphoglycerophosphomonoradylglycerols [GP1206]
  - Monoacylglycerophosphoglycerophosphomonoradylglycerols [GP1207]
  - 1-Alkyl glycerophosphoglycerophosphodiradylglycerols [GP1208]
  - 1-Alkyl glycerophosphoglycerophosphomonoradylglycerols [GP1209]
  - 1Z-Alkenylglycerophosphoglycerophosphodiradylglycerols [GP1210]
  - 1Z-Alkenylglycerophosphoglycerophosphomonoradylglycerols [GP1211]
- CDP-glycerols [GP13]
  - CDP-diacylglycerols [GP1301]
  - CDP-1-alkyl,2-acylglycerols [GP1302]
  - CDP-1Z-alkenyl,2-acylglycerols [GP1303]
  - CDP-dialkylglycerols [GP1304]
  - CDP-monoacylglycerols [GP1305]
  - CDP-1-alkyl glycerols [GP1306]
  - CDP-1Z-alkenylglycerols [GP1307]
- Glycerophosphoglucose lipids [GP14]
  - Diacylglycerophosphoglucose lipids [GP1401]
  - 1-Alkyl,2-acylglycerophosphoglucose lipids [GP1402]
  - 1Z-Alkenyl,2-acylglycerophosphoglucose lipids [GP1403]
  - Monoacylglycerophosphoglucose lipids [GP1404]
  - 1-Alkyl glycerophosphoglucose lipids [GP1405]
  - 1Z-Alkenylglycerophosphoglucose lipids [GP1406]
- Glycerophosphoinositolglycans [GP15]
  - Diacylglycerophosphoinositolglycans [GP1501]
  - 1-Alkyl,2-acylglycerophosphoinositolglycans [GP1502]
  - 1Z-Alkenyl,2-acylglycerophosphoinositolglycans [GP1503]
  - Monoacylglycerophosphoinositolglycans [GP1504]
  - 1-Alkyl glycerophosphoinositolglycans [GP1505]
  - 1Z-Alkenylglycerophosphoinositolglycans [GP1506]
- Glycerophosphonocholines [GP16]
  - Diacylglycerophosphonocholines [GP1601]
  - 1-Alkyl,2-acylglycerophosphonocholines [GP1602]
  - 1Z-Alkenyl,2-acylglycerophosphonocholines [GP1603]
  - Dialkylglycerophosphonocholines [GP1604]
  - Monoacylglycerophosphonocholines [GP1605]
  - 1-Alkyl glycerophosphonocholines [GP1606]
  - 1Z-Alkenylglycerophosphonocholines [GP1607]
- Glycerophosphonoethanolamines [GP17]
  - Diacylglycerophosphonoethanolamines [GP1701]
  - 1-Alkyl,2-acylglycerophosphonoethanolamines [GP1702]
  - 1Z-Alkenyl,2-acylglycerophosphonoethanolamines [GP1703]
  - Dialkylglycerophosphonoethanolamines [GP1704]
  - Monoacylglycerophosphonoethanolamines [GP1705]
  - 1-Alkyl glycerophosphonoethanolamines [GP1706]
  - 1Z-Alkenylglycerophosphonoethanolamines [GP1707]
- Di-glycerol tetraether phospholipids (caldarchaeols) [GP18]
- Glycerol-nonitol tetraether phospholipids [GP19]
- Oxidized glycerophospholipids [GP20]
- Other [GP00]

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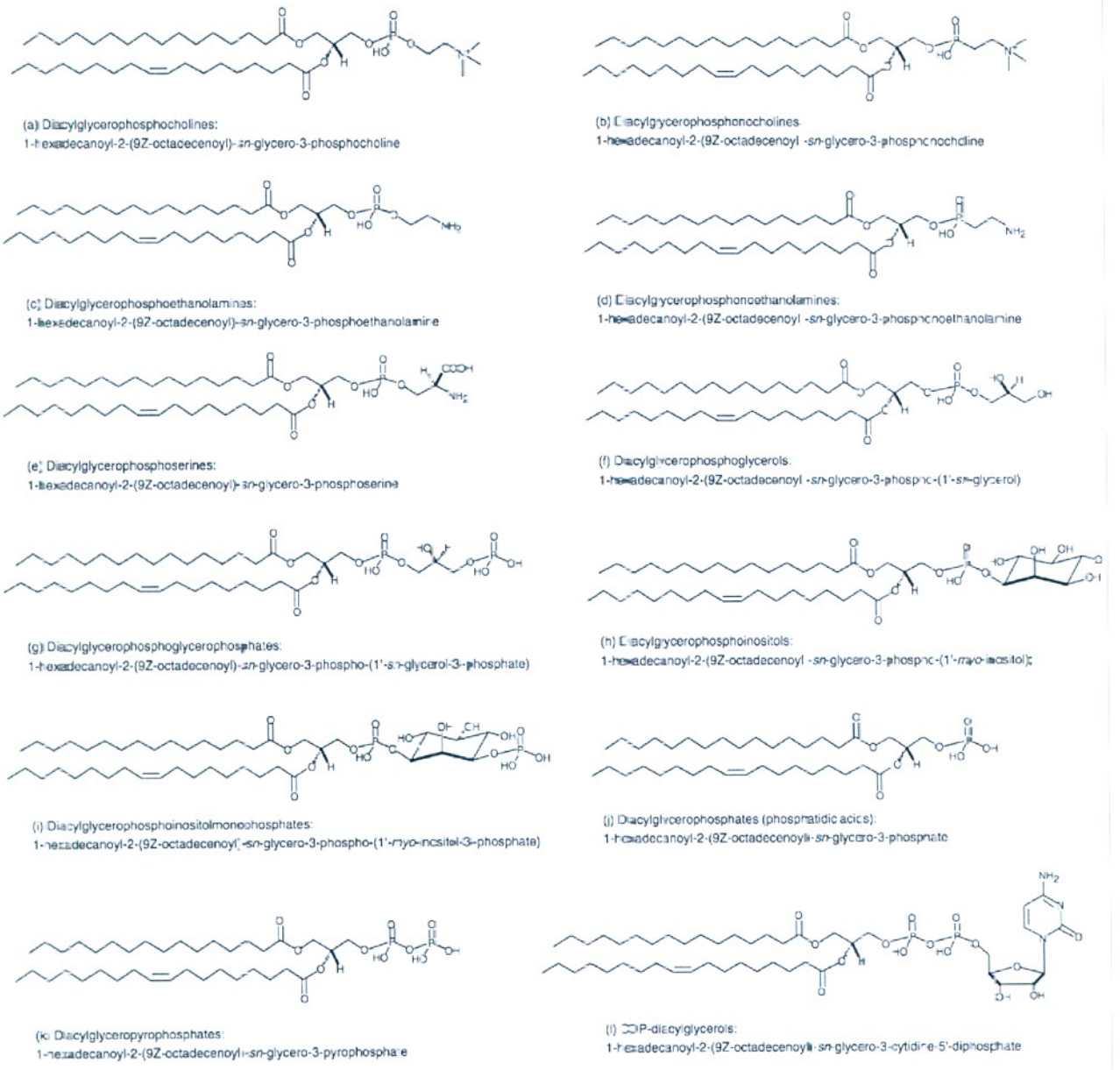


Fig. 2. Representative structures for glycerophospholipids.

ized by the presence of one or more sugar residues attached to glycerol via a glycosidic linkage (19). Examples of structures in this category are shown in **Fig. 3**. Macrocyclic ether lipids also occur as glycerolipids in the membranes of archaebacteria (20).

Glycerophospholipids [GP]

The glycerophospholipids are ubiquitous in nature and are key components of the lipid bilayer of cells. Phospholipids may be subdivided into distinct classes (**Table 6**) based on the nature of the polar "head group" at the *sn*-3 position of the glycerol backbone in eukaryotes and eubacteria or the *sn*-1 position in the case of archaebacteria (21). In the case of the glycerophosphoglycerols and glycerophosphoglycerophosphates, a second glycerol unit constitutes part of the head group, whereas for the glycerophosphoglycerophosphoglycerols (cardiolipins), a third glycerol unit is typically acylated at the *sn*-1′ and *sn*-2′ positions to create a pseudosymmetrical molecule. Each head group class is further differentiated on the basis of the *sn*-1 and *sn*-2 substituents on the glycerol backbone. Although the glycerol backbone is symmetrical, the second carbon becomes a chiral center when the *sn*-1 and *sn*-3 carbons have different substituents. A large number of trivial names are associated with phospholipids. In the systematic nomenclature, mono/di-radylglycerophospholipids with different acyl or alkyl substituents are designated by similar conventions for naming of classes (see below) and are grouped according to the common polar moieties (i.e., head groups).

Typically, one or both of these hydroxy groups are acylated with long-chain fatty acids, but there are also alkyl-linked and 1Z-alkenyl-linked (plasmalogen) glycero-

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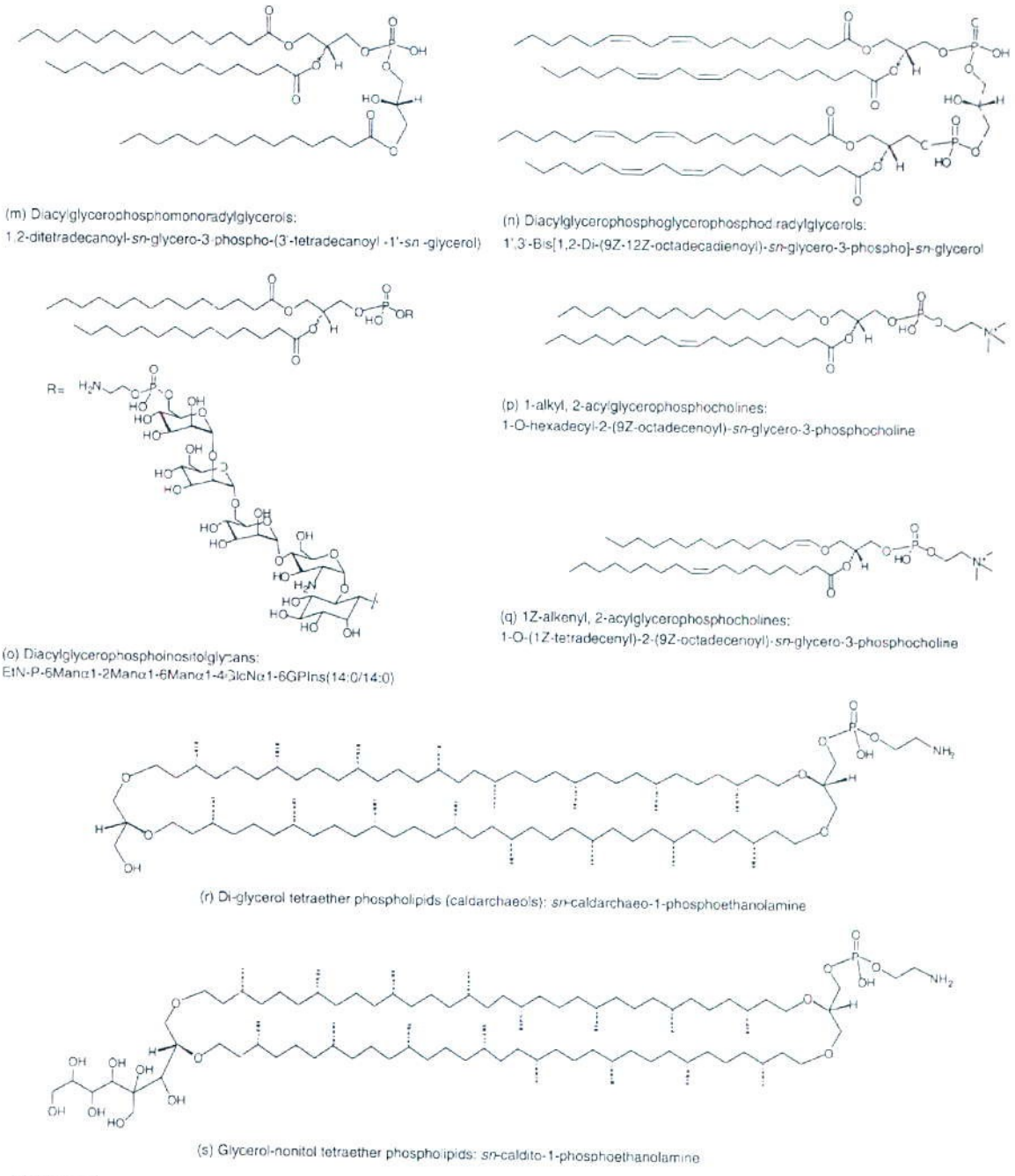


Fig. 4. Continued.

phospholipids, as well as dialkylether variants in prokaryotes. The main biosynthetic pathways for the formation of GPCho and GPEtn (see Table 3 for shorthand notation) were elucidated through the efforts of Kennedy and coworkers (22) in the 1950s and 1960s, and more detailed interconversion pathways to form additional classes of phospholipids were described more recently. In addition to serving as a primary component of cellular membranes and binding sites for intracellular and intercellular proteins, some glycerophospholipids in eukaryotic cells are either precursors of, or are themselves, membrane-derived second messengers. A separate class, called oxidized glycerophospholipids, is composed of molecules in which one or more of the side chains have been oxidized. Several overviews are available on the classification, nomenclature, metabolism, and profiling of glycerophospholipids (18, 23–26). Structures from this category are shown in **Fig. 4**.

Sphingolipids [SP]

Sphingolipids are a complex family of compounds that share a common structural feature, a sphingoid base backbone that is synthesized de novo from serine and a long-chain fatty acyl-CoA, then converted into ceramides, phosphosphingolipids, glycosphingolipids, and other species,

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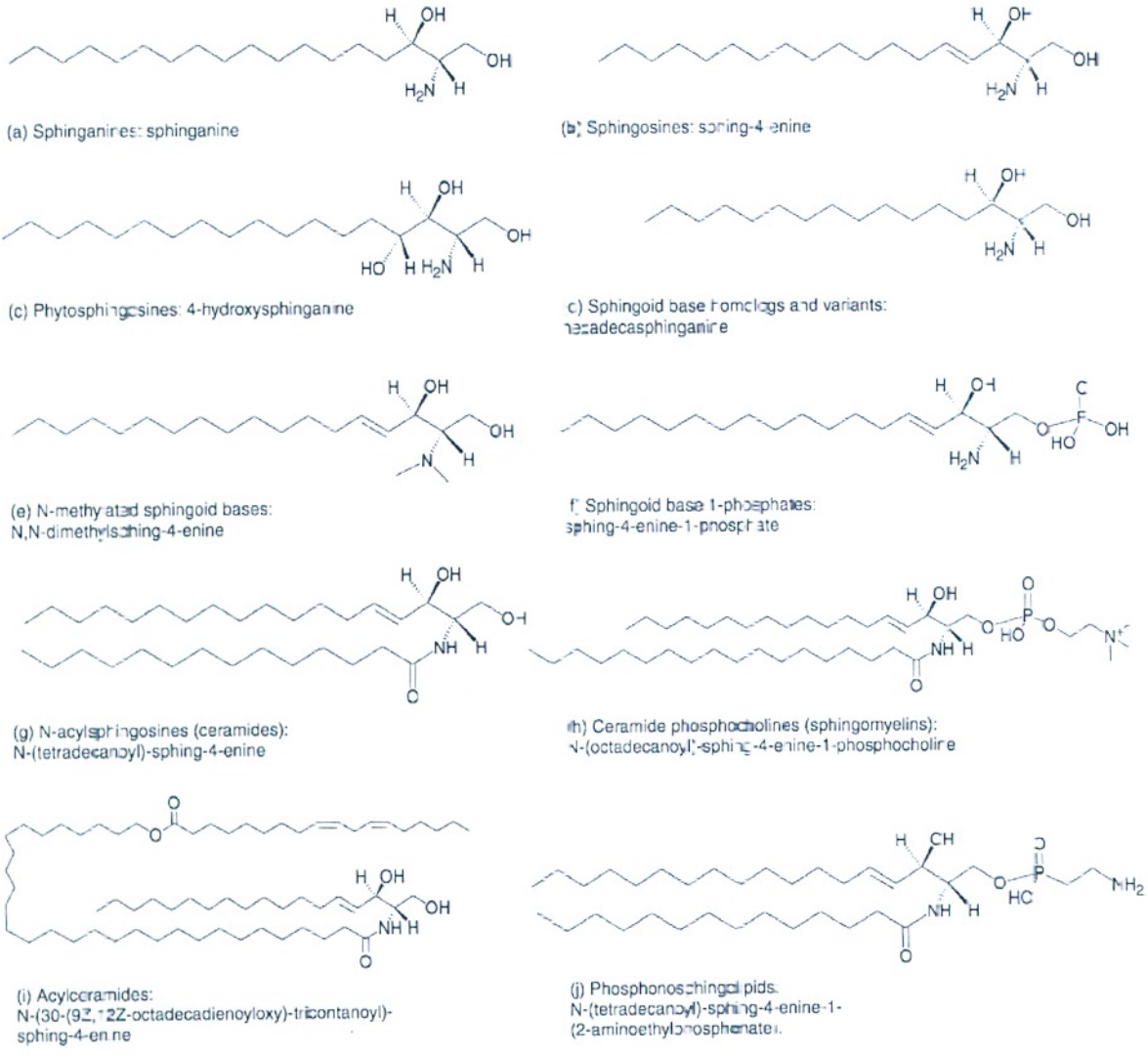


Fig. 5. Representative structures for sphingolipids.

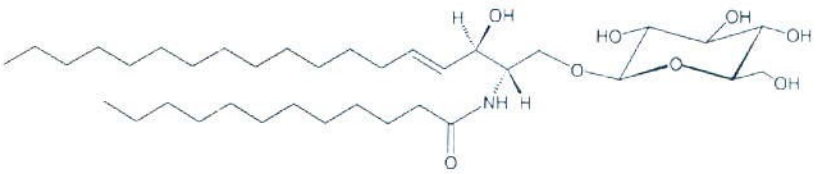
including protein adducts (27, 28). A number of organisms also produce sphingoid base analogs that have many of the same features as sphingolipids (such as long-chain alkyl and vicinal amino and hydroxyl groups) but differ in other features. These have been included in this category because some are known to function as inhibitors or antagonists of sphingolipids, and in some organisms, these types of compounds may serve as surrogates for sphingolipids.

Sphingolipids can be divided into several major classes (**Table 7**): the sphingoid bases and their simple derivatives (such as the 1-phosphate), the sphingoid bases with an amide-linked fatty acid (e.g., ceramides), and more complex sphingolipids with head groups that are attached via phosphodiester linkages (the phosphosphingolipids) via glycosidic bonds (the simple and complex glycosphingolipids such as cerebrosides and gangliosides), and other groups (such as phosphono- and arseno-sphingolipids). The IUPAC has recommended a systematic nomenclature for sphingolipids (3).

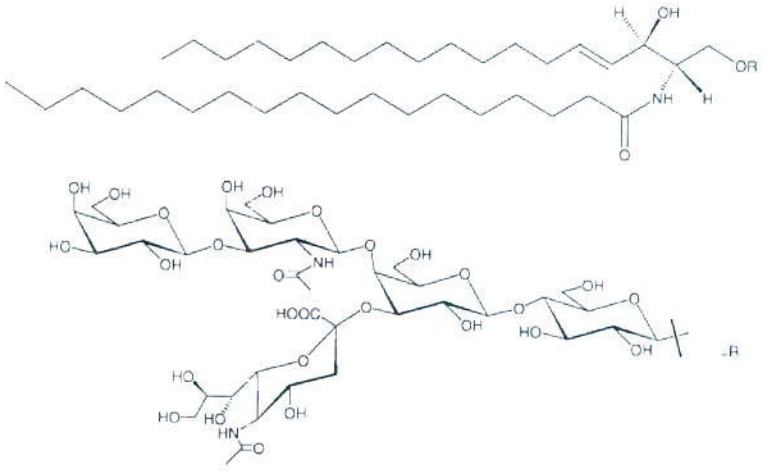
The major sphingoid base of mammals is commonly referred to as "sphingosine," because that name was affixed by the first scientist to isolate this compound (29). Sphingosine is (2*S*,3*R*,4*E*)-2-aminooctadec-4-ene-1,3-diol (it is also called D-*erythro*-sphingosine and sphing-4-enine). This is only one of many sphingoid bases found in nature, which vary in alkyl chain length and branching, the number and positions of double bonds, the presence of additional hydroxyl groups, and other features. The structural variation has functional significance, for example, sphingoid bases in the dermis have additional hydroxyls at position 4 (phytoceramides) and/or 6 that can interact with neighboring molecules, thereby strengthening the permeability barrier of skin. Sphingoid bases are found in a variety of derivatives, including the 1-phosphates, lysosphingolipids (such as sphingosine 1-phosphocholine as well as sphingosine 1-glycosides), and *N*-methyl derivatives (*N*-methyl, *N*,*N*-dimethyl, and *N*,*N*,*N*-trimethyl). In addition, a large number of organisms, such as fungi and sponges, produce compounds with structural similarity to sphingoid bases, some of which (such as myriocin and the fumonisins) are potent inhibitors of enzymes of sphingolipid metabolism.

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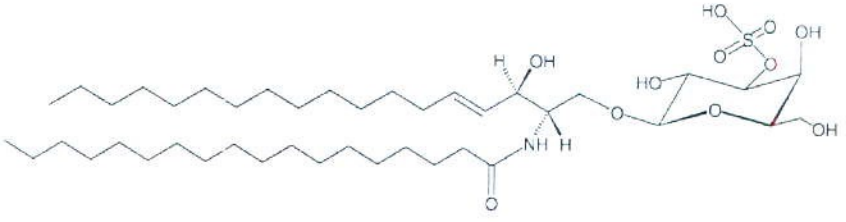
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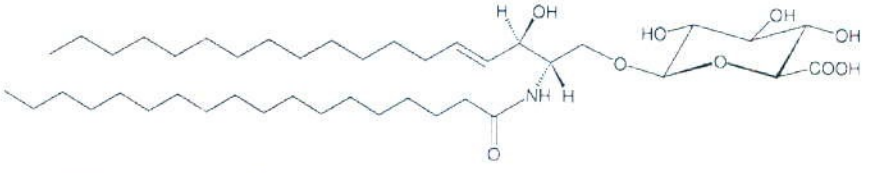
(k) Neutral Glycosphingolipids: Simple Glc series:
Glcβ-Cer(d18:1/12:0)



(l) Acidic Glycosphingolipids: Gangliosides:
Galβ1-3GalNAcβ1-4(Neu5Acα2-3)Galβ1-4Glcβ-Cer(d18:1/18:0)



(m) Acidic Glycosphingolipids: Sulfosphingolipids:
(3'-sulfo)Galβ-Cer(d18:1/18:0)



(n) Acidic Glycosphingolipids: Glucuronosphingolipids:
GlcUAβ-Cer(d18:1/18:0)

Fig. 5. Continued.

Ceramides (*N*-acyl-sphingoid bases) are a major subclass of sphingoid base derivatives with an amide-linked fatty acid. The fatty acids are typically saturated or monounsaturated with chain lengths from 14 to 26 carbon atoms; the presence of a hydroxyl group on carbon 2 is fairly common. Ceramides sometimes have specialized fatty acids, as illustrated by the skin ceramide in **Fig. 5i**, which has a 30 carbon fatty acid with a hydroxyl group on the terminal (ω) carbon. Ceramides are generally precursors of more complex sphingolipids. The major phosphosphingolipids of mammals are sphingomyelins (ceramide phosphocholines), whereas insects contain mainly ceramide phosphoethanolamines and fungi have phytoceramidephosphoinositols and mannose-containing head groups.

Glycosphingolipids (4) are classified on the basis of carbohydrate composition: *1*) neutral glycosphingolipids contain one or more uncharged sugars such as glucose (Glu), galactose (Gal), *N*-acetylglucosamine (GlcNAc), *N*-acetylga-

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TABLE 7. Sphingolipids [SP] classes and subclasses

- Sphingoid bases [SP01]
  - Sphing-4-enines (sphingosines) [SP0101]
  - Sphinganines [SP0102]
  - 4-Hydroxysphinganines (phytosphingosines) [SP0103]
  - Sphingoid base homologs and variants [SP0104]
  - Sphingoid base 1-phosphates [SP0105]
  - Lysosphingomyelins and lysoglycosphingolipids [SP0106]
  - *N*-Methylated sphingoid bases [SP0107]
  - Sphingoid base analogs [SP0108]
- Ceramides [SP02]
  - *N*-Acylsphingosines (ceramides) [SP0201]
  - *N*-Acylsphinganines (dihydroceramides) [SP0202]
  - *N*-Acyl-4-hydroxysphinganines (phytoceramides) [SP0203]
  - Acylceramides [SP0204]
  - Ceramide 1-phosphates [SP0205]
- Phosphosphingolipids [SP03]
  - Ceramide phosphocholines (sphingomyelins) [SP0301]
  - Ceramide phosphoethanolamines [SP0302]
  - Ceramide phosphoinositols [SP0303]
- Phosphonosphingolipids [SP04]
- Neutral glycosphingolipids [SP05]
  - Simple Glc series (GlcCer, LacCer, etc.) [SP0501]
  - GalNAcβ1-3Galα1-4Galβ1-4Glc- (globo series) [SP0502]
  - GalNAcβ1-4Galβ1-4Glc- (ganglio series) [SP0503]
  - Galβ1-3GlcNAcβ1-3Galβ1-4Glc- (lacto series) [SP0504]
  - Galβ1−4GlcNAcβ1-3Galβ1-4Glc- (neolacto series) [SP0505]
  - GalNAcβ1-3Galα1-3Galβ1-4Glc- (isoglobo series) [SP0506]
  - GlcNAcβ1-2Manα1-3Manβ1-4Glc- (mollu series) [SP0507]
  - GalNAcβ1-4GlcNAcβ1-3Manβ1-4Glc- (arthro series) [SP0508]
  - Gal-Galα series) [SP0509]
  - Other [SP0510]
- Acidic glycosphingolipids [SP06]
  - Gangliosides [SP0601]
  - Sulfoglycosphingolipids (sulfatides) [SP0602]
  - Glucuronosphingolipids [SP0603]
  - Phosphoglycosphingolipids [SP0604]
  - Other [SP0600]
- Basic glycosphingolipids [SP07]
- Amphoteric glycosphingolipids [SP08]
- Arsenosphingolipids [SP09]
- Other [SP00]

lactosamine (GalNAc), and fucose (Fuc), which are grouped into families based on the nature of the glyco-substituents as shown in the listing; *2*) acidic glycosphingolipids contain ionized functional groups (phosphate or sulfate) attached to neutral sugars or charged sugar residues such as sialic acid (*N*-acetyl or *N*-glycoloyl neuraminic acid). The latter are called gangliosides, and the number of sialic acid residues is usually denoted with a subscript letter (i.e., mono-, di- or tri-) plus a number reflecting the subspecies within that category; *3*) basic glycosphingolipids *4*) amphoteric glycosphingolipids. For a few glycosphingolipids, historically assigned names as antigens and blood group structures are still in common use (e.g., Lewis x and sialyl Lewis x). Some aquatic organisms contain sphingolipids in which the phosphate is replaced by a phosphono or arsenate group. The other category includes sphingolipids that are covalently attached to proteins; for example, ω-hydroxyceramides and ω-glucosylceramides are attached to surface proteins of skin, and inositol-phosphoceramices are used as membrane anchors for some fungal proteins in a manner analogous to the glycosylphosphatidylinositol anchors that are attached to proteins in other eukaryotes. Some examples of sphingolipid structures are shown in Fig. 5.

TABLE 8. Sterol lipids [ST] classes and subclasses

- Sterols [ST01]
- Cholesterol and derivatives [ST0101]
  - Cholesteryl esters [ST0102]
  - Phytosterols and derivatives [ST0103]
  - Marine sterols and derivatives [ST0104]
  - Fungal sterols and derivatives [ST0105]
- Steroids [ST02]
  - C_{18} steroids (estrogens) and derivatives [ST0201]
  - C_{19} steroids (androgens) and derivatives [ST0202]
  - C_{21} steroids (gluco/mineralocorticoids, progestogins) and derivatives [ST0203]
- Secosteroids [ST03]
  - Vitamin D_2 and derivatives [ST0301]
  - Vitamin D_3 and derivatives [ST0302]
- Bile acids and derivatives [ST04]
  - C_{24} bile acids, alcohols, and derivatives [ST0401]
  - C_{25} bile acids, alcohols, and derivatives [ST0402]
  - C_{27} bile acids, alcohols, and derivatives [ST0403]
  - C_{28} bile acids, alcohols, and derivatives [ST0404]
- Steroid conjugates [ST05]
  - Glucuronides [ST0501]
  - Sulfates [ST0502]
  - Glycine conjugates [ST0503]
  - Taurine conjugates [ST0504]
- Hopanoids [ST06]
- Other [ST00]

Sterol lipids [ST]

The sterol category is subdivided primarily on the basis of biological function. The sterols, of which cholesterol and its derivatives are the most widely studied in mammalian systems, constitute an important component of membrane lipids, along with the glycerophospholipids and sphingomyelins (30). There are many examples of unique sterols from plant, fungal, and marine sources that are designated as distinct subclasses in this schema (**Table 8**). The steroids, which also contain the same fused four ring core structure, have different biological roles as hormones

TABLE 9. Prenol lipids [PR] classes and subclasses

- Isoprenoids [PR01]
  - C_5 isoprenoids [PR0101]
  - C_{10} isoprenoids (monoterpenes) [PR0102]
  - C_{15} isoprenoids (sesquiterpenes) [PR0103]
  - C_{20} isoprenoids (diterpenes) [PR0104]
  - C_{25} isoprenoids (sesterterpenes) [PR0105]
  - C_{30} isoprenoids (triterpenes) [PR0106]
  - C_{40} isoprenoids (tetraterpenes) [PR0107]
  - Polyterpenes [PR0108]
- Quinones and hydroquinones [PR02]
  - Ubiquinones [PR0201]
  - Vitamin E [PR0202]
  - Vitamin K [PR0203]
- Polyprenols [PR03]
  - Bactoprenols [PR0301]
  - Bactoprenol monophosphates [PR0302]
  - Bactoprenol diphosphates [PR0303]
  - Phytoprenols [PR0304]
  - Phytoprenol monophosphates [PR0305]
  - Phytoprenol diphosphates [PR0306]
  - Dolichols [PR0307]
  - Dolichol monophosphates [PR0308]
  - Dolichol diphosphates [PR0309]
- Other [PR00]

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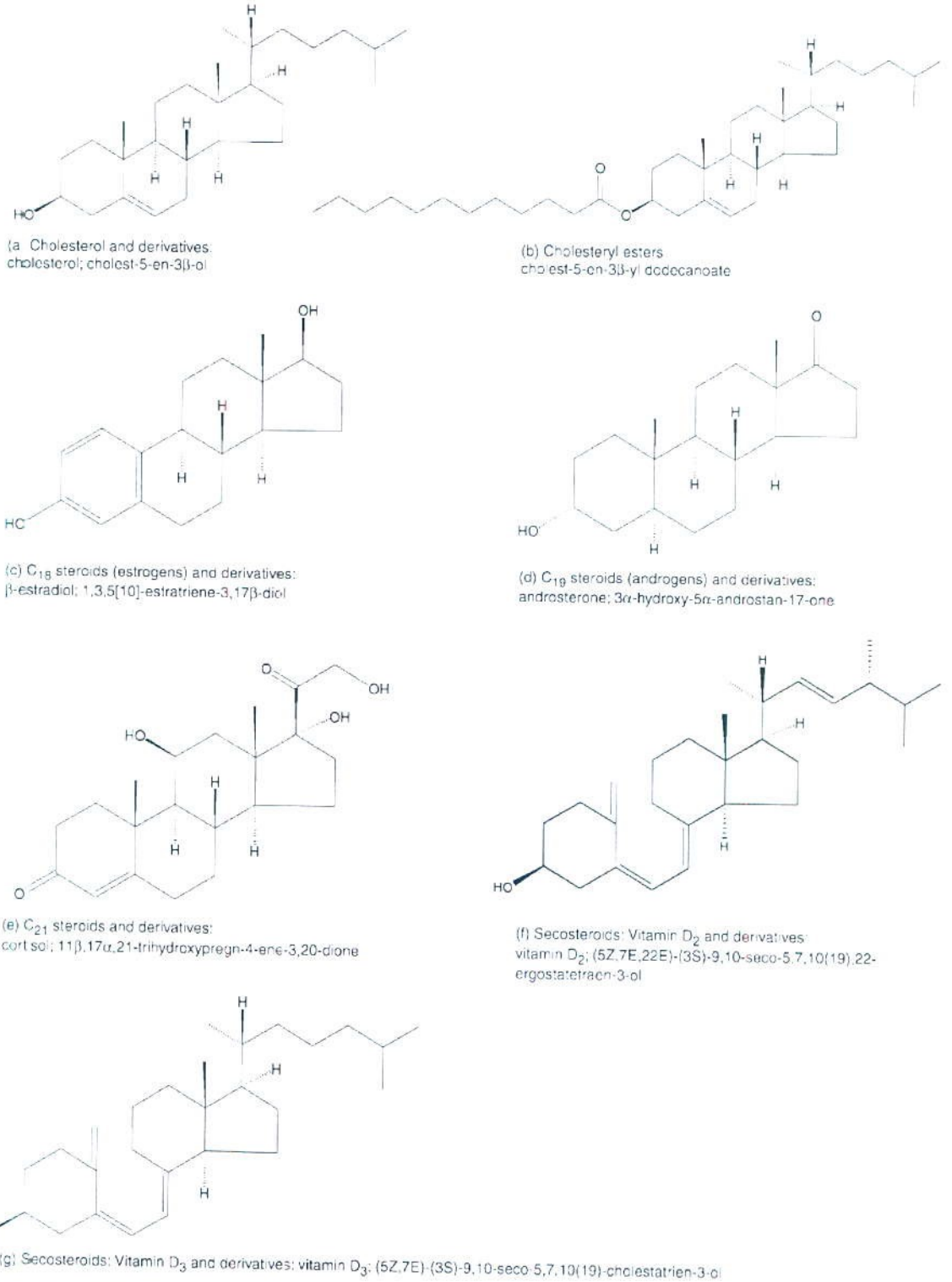
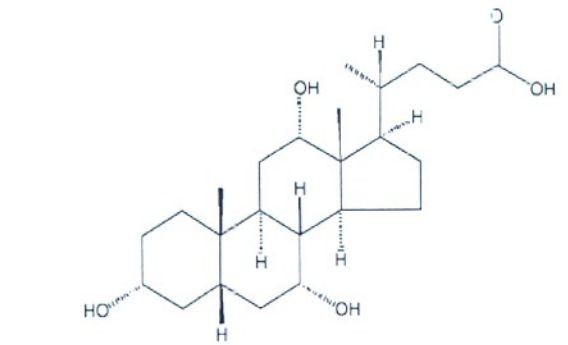


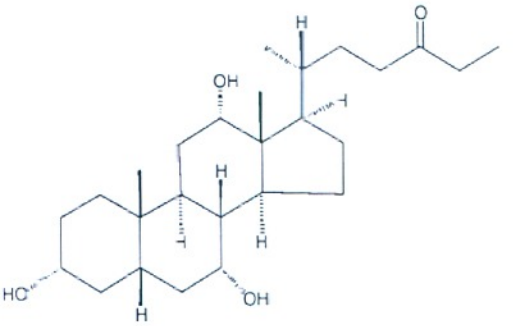
Fig. 6. Representative structures for sterol lipids.

and signaling molecules (31). These are subdivided on the basis of the number of carbons in the core skeleton. The C_{18} steroids include the estrogen family, whereas the C_{19} steroids comprise the androgens such as testosterone and androsterone. The C_{21} subclass, containing a two carbon side chain at the C_{17} position, includes the progestogens as well as the glucocorticoids and mineralocorticoids. The secosteroids, comprising various forms of vitamin D, are characterized by cleavage of the B ring of the core structure, hence the "seco" prefix (32). Additional classes within the sterols category are the bile acids (33), which in mammals are primarily derivatives of cholan-

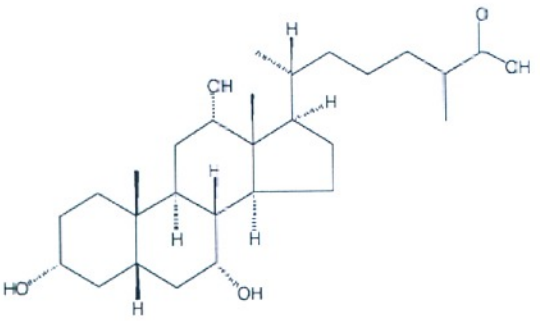
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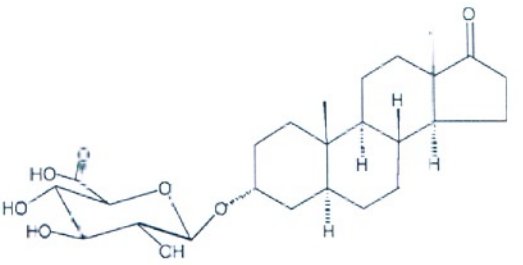
(h) C_{24} bile acids, alcohols, and derivatives: cholic acid; 3α,7α,12α-trihydroxy-5β-cholan-24-oic acid



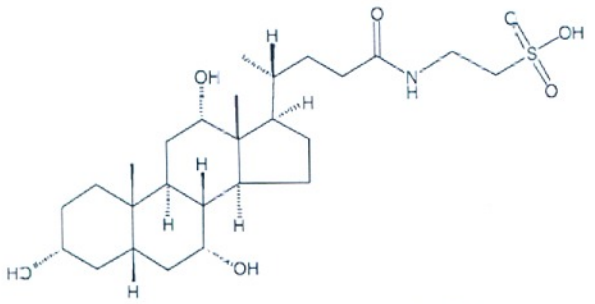
(i) C_{26} bile acids, alcohols, and derivatives: 3α,7α,12α-trihydroxy-27-nor-5β-cholestan-24-one



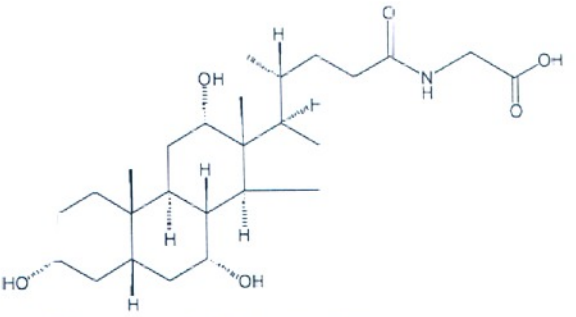
(j) C_{27} bile acids, alcohols, and derivatives: 3α,7α,12α-trihydroxy-5β-cholestan-26-oic acid



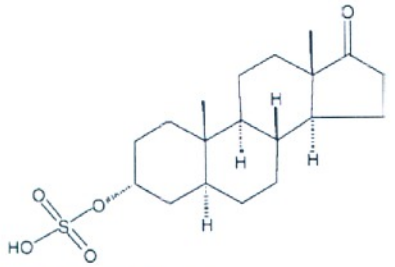
(k) Steroid conjugates: Glucuronides: 5α-androstane-3α-ol-17-one glucuronide



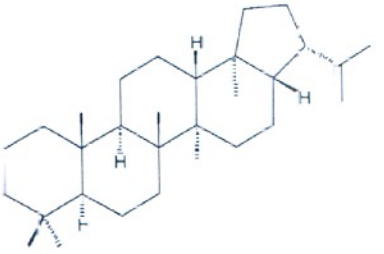
(l) Steroid conjugates: Taurine conjugates: taurocholic acid; N-(3α,7α,12α-trihydroxy-5β-cholan-24-oyl)-taurine



(m) Steroid conjugates: Glycine conjugates: glycocholic acid; N-(3α,7α,12α-trihydroxy-5β-cholan-24-oyl)-glycine



(n) Steroid conjugates: Sulfates: 5α-androstane-3α-ol-17-one sulfate



(o) Hopanoids: diploptene; hop-22(29)-ene

Fig. 6. Continued.

24-oic acid synthesized from cholesterol in the liver and their conjugates (sulfuric acid, taurine, glycine, glucuronic acid, and others). Sterol lipid structures are shown in **Fig. 6**.

Prenol lipids [PR]

Prenols are synthesized from the five carbon precursors isopentenyl diphosphate and dimethylallyl diphosphate that are produced mainly via the mevalonic acid pathway

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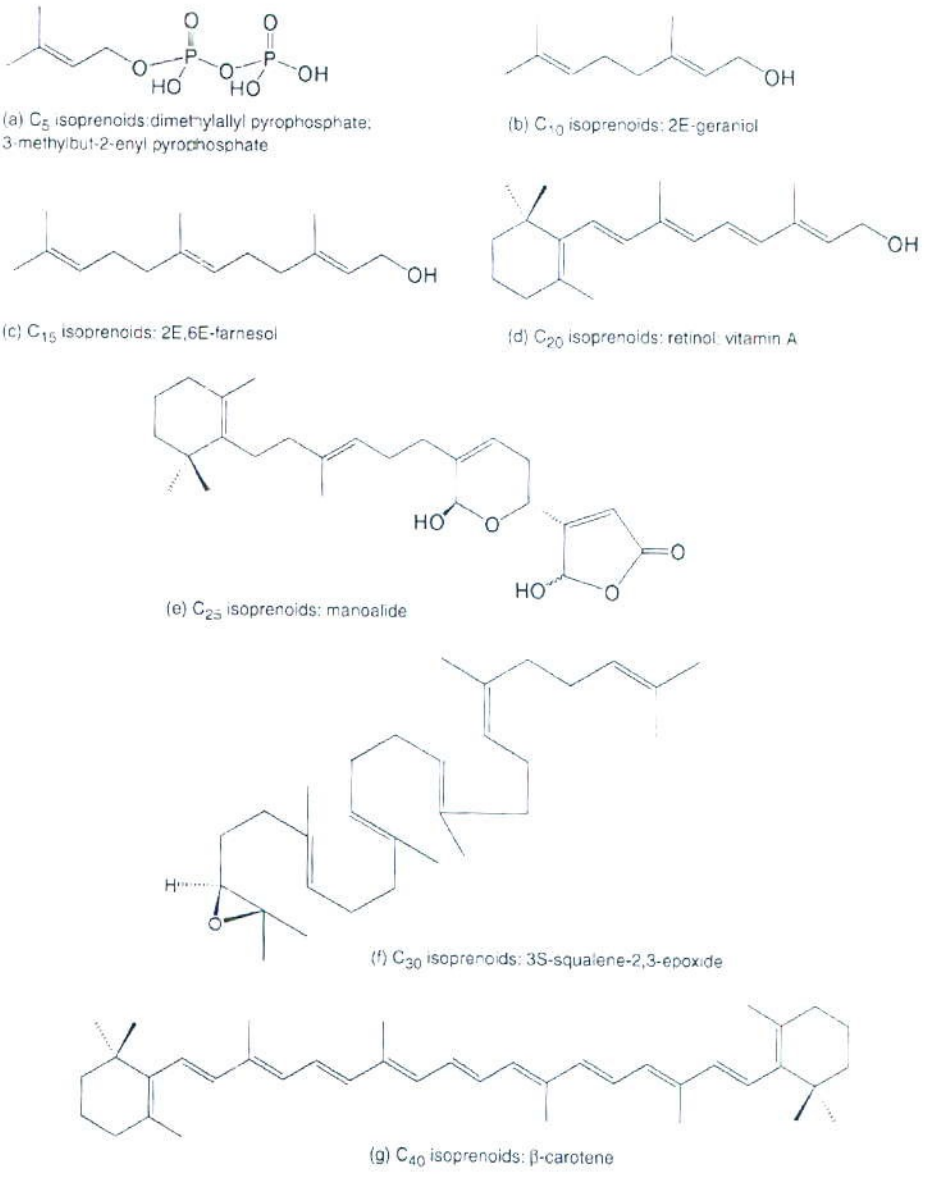


Fig. 7. Representative structures for prenol lipids.

(34). In some bacteria (e.g., *Escherichia coli*) and plants, isoprenoid precursors are made by the methylerythritol phosphate pathway (35). Because the simple isoprenoids (linear alcohols, diphosphates, etc.) are formed by the successive addition of C_5 units, it is convenient to classify them in this manner (**Table 9**), with a polyterpene subclass for those structures containing more than 40 carbons (i.e., >8 isoprenoid units) (36). Note that vitamin A and its derivatives and phytanic acid and its oxidation product pristanic acid are grouped under C_{20} isoprenoids. Carotenoids are important simple isoprenoids that function as antioxidants and as precursors of vitamin A (37). Another biologically important class of molecules is exemplified by the quinones and hydroquinones, which contain an isoprenoid tail attached to a quinonoid core of nonisoprenoid origin. Vitamins E and K (38, 39) as well as the ubiquinones (40) are examples of this class.

Polyprenols and their phosphorylated derivatives play important roles in the transport of oligosaccharides across membranes. Polyprenol phosphate sugars and polyprenol diphosphate sugars function in extracytoplasmic glycosylation reactions (41), in extracellular polysaccharide biosynthesis [for instance, peptidoglycan polymerization in bacteria (42)], and in eukaryotic protein *N*-glycosylation (43, 44). The biosynthesis and function of polyprenol phosphate sugars differ significantly from those of the polyprenol diphosphate sugars; therefore, we have placed them in separate subclasses. Bacteria synthesize polyprenols (called bactoprenols) in which the terminal isoprenoid unit attached to oxygen remains unsaturated, whereas in animal polyprenols (dolichols) the terminal isoprenoid is reduced. Bacterial polyprenols are typically 10 to 12 units long (40), whereas dolichols usually consist of 18 to 22 isoprene units. In the phytoprenols of plants, the three distal

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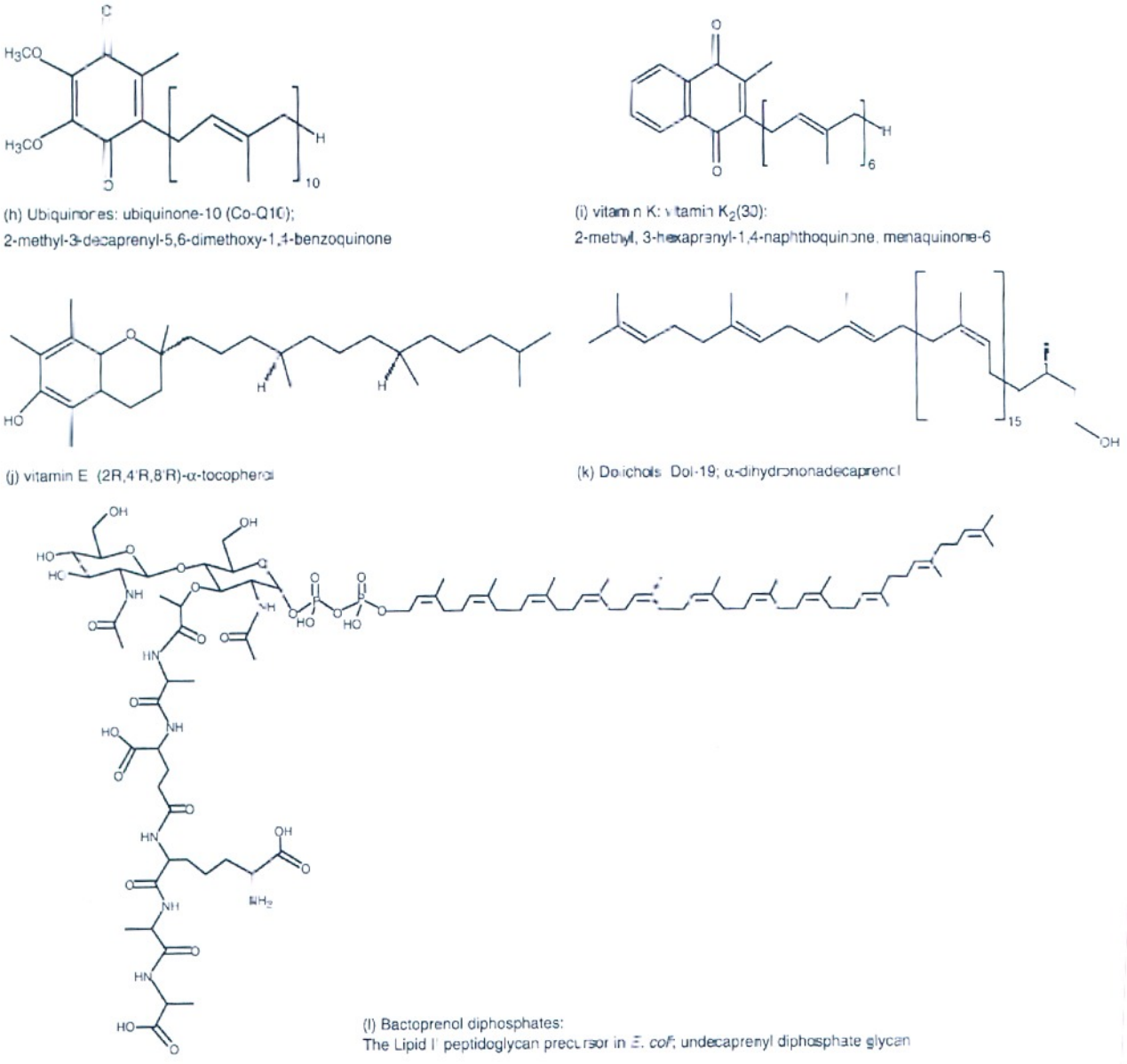


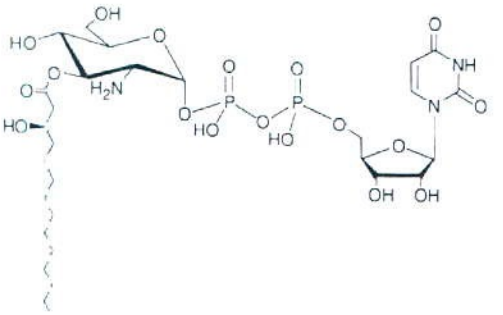
Fig. 7. Continued.

units are reduced. Several examples of prenol lipid structures are shown in **Fig. 7**.

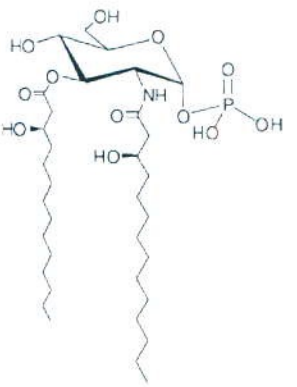
Saccharolipids [SL]

We have avoided the term "glycolipid" in the classification scheme to maintain a focus on lipid structures. In fact, all eight lipid categories in the present scheme include important glycan derivatives, making the term glycolipid incompatible with the overall goal of lipid categorization. We have, in addition, coined the term "saccharolipids" to describe compounds in which fatty acids are linked directly to a sugar backbone, forming structures that are compatible with membrane bilayers. In the saccharolipids (**Table 10**), a sugar substitutes for the glycerol backbone that is present in glycerolipids and glycerophospholipids. Saccharolipids can occur as glycan or as phosphorylated derivatives. The most familiar saccharolipids are the acylated glucosamine precursors of the lipid A component of the lipopolysaccharides in Gram-negative bacteria (41). Typical lipid A molecules are disaccharides of glucosamine, which are derivatized with as many as seven fatty acyl chains (41, 45). Note that in naming these compounds, the total number of fatty acyl groups are counted regardless of the nature of the linkage (i.e., amide or ester). The minimal lipopolysaccharide required for growth in *E. coli* is a hexa-acylated lipid A that is glycosylated with two 3-deoxy-D-manno-octulosonic acid residues (see below). In some bacteria, the glucosamine backbone of lipid A is replaced by 2,3-diamino-2,3-dideoxyglucose (46); therefore, the class has been designated "Acylaminosugars." Included also in this class are the Nod factors of nitrogen-fixing bacteria (47), such as *Sinorhizobium meliloti*. The Nod factors are oligosaccharides of glucosamine that are usually derivatized with a single fatty acyl chain. Additional saccharolipids include

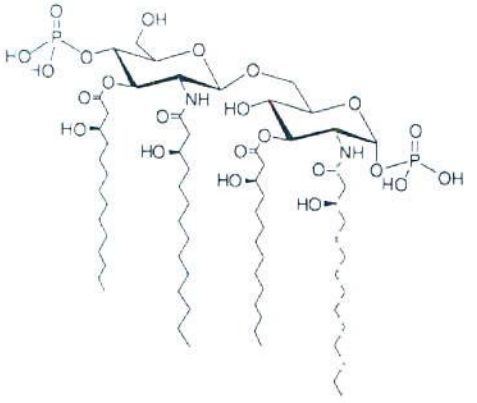
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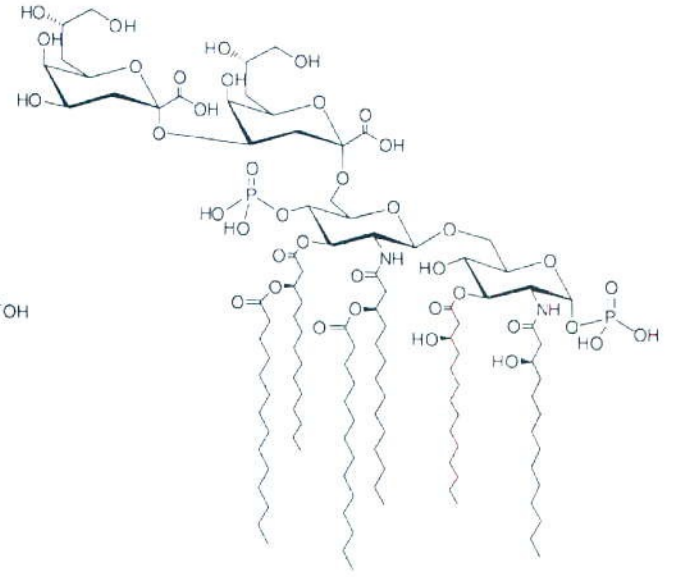
(a) Acylaminosugars: Monoacylaminosugars: UDP-3-O-(3R-hydroxy-tetradecanoyl)-GlcN



(b) Acylaminosugars: Diacylaminosugars: lipid X



(c) Acylaminosugars: Tetraacylaminosugars: lipid IV_A



(d) Acylaminosugar glycans: Kdo_2-lipid A

Fig. 8. Representative structures for saccharolipids.

fatty acylated derivatives of glucose, which are best exemplified by the acylated trehalose units of certain mycobacterial lipids (11). Acylated forms of glucose and sucrose also have been reported in plants (48). Some saccharolipid structures are shown in **Fig. 8**.

TABLE 10. Saccharolipids [SL] classes and subclasses

Acylaminosugars [SL01]
Monoacylaminosugars [SL0101]
Diacylaminosugars [SL0102]
Triacylaminosugars [SL0103]
Tetraacylaminosugars [SL0104]
Pentaacylaminosugars [SL0105]
Hexaacylaminosugars [SL0106]
Heptaacylaminosugars [SL0107]
Acylaminosugar glycans [SL02]
Acyltrehaloses [SL03]
Acyltrehalose glycans [SL04]
Other [SL00]

Polyketides [PK]

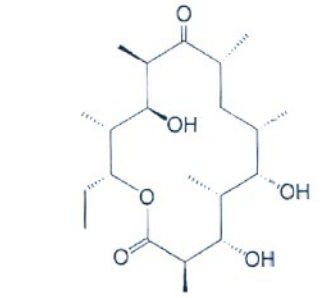
Polyketides are synthesized by classic enzymes as well as iterative and multimodular enzymes with semiautonomous active sites that share mechanistic features with the fatty acid synthases, including the involvement of specialized acyl carrier proteins (49, 50); however, polyketide synthases generate a much greater diversity of natural product structures, many of which have the character of lipids. The class I polyketide synthases form constrained macrocyclic lactones, typically ranging in size from 14 to 40 atoms, whereas class II and III polyketide synthases generate complex aromatic ring systems (**Table 11**). Polyketide back-

TABLE 11. Polyketides [PK] classes and subclasses

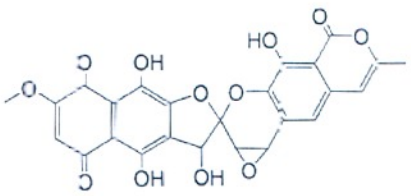
Macrolide polyketides [PK01]
Aromatic polyketides [PK02]
Nonribosomal peptide/polyketide hybrids [PK03]
Other [PK00]

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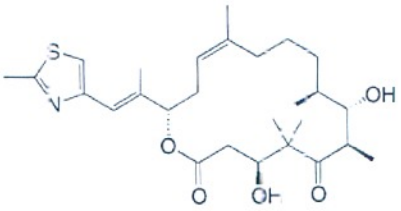
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(a) Macrolide polyketides: 6-deoxyerythronolide B



(b) Aromatic polyketides: griseorhodin A



(c) Polyketide hybrids: epothilone D

Fig. 9. Representative structures for polyketides.

bones are often further modified by glycosylation, methylation, hydroxylation, oxidation, and/or other processes. Some polyketides are linked with nonribosomally synthesized peptides to form hybrid scaffolds. Examples of the three polyketide classes are shown in **Fig. 9**. Many commonly used antimicrobial, antiparasitic, and anticancer agents are polyketides or polyketide derivatives. Important examples of these drugs include erythromycins, tetracylines, nystatins, avermectins, and antitumor epothilones. Other polyketides are potent toxins. The possibility of recombining and reengineering the enzymatic modules that assemble polyketides has recently stimulated the search for novel "unnatural" natural products, especially in the antibiotic arena (51, 52).

We consider this minimal classification of polyketides as the first step in a more elaborate scheme. It will be important ultimately to include as many polyketide structures as possible in a lipid database that can be searched for substructure and chemical similarity.

DISCUSSION

The goals of the LIPID MAPS initiative are to characterize known lipids and identify new ones, to quantitate temporal and spatial changes in lipids that occur with cellular metabolism, and to develop bioinformatics approaches that establish dynamic lipid networks; the goals of Lipid Bank (Japan) are to annotate and curate lipid structures and the literature associated with them; and the goals of the European Lipidomics Initiative are to coordinate and organize scientific interactions and workshops associated with lipid research. To coordinate the independent efforts from three continents and to facilitate collaborative work, a comprehensive classification of lipids with a common platform that is compatible with informatics requirements must be developed to deal with the massive amounts of data that will be generated by the lipid community. The proposed classification, nomenclature, and chemical representation system was initially designed to accommodate the massive data that will result from the LIPID MAPS effort, but it has been expanded to accommodate as many lipids as possible. We also have attempted to make the system compatible with existing lipid databases and the lipids currently annotated in them. It is designed to be expandable should new categories, classes, or subclasses be required in the future, and updates will be maintained on the LIPID MAPS website. The development of this system has been enriched by interaction with lipidologists across the world in the hopes that this system will be internationally accepted and used.

The authors appreciate the agreement of the International Lipids Classification and Nomenclature Committee to advise on future issues involving the maintenance of these recommendations. This committee currently includes Edward A. Dennis (chair), Christian Raetz and Robert Murphy representing LIPID MAPS, Friedrich Spener representing the International Conference on the Biosciences of Lipids, Gerrit van Meer representing the European Lipidomics Initiative, and Yousuke Seyama and Takao Shimizu representing the LipidBank of the Japanese Conference on the Biochemistry of Lipids. The authors are most appreciative of informative discussions and encouragement of this effort with Professor Richard Cammack, King's College, London, who is the Chairman of the Nomenclature Committee of IUBMB and the IUPAC/IUBMB Joint Commission on Biochemical Nomenclature. The authors thank the Consortium for Functional Glycomics (headed by Ram Sasisekharan at the Massachusetts Institute of Technology) for providing us with their text nomenclature for glycosylated structures. We are grateful to Dr. Jean Chin, Program Director at the National Institutes of General Medical Sciences, for her valuable input to this effort. This work was supported by the LIPID MAPS Large-Scale Collaborative Grant GM-069338 from the National Institutes of Health.

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ERRATA

It has been brought to the *Journal*'s attention that the Web site URL for LIPIDAT referenced in "A comprehensive classification system for lipids" (*J. Lipid Res.* 2005. 46: 839–862) has been changed. The Web site has moved from http://www.lipidat.chemistry.ohio-state.edu/ to http://www.lipidat.tcd.ie/. The URL in the article has been replaced in the online version of the article.

DOI 10.1194/jlr.E400004ERR

The authors of the article "Targeted disruption of steroidogenic acute regulatory protein D4 leads to modest weight reduction and minor alterations in lipid metabolism" (*J. Lipid Res.* 2010. 51: 1134–1143) have advised the *Journal* that the unit of measure for the bile acids of gall bladder bile in Table 3 (on page 1141) was incorrectly stated as mg/dl. The correct unit should be **mM**. This error appeared initially online but has since been corrected.

DOI 10.1194/jlr.M9003095ERR

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The Nomenclature of Lipids[a]

(Recommendations 1976)[b,c]

IUPAC-IUB Commission on Biochemical Nomenclature[d]

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[a] Document[c] of the IUPAC-IUB Commission on Biochemical Nomenclature (CBN) approved by IUPAC and IUB in 1976, and published with the cooperation of the IUB Commission of Editors of Biochemical Journals[d]. Comments on these Recommendations and suggestions for future revisions may be sent to any member of CBN[d].

[b] These Recommendations are a revision and extension of "The Nomenclature of Lipids", which appeared in 1967, as amended in 1970[1].

[c] Reprints of this document, supplied by the publishing journals, may be obtained from W. E. Cohn (Director of the NAS-NRC Office of Biochemical Nomenclature), Biology Division, Oak Ridge National Laboratory, P. O. Box Y, Oak Ridge, Tenn., U.S.A., 37830.

[d] Members of CBN are: O. Hoffmann-Ostenhof (Chairman), W. E. Cohn (Secretary), A. E. Braunstein, H. B. F. Dixon, B. L. Horecker, W. B. Jakoby, P. Karlson, W. Klyne, C. Liébecq, E. C. Webb.

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In 1967, a "Document for Discussion" on lipid nomenclature[1] was issued by CBN. It included a special system for the designation of configuration in glycerol derivatives that deviated considerably from standard stereochemical nomenclature. This system is based upon a fixed numbering ("stereo-specific numbering") for glycerol, regardless of substituents. It was hoped[1] that "discussion will lead shortly to the formulation" of recommendations acceptable to chemists in the field of lipids.

In subsequent years, there has been little discussion about this principle of stereospecific numbering; it has been well accepted within the field of glycerol derivatives, for which it has been especially useful[e], and is widely used. However, during this same period, many new and complex lipids and glycolipids have been isolated. Moreover, the Commissions on the Nomenclature of Organic Chemistry (CNOC) and Inorganic Chemistry (CNIC) issued, in 1973, "Nomenclature of Organic Chemistry, Section D"[2], which includes a section on the nomenclature of phosphorus-containing organic compounds and necessitates a reconsideration of the earlier nomenclature[1] in this area.

The present "Recommendations 1976" are based on reports of working groups on lipids[f] and glycolipids[g]. The main features are:

1. the system of stereospecific numbering is retained,
2. semisystematic nomenclature is extended to the plasmalogens;
3. a semisystematic nomenclature for higher glycosphingolipids, based on trivial names for specific tri- and tetrasaccharides, is proposed.

RECOMMENDATIONS

I. FATTY ACIDS, NEUTRAL FATS, LONG-CHAIN ALCOHOLS AND LONG-CHAIN BASES

A. Generic terms

Lip-1.1. The term **fatty acid** designates any one of the aliphatic monocarboxylic acids that can be liberated by hydrolysis from naturally occurring fats and oils. In the terms "free fatty acids" or "nonesterified fatty acids", now widely in use, "free" and "nonesterified" are actually redundant and should be omitted (See Lip-1.14). [The designation "aliphatic carboxylate (C_{10}-C_{26}, nonesterified)" used by the Commission on Quantities and Units in Clinical Chemistry is correct, but rather cumbersome.] Whenever the *sum* of fatty acids and their esters is determined by an analytical method, this should be explicitly stated. (See also Lip-1.6).

Lip-1.2. **Neutral fats** are mono-, di- or triesters of glycerol with fatty acids, and are therefore termed monoacylglycerol, diacylglycerol or triacylglycerol, as appropriate. "Acylglycerols" includes mixtures of any or all of these.

Comments

i) The term "acyl" is used in Organic Nomenclature [3] to denote the radical formed by loss of the OH group from the acid function of any acid (cf. Lip-1.6). We are concerned here with acyl radicals of aliphatic carboxylic acids with four or more carbon atoms, the larger members of which ($> C_{10}$) are also known as "higher fatty acids."

[e] CBN does not wish to imply that the idea of stereospecific numbering should be applied to other groups of compounds. It is the symmetry of glycerol itself but the asymmetry of its derivatives carrying different substituents at *O*-1 and *O*-3, as well as the unique place of these compounds in lipid metabolism, that makes this special treatment desirable.

[f] Members of the Working Group on Lipid Nomenclature: H. Hirschmann (U.S.A.), P. Karlson (Germany, corvenor), W. Stoffel (Germany), F. Snyder (U.S.A.), S. Veibel (Denmark), F. Vögtle (Germany).

[g] Members of the Working Group on Glycolipid Nomenclature: S. Basu (U.S.A.), R. O. Brady (U.S.A.), R. M. Burton (U.S.A.), R. Caputto (Argentina), S. Gatt (Israel), S. I. Hakomori (U.S.A.), M. Philippart (U.S.A.), L. Svennerholm (Sweden), D. Shapiro (Israel), C. C. Sweeley (U. S. A.), H. Wiegandt (Germany; convenor).

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ii) The old terms monoglyceride, diglyceride and triglyceride are discouraged and should progressively be abandoned, not only for consistency, but mainly because strict interpretation does not convey the intended meaning. "Triglyceride", taken literally, indicates three *glycerol* residues (e.g., cardiolipin), diglyceride two (e.g., phosphatidylglycerol), and a monoglyceride is a mono-*acyl*glycerol.

Lip-1.3. The generic term "long-chain alcohol" or "fatty alcohol" refers to an aliphatic compound with a chain-length greater than C_{10} that possesses a terminal CH_2OH group. Such alcohols should be named according to systematic nomenclature[3]. (See Lip-1.7).

Lip-1.4. The term **sphingoid** or **sphingoid base** refers to sphinganine (*cf.* Lip-1.8), [D-*erythro*-2-amino-1,3-octadecanediol (I)], its homologs and stereoisomers (II, III), and to the hydroxy and unsaturated derivatives of these compounds (IV - VI). The term "long-chain base" may be used in a wider sense to indicate any base containing a long-chain aliphatic radical.

Lip-1.5. The following generic terms are used for the following groups of compounds:

a) **sphingolipid**, for any lipid containing a sphingoid;
b) **ceramide**, for an *N*-acylated sphingoid;
c) **sphingomyelin**, for a ceramide-1-phosphocholine (see ref.[2] for this use of "phospho"; also Lip-2.11);
d) **glycosphingolipid**, for any lipid containing a sphingoid and one or more sugars. (See sections I, B, 2 and II, A for other generic terms).

3. Individual compounds

1. *Fatty acids and alcohols*

Lip-1.6. Fatty acids (cf. Lip-1.1) and their acyl radicals (cf. Lip-1.2, comment i) are named according to the IUPAC Rules for the Nomenclature of Organic Chemistry (ref.[3], Rule C-4). (A list of trivial names is given in Appendix A.) Fatty acids are numbered with the carbon atom of the carboxyl group as C-1. By standard biochemical convention, the ending -ate in, e.g., palmitate denotes any mixture of the free acid and its ionized form in which the cations are not specified. The ending -ate is also used to designate esters, e.g., cholesteryl palmitate, ethylidene dilaurate, etc. (cf. Lip-1.12). Structural isomers of polyunsaturated acids, hitherto distinguished by Greek letters (e.g., α- and γ-linolenic acids), are better distinguished by the locants of the unsaturated linkages (e.g., (9,12,15)- and (6,9,12)-linolenic acids, respectively). (See Lip-1.15). However, the Greek letter prefixes may be useful in (defined) abbreviations (see Appendix A).

Lip-1.7. Long-chain alcohols (fatty alcohols) and the radicals derived from them should be designated by their systematic names (ref.[3], Rules C-201 and A-1 *et seq.*), but not by trivial names that are derived from those of fatty acids.

Examples: 1-hexadecanol and hexadecyl-, not palmityl alcohol and palmityl-; 1-dodecanol and dodecyl-, not lauryl alcohol and lauryl-.

2. *Sphinganine and derivatives*

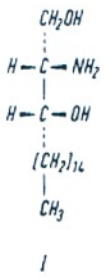
Lip-1.8. The compound previously known as dihydrosphingosine [2*D*-amino-1,3*D*-octadecanediol or D-*erythro*-2-amino-1,3-octadecanediol or (2*S*, 3*R*)-2-amino-1,3-octadecanediol] is called **sphinganine** (I).

Lip-1.9. Trival names of higher or lower homologs of sphinganine may be derived by adding a prefix (ref.[3], Rule A-1) denoting the total number of carbon atoms in the main chain of the homolog, e.g., icosasphinganine* for the C_{20} compound (III), hexadecasphinganine for the C_{16} compound.

Lip-1.10. Affixes denoting substitution of sphinganine (hydroxy, oxo, methyl, etc.) are used as usual, according to existing rules[3]. The configurations of additional substituents should be specified by the prefixes "*D*" or "*L*" (italic capitals, cf. ref.[4]) following the locant of substitution. These prefixes refer to the orientation of the functional groups to the right or left, respectively, of the carbon chain when written vertically in a Fischer projection with C-1 at the top (cf. Formulae I - VI). If the configuration is unknown, the prefix "*X*" may be used. In the case of a racemic mixture, *rac* should be used as a prefix to the name.

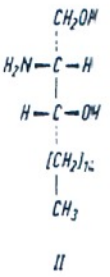
* Formerly eicosasphinganine (see footnote *d* in Appendix A).

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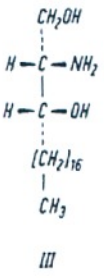
I

Sphinganine
[D-*erythro* or 2*S*,3*R* configuration implied]



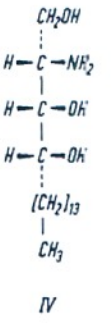
II

(2*R*,3*R*)- (or D-*threo*-)
2-Amino-1,3-octadecanediol



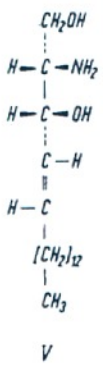
III

Icosasphinganine*



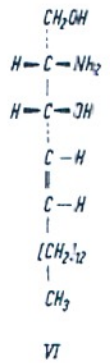
IV

4*D*-Hydroxysphinganine;
(2*S*,3*S*,4*R*)-2-amino-1,3,4-octadecanetriol;
(phytosphingosine).



V

Sphingosine;
trans-4-sphingenine;
(4*E*)-sphingenine;
(2*S*,3*R*,4*E*)-2-amino-4-octadecene-1,3-diol.



VI

cis-4-Sphingenine;
(4*Z*)-sphingenine.

* Formerly eicosasphinganine (see footnote *d* in Appendix A).

Sphingoids differing from sphinganine in their configurations at C-2 and/or C-3 should *not* be named as derivatives of sphinganine, but with fully systematic names[3], using the prefixes D-*threo*, L-*erythro*, as appropriate, e.g., D-*threo*-2-amino-1,3-octadecanediol, or (2*R*, 3*R*)-2-amino-1,3-octadecanediol, for II (cf. Rule Carb-8 in ref.[5]). (cf. Lip-1.11, ex. 4).

Comment. The semisystematic names for the sphingoids are significantly shorter than the fully systematic names only if the terms chosen imply not only substituents but also configurations. Therefore, the name "sphinganine" specifies the D-*erythro* configuration, and it is logical that the names of stereoisomers of sphinganine differing in configuration at C-2 and/or C-3 should not include "sphinganine" as a root. (This recommendation differs from that in the previous document[1].)

The configurations usually encountered have identical configurational prefixes only if a *D*/*L* but not if the *R*/*S* system[6] is used; e.g., C-3 is *D* and *R* in icosasphinganine (III) and *D* and *S* in 4*D*-hydroxysphinganine (IV). Whenever it is desirable to use the *R*/*S* system, the fully systematic name should be used with the specification of configuration at every center (and, when applicable, of the configuration at the double bond).

Examples:
(2*R*,3*R*)-2-amino-1,3-octadecanediol, for II;
(2*S*,3*S*,4*R*)-2-amino-1,3,4-octadecanetriol for IV;
(2*S*,3*R*,4*E*)-2-amino-4-octadecene-1,3-diol for sphingosine (V). (See also Lip-1.11.)

Lip-1.11. Names for unsaturated compounds are derived from the names of the corresponding saturated compounds by the appropriate infixes, namely ene, diene, yne, etc.[3]. If the geometry of the double bond is known, it should be indicated by the more modern *E*/*Z* system (cf.[6], Rule E-2.2), e.g., (4*E*)-sphinganine for sphingosine (V).

The trivial name **sphingosine** (V) is retained. If trivial names other than sphingosine are used, they should be defined in each paper in terms of this nomenclature, or of the general nomenclature of organic chemistry[3].

Other names for the substances described in Lip-1.10 and Lip-1.11:
4*D*-hydroxysphinganine for IV, formerly known as phytosphingosine;
(4*E*)-sphingenine for sphingosine (V);
(4*Z*)-sphingenine for the geometric isomer of sphingosine (VI);
D-*threo*-2-amino-1,3-octadecanediol for the C-2 epimer of sphinganine (II); cf. Lip-1.10 Ex. 1.

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3. *Glycerol derivatives*

Lip-1.12. Esters, ethers and other *O*-derivatives of glycerol are designated according to Rule Carb-15 of the Rules of Carbohydrate Nomenclature[5] i.e. by a prefix, denoting the substituent, preceded by a locant. If the substitution is on a carbon atom, the compound is designated by its systematic name and not as a derivative of glycerol (e.g., 1,2,3-nonadecanetriol for $C_{16}H_{33}CHOH$-$CHOH$-CH_2OH, which could be considered as 1-*C*-hexadecylglycerol). It is permissible to omit the locant *"O"* if the substitution is on the oxygen atoms of glycerol.

Examples: tristearoylglycerol or tri-*O*-stearoylglycerol or glycerol tristearate, or glyceryl tristearate; 1,3-benzylideneglycerol or 1,3-*O*-benzylideneglycerol; glycerol 2-phosphate (a permissible alternative to this term is 2-phosphoglycerol).

Comment. The alternative system set forth in Rule Carb-16 of the Rules on Carbohydrate Nomenclature[5], i.e. the use of the suffix *-ate*, is less suitable for glycerol esters, with the exception of the phosphates (see Examples). However, this system may be used to designate esters of monofunctional alcohols, e.g. cholesteryl palmitate (cf. Lip-1.6).

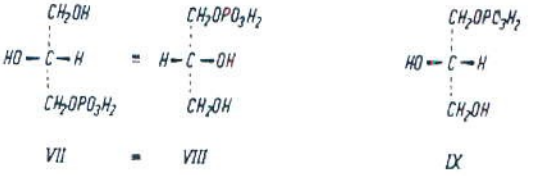
Lip-1.13. **Stereospecific numbering.** In order to designate the configuration of glycerol derivatives, the carbon atoms of glycerol are numbered stereospecifically. The carbon atom that appears on top in that Fischer projection that shows a vertical carbon chain with the hydroxyl group at carbon-2 to the left is designated as C-1. To differentiate such numbering from conventional numbering conveying no steric information, the prefix *"sn"* (for *stereospecifically numbered*) is used. This term is printed in lower-case italics, even at the beginning of a sentence, immediately preceding the glycerol term, from which it is separated by a hyphen. The prefix *"rac-"* (for *racemo*) precedes the full name if the product is an equal mixture of both antipodes; the prefix *"X-"* may be used when the configuration of the compound is either unknown or unspecified (cf. Lip-1.10).

Examples:
sn-glycerol 3-phosphate for the stereoisomer (VII ≡ VIII), previously known as either L-α-glycerophosphoric acid or as D-glycerol 1-phosphate;
rac-1-hexadecylglycerol;
1,2-dipalmitoyl-3-stearoyl-*X*-glycerol.

Comments

i) The problem of distinguishing between stereoisomers was discussed *in extenso* in the 1967 document[1]. In brief, difficulties arise because glycerol is a prochiral compound. The parent substance of many phospholipids, natural glycerol phosphate, has been named both as L-α-glycerol phosphate[7] (VII) and, according to standard rules of nomenclature, D-glycerol 1-phosphate[8] (VIII). When the *R/S* system (sequence rule) is applied, substitution of one of the primary hydroxyl groups often leads to changes in the configurational prefix, thus obscuring chemical and biogenetical relationships; it is generally inapplicable to the steric description of such mixtures as occur in triacylglycerols isolated from natural sources. The stereospecific numbering of glycerol and its derivatives as proposed by Hirschmann[9], described above (and in ref.[1]), avoids these difficulties; it has proved useful and is widely accepted.

ii) The enantiomer of *sn*-glycerol 3-phosphate (VII) is *sn*-glycerol 1-phosphate (IX), as is evident from the structures.



sn-Glycerol 3-phosphate [L-(glycerol 3-phosphate) ≡ D-(glycerol 1-phosphate)]

sn-Glycerol 1-phosphate [L-(glycerol 1-phosphate) ≡ D-(glycerol 3-phosphate)]

C. Symbols and abbreviations

Lip-1.14. The term "fatty acids" (cf. Lip-1.1) should not be abbreviated. The use of abbreviations like "FFA" for "free fatty acids" or "NEFA" for "non-esterified fatty acids" is strongly discouraged.

Comment. The words "acids" and "esters" serve to distinguish the "free" (nonesterified) and "bound" (esterified) fatty acids, and are as short as or shorter than the abbreviations themselves.

Lip-1.15. In tables and discussions where various fatty acids are involved, the notation giving the number of carbon atoms and of double bonds (separated by a colon) is acceptable, e.g. 16:0 for palmitic acid, 18:1 for oleic acid. Also, terms such as "(18:0)acyl" may be used to symbolize radicals of fatty acids. (See Appendix A).

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Comment. This system is already widely used. It should, however, be kept in mind that it sometimes does not completely specify the fatty acid. For example, α-linolenic acid and γ-linolenic acid are both 18:3 acids; the designation 18:3 is therefore ambiguous. In such a case, the position of double bonds should be indicated, e.g. 18:3(9 12,15) for (9,12,15)-linolenic acid, formerly known as α-linolenic acid.

Lip-1.16. It is sometimes desirable (for example, in discussing the biosynthesis of lipids) to indicate the position of each double bond with reference not to the carboxyl group (always C-1), but to the end of the chain remote from the carboxyl. If n is the number of carbon atoms in the chain (i.e., the locant of the terminal methyl group) and x is the (lower) locant of the double bond, the position of the double bond may be defined as (n minus x). Thus, the common position of the double bond in oleic and nervonic acids may be given as 18 − 9 and 24 − 9, respectively. This structural regularity should not be expressed as ω9.

Lip-1.17. The system described in Lip-1.15 may also be used to denote alcohols and aldehydes related to fatty acids, provided that the nature of the residue is clearly indicated either by the appropriate name of the compound(s) [e.g. (18:1)-alcohol] or in the heading of the table. The 1-ene of alk-1-en-1-yl (i.e., 1-alkenyl) compounds is not counted in this system (see Lip-2.10. comment).

Lip-1.18. For many complex lipids, a representation of the structures using symbols rather than structural formulae may be useful. Symbols proposed for various constituents are given in Appendix B (see also ref.[10]), and, for glycolipids, in Lip-3.13. They are constructed in analogy to those in use for amino acids[11], nucleosides[12] and saccharides[13].

II. PHOSPHOLIPIDS

A. Generic terms

The Rules of The Nomenclature of Organic Phosphorus Compounds (also known as D-Rules)[2] recognize, for biochemical usage, the prefix phospho- as an alternate to *O*-phosphono- (or *N*-phosphono). By a similar convention[10], -phospho- may be used as an infix to designate the phosphodiester bridge present in such compounds as glycerophosphocholine. The use of root names like "phosphatidic acid" is retained and extended (Lip-2.3 - 2.4).

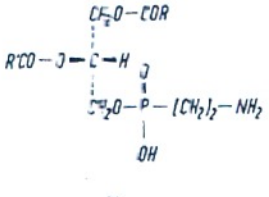
Lip-2.1. **Phospholipid** may be used for any lipid containing phosphoric acid as mono- or diester. Likewise, lipids containing *C*-phosphono groups (e.g. compound X) may be termed "phosphonolipids."

Lip-2.2. **Glycerophospholipid** signifies any derivative of glycerophosphoric acid that contains at least one *O*-acyl, or *O*-alkyl, or *O*-(1-alkenyl) group attached to the glycerol residue. Generic names for other classes of phospholipids may be coined according to this scheme, e.g., **sphingophospholipid, inositolphospholipid.**

Comment. The old terms, "phosphatide," "phosphoglyeride," and "phosphoinositide" are no longer recommended because they do not convey the intended meaning (see also Lip-1.2).

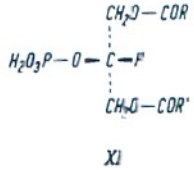
Lip-2.3. **Phosphatidic acid** signifies a derivative of a glycerol phosphate (glycerophosphate) in which both remaining hydroxyl groups of glycerol are esterified with fatty acids. The position of the phosphate group may be emphasized by stereospecific numbering.

Comment. For the most common (3-*sn*)-phosphatidic acid and its derivatives, the locants are often omitted. However, "phosphatidyl" without locants can lead to



X

A phosphonolipid



XI

2-Phosphatidic acid

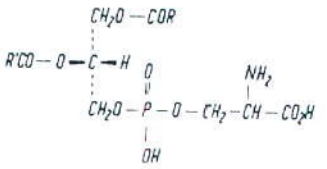
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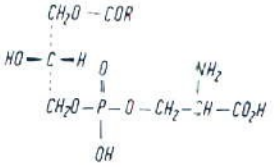
ambiguities. It is therefore preferable to use the proper locants, for example, 2-phosphatidic acid for compound XI, and 3-*sn*-phosphatidylserine for XII a.

Lip-2.4. The common glycerophospholipids are named as derivatives of phosphatidic acid, e.g. 3-*sn*-phosphatidylcholine (this term is preferred to the trivial name, lecithin; the systematic name is 1,2-diacyl-*sn*-glycero-3-phosphocholine); 3-*sn*-phosphatidylserine; 1-phosphatidylinositol (see comment ii below); 1,3-bis(3-*sn*-phosphatidyl)-glycerol.



XII a

Phosphatidylserine (3-*sn*-phosphatidylserine)



XII b

A 2-lysophospholipid

Comments

i) It is understood that, in combination with compounds like ethanolamine (properly, 2-aminoethanol) or serine, which bear both hydroxyl and amino groups, substitution by phosphorus is at the hydroxyl group of the ethanolamine or serine. Substitution at any other position, or where confusion may arise, requires a locant.

ii) The phosphorylated derivatives of 1-(3-*sn*-phosphatidyl)inositol should be called 1-phosphatidylinositol 4-phosphate and 1-phosphatidylinositol 3,4-bisphosphate, respectively. The use of "diphosphoinositide" and "triphosphoinositide" for these is discouraged, as these names do not convey the chemical structures of the compounds and can be misleading. (Cf. also Table IV in ref. [10]).

Lip-2.5. As an alternative, generic names may be coined according to Lip-1.13, i.e. using glycerol phosphate (glycerophosphate) as the stem. In this case, the stereospecific numbering of glycerol should be used to indicate the position of the phosphoric residue as well as the other substituents (acyl-, alkyl-, 1-alkenyl). If the nature of these substituents cannot be specified, the prefix "radyl" may be used.

Lip-2.6. Derivatives of phosphatidic acids resulting from hydrolytic removal of one of the two acyl groups may be designated by the old prefix **lyso** e.g. lysophosphatidylethanolamine for compound XII b. A locant may be added to designate the site of (hydro)lysis, 2-lyso designating hydrolysis at position 2, leaving a free hydroxyl group at this carbon atom.

Comment. The "lyso" terms originated from the fact that these compounds are hemolytic. It is here redefined to indicate a limited hydrolysis of the phosphatidyl derivative (i.e., "deacyl").

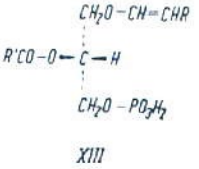
Lip-2.7. The term **plasmalogen** may be used as a generic term for glycerophospholipids in which the glycerol moiety bears an 1-alkenyl ether group.

Lip-2.8. The term **plasmenic acid** signifies a derivative of *sn*-glycero-3-phosphate in which carbon-1 bears an *O*-(1-alkenyl) residue, and position 2 is esterified with a fatty acid (XIII). This term can also be used to name derivatives, e.g. plasmenylethanolamine.

Comments

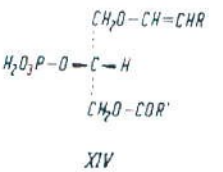
i) The use of "phosphatidyl" as a name for the acyl radical of phosphatidic acid has facilitated the nomenclature of its various compounds (see Lip-2.4). Therefore, it seems logical to offer a similar short term for XIII, i.e., "plasmenic acid," as an alternative to the more systematic name, 2-acyl-1-alkenyl-*sn*-glycerol 3-phosphate, which, of course, may be used if desired. "Plasmenic" is a contraction of "plasmalogenic", and may be especially useful in naming derivatives, e.g., plasmenylserine.

ii) Isomers like those bearing the phosphate residue in position 2 (e.g. compound XIV) should not be named in this way but as derivatives of the corresponding glycerophosphate, using stereospecific numbering.



XIII

A plasmenic acid

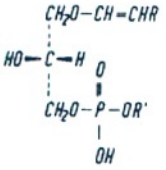


XIV

3-Acyl-1-(1-alkenyl)-*sn*-glycerol 2-phosphate

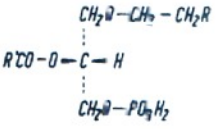
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Lip-2.9. The term **lysoplasmenic acid** may be used for a derivative of *sn*-glycero-3-phosphate that has an *O*-(1-alkenyl) residue on carbon-1, the hydroxyl group in position 2 being unsubstituted (XVa). This name may also be used in combinations like "lysoplasmenylethanolamine" (XVb).



XV

XVa: (R′ = H):
a lysoplasmenic acid
XVb: (R′ = $CH_2CH_2NH_2$)
a lysoplasmenylethanolamine



XVI

A plasmanic acid

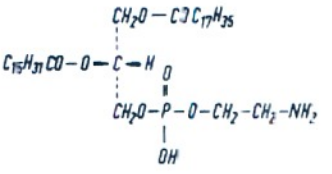
Lip-2.10. For compounds of type XVI, bearing a saturated ether group in position 1 and an acyl group in position 2 of *sn*-glycero-3-phosphate, the term **plasmanic acid** is proposed. Compounds deacylated in position 2, or with a substituent on the phosphoric residue, can be treated as are the plasmenic acids (Lip-2.9).

Comment. The proposed names will be especially useful for naming phosphoric diesters (phosphodiesters), such as e.g. plasmanylethanolamine, instead of 2-acyl-1-alkyl-*sn*-glycero-3-phosphoethanolamine. The terms "plasmanic acid" and "plasmanyl" may also be applied to ethers with an alkyl group bearing a double bond within the chain, e.g. a 9-hexadecenyl residue (derived from palmitoleic acid). In such cases, the proper term "alkenyl", if used without the ene locant(s), would be misleading. (See Lip-1.17).

B. Individual compounds

Lip-2.11. Individual glycerophospholipids in which the substituents can be specified are named according to existing Rules[2,3,5,6], using the infix -phospho-[2,10] to indicate the phosphodiester bridge.

Example. 2-Palmitoyl-1-stearoyl-*sn*-glycero-3-phosphoethanolamine for compound XVII.



XVII

2-Palmitoyl-1-stearoyl-*sn*-glycero-3-phosphoethanolamine

Lip-2.12. The ketone derived from glycerol, 1,3-dihydroxy-2-propanone, also known as dihydroxyacetone, may be termed "glycerone", if desired. The name is a contraction of "glycero-ketone", and may be useful to emphasize the relationship with glycerol, glyceraldehyde (glyceral), and glycerate. It also permits a simple symbolism (Appendix B) and the naming of derived lipids, e.g., 1-palmitoyl-3-phosphoglycerone.

III. GLYCOLIPIDS

A. General considerations

Glycolipids (a contraction of glycosyllipids) are generally named as glycosyl derivatives of the corresponding lipid, e.g., diacylgalactosylglycerol, glucosylceramide. Because of the heterogeneity of the fatty acids and long-chain bases encountered in most cases, a generic name for the lipid moiety is needed, i.e. ceramide. With higher glycosphingolipids, especially the gangliosides, naming problems arise from the complexity of the carbohydrate moiety of these compounds. The systematic names of the oligosaccharides linked to ceramide are so cumbersome that they are of the same practical value as, e.g., the systematic name for a peptide hormone such as insulin. It was felt that this difficulty could be overcome only by creating suitable trivial names for some

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parent oligosaccharides. In constructing these names (see Table I) the following principles were observed

1. The number of monosaccharide units in an oligosaccharide is indicated by the suffixes -biose, -triaose, -tetraose, etc. This follows the well-established practice in the carbohydrate field (cf. cellobiose, cellotetraose, maltotetraose, etc.), with the exception that the suffix -triose, as used in maltotriose, has been changed to *triaose* to avoid confusion with the monosaccharides called trioses.

2. The oligosaccharides are grouped in series according to their structure and biogenetic relationship.

3. Differences in linkage (e.g., 1 → 4 versus 1 → 3) in otherwise identical sequences are indicated by iso- or neo-, used as a prefix.

On the basis of these names, the semisystematic nomenclature for neutral glycosphingolipids and gangliosides described below is recommended. A set of symbols has been devised that allows a simple representation of complex neutral and acidic glycosphingolipids (Table I).

B. Generic terms

Lip-3.1. The term **glycolipid** designates any compound containing one or more monosaccharide residues linked by a glycosyl linkage to a lipid part (e.g., a mono- or diacylglycerol, a long-chain base (sphingoid) like sphingosine, or a ceramide).

Lip-3.2. The term **glycoglycerolipid** may be used to designate glycolipids containing one or more glycerol residues.

Lip-3.3. The term **glycosphingolipid**, as hitherto, includes all compounds containing at least one monosaccharide and a sphingoid. The glycosphingolipids can be subdivided as follows:
Neutral glycosphingolipids:
monoglycosyl- and oligoglycosylsphingoids;
monoglycosyl- and oligoglycosylceramides.
Acidic glycosphingolipids:
sialosylglycosylsphingolipids (gangliosides);
sulfoglycosylsphingolipids (formerly "sulfatides", which is not recommended) (*cf.* Lip-3.1.).

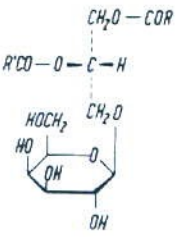
Lip-3.4. **Psychosine** may be used as a generic name for 1-monoglycosylsphingoids, although the latter is preferred. The nature of the monosaccharide and the sphingoid is not specified in this name.

Lip-3.5. The term **fucolipid** may be used to designate fucose-containing neutral or acid glycolipids.

C. Individual compounds*

Lip-3.6. Glycoglycerolipids may be named either as glycosyl compounds according to Rule Carb-24 or as glycosides according to Rule Carb-23[5].

Example: compound XVIII may be named either 1,2-diacyl-3-β-D-galactosyl-*sn*-glycerol or 1,2-diacyl-*sn*-glycerol 3-β-D-galactoside.



XVIII

Comment. The first form is preferred, as the glycosphingolipids are also named this way.

Lip-3.7. A glycosphingolipid is generally named as a **glycosylsphingoid** or a **glycosylceramide**, using the appropriate trivial name of the mono- or oligosaccharide residue for "glycosyl." It is understood that the sugar residue is attached to the C-1 hydroxyl group of the ceramide. For glycosphingolipids carrying two to four saccharide residues, the trivial names listed in Table I are recommended.

Comment. It is strongly recommended that the name of the oligosaccharide be defined in each publication by means of the standard symbols for sugars (as in Table I, column 1) rather than by the full name, which is often so long as to be confusing.

Lip-3.8. The trivial name **cerebroside** designates 1-β-glycosylceramide (the natures of the sphingoid and of the fatty acid are not specified in this name).

* "Individual" in this section refers to the carbohydrate moiety only.

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Lip-3.9. Glycosphingolipids carrying fucose either as a branch or at the end of an oligohexosylceramide are named as "fucosyl(*X*)osylceramide" where (*X*) stands for the root name of the oligosaccharide. The location of the fucosyl residue is indicated by a Roman numeral designating the position of the monosaccharide residue in the parent oligosaccharide (counting from the ceramide end) to which the fucose residue is attached, with an Arabic numeral superscript indicating the position within that residue to which the fucose is attached. If necessary, the anomeric symbol can be used as usual, i.e., preceding "fucosyl-."

Examples for Lip-3.7 and Lip-3.9 (structures given in the symbols of Lip-3.13):*
lactosylceramide for Gal(β1→4)GlcCer;
mucotriaosylceramide for Gal(β1→4)Gal(β1→4)GlcCer;
III^2-α-fucosylisoglobotriaosylceramide for Fuc(α1→2)-Gal(α1→3)Gal(β1→4)Glc(β1→1)Cer

Lip-3.10 **Sialoglycosphingolipids** (synonym: **gangliosides**) are glycosphingolipids carrying one or more sialic residues. **Sialic acid** is the generic term for *N*-acetyl- or *N*-glycoloylneuraminic acids (cf. Section 3 in ref.[11]). Gangliosides are named as *N*-acetyl- (or *N*-glycoloyl-) neuraminosyl-(*X*)-osylceramide, where (*X*) stands for the root name of the neutral oligosaccharide to which the sialosyl residue is attached (cf. Table I). The position of the sialosyl residue is indicated in the same way as in the case of fucolipids (see Lip-3.9), e.g. II^3-*N*-acetylneuraminosyllactosylceramide for AcNeu(α2→3)Gal(β1→4)Glc(β1→1)Cer.

Lip-3.11. Glycosphingolipids carrying a sulfuric ester (sulfate) group, formerly called sulfatides, are preferably named as sulfates of the parent neutral glycosphingolipid. The location of the sulfate group may be indicated as in Lip-3.9.

Example: lactosylceramide II^3-sulfate

Lip-3.12. Phosphoglycosphingolipids with phosphodiester structures are named according to the recommendation for the phospholipids (see Section II).

* D is omitted by convention in the abbreviated formulas, but D (or L) may be inserted when desirable. Hyphens may replace left-to-right arrows (see Section 3.4 of ref.[13]).

D. Symbols and abbreviations

Lip-3.13. Simple or complex glycosphingolipids can be represented according to existing rules, using the symbols Cer, Sph, AcNeu, etc. (Appendix B), together with the recommended[13] symbols for the hexoses (Glc, Gal, etc.).

Examples are given above, and in Table I and Appendix C.

However, due to the complexity of the higher glycosphingolipids, this often results in very long and cumbersome series that are not easy to comprehend. *It is therefore recommended* that the oligosaccharides listed in Table I be represented by specific symbols in which the number of monosaccharide units (-oses) is indicated by Ose$_n$, preceded by two letters representing the trivial name of the oligosaccharide (column 3). For a short form, which may be required in the case of limited space or frequent repetition, Ose can be omitted (column 4); however, the long form is preferred as being more evocative.

Examples:
(i) McOse$_3$Cer for mucotriaosylceramide, Gal(β1-4)Gal(β1-4)Glc(1-1)Cer;
(ii) II^{3}AcNeu-GgOse$_4$Cer for II^3-*N*-acetylneuraminosylgangliotetraosylceramide, Galβ1→3GalNAcβ1→4Gal-(3←2αNeuAc)β1→4Glcβ1→1Cer (see Lip-3.14 for this mode of representing a branched chain).

Abbreviations for the more important gangliosides are given in Appendix C.

Lip-3.14. When it is desirable to represent a branched oligosaccharide on a single line, as in running text or a table, the parentheses surrounding the locants in the main chain may be omitted and used instead to enclose the symbols for the branched portion(s) of the molecule. The branches follow, in parentheses and with appropriate arrows, the residues to which they are attached.

Examples:
(i) NeuGcα2→3Galβ1→3GalNAcβ1→4Gal(3←2αNeuGc)-β1→4Glcβ1→1Cer;
(ii) NeuAcα2→3Galβ1→3GalNAcβ1→4Gal(3←2αNeuAc-8←2αNeuAc)β1→4Glcβ1→1Cer;
(iii) GalNAcα1→3Gal(2←1αFuc)β1→4GlcNAc(3←1αFuc)-β1→3Galβ1→4Glcβ1→1Cer ≡ III^{3}IV^2-α,α-Difucosyl-IV^3-α-2-acetamido-2-deoxygalactosylneolactotetraosylceramide ≡ III^{3}IV^2(Fucα)$_2$,IV^{3}GalNAcα-nLcOse$_4$Cer.

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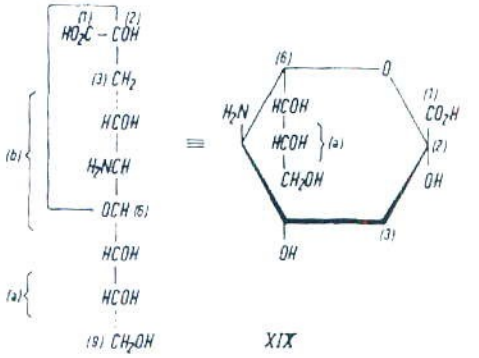
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IV. NEURAMINIC ACID

Lip-4.1. The compound 5-amino-3,5-dideoxy-D-*glycero*-D-*galacto*-nonulosonic acid is **neuraminic acid** (XIX), with the symbol Neu[11].

Lip-4.2 The term "sialic acid" signifies the *N*-acylneuraminic acids and their esters and other derivatives of the alcoholic hydroxy groups.

Lip-4.3. The radicals resulting from the removal of a hydroxyl group of neuraminic acid or sialic acid are designated as **neuraminoyl** or **sialoyl**, respectively, if the hydroxyl is removed from the carboxyl group, and as **neuraminosyl** and **sialosyl**, respectively, if the hydroxyl group is removed from the anomeric carbon atom of the cyclic structure



XIX

Neuraminic acid
5-Amino-3,5-dideoxy-D-*glycero*-D-*galacto*-nonulopyranosonic acid
(a) (b)

Table I. Names and abbreviations of simple glycolipids and of their oligosaccharides.

Glycolipid structure[a]	*Oligosaccharide*		
	Trivial name[b]	*Symbol*[c]	*Short symbol*[d]
Gal(α1-4)Gal(β1-4)GlcCer	Globotriaose	$GbOse_3$	Gb_3
GalNAc(β1-3)Gal(α1-4)Gal(β1-4)GlcCer	Globotetraose	$GbOse_4$	Gb_4
Gal(α1-3)Gal(β1-4)GlcCer	Isoglobotriaose	$iGbOse_3$	iGb_3
GalNAc(β1-3)Gal(α1-3)Gal(β1-4)GlcCer	Isoglobotetraose	$iGbOse_4$	iGb_4
Gal(β1-4)Gal(β1-4)GlcCer	Mucotriaose	$McOse_3$	Mc_3
Gal(β1-3)Gal(β1-4)Gal(β1-4)GlcCer	Mucotetraose	$McOse_4$	Mc_4
GlcNAc(β1-3)Gal(β1-4)GlcCer	Lactotriaose	$LcOse_3$	Lc_3
Gal(β1-3)GlcNAc(β1-3)Gal(β1-4)GlcCer	Lactotetraose	$LcOse_4$	Lc_4
Gal(β1-4)GlcNAc(β1-3)Gal(β1-4)GlcCer	Neolactotetraose	$nLcOse_4$	nLc
GalNAc(β1-4)Gal(β1-4)GlcCer	Gangliotriaose	$GgOse_3$	Gg_3
Gal(β1-3)GalNAc(β1-4)Gal(β1-4)GlcCer	Gangliotetraose	$GgOse_4$	Gg_4
Gal(α1-4)GalCer	Galabiose	$GaOse_2$	Ga_2
Gal(1-4)Gal(α1-4)GalCer	Galatriaose	$GaOse_3$	Ga_3
GalNAc(1-3)Gal(1-4)Gal(α1-4)GalCer	*N*-Acetylgalactosaminylgalatriaose	$GalNAc1\text{-}3GaOse_3$	—

[a] Symbols and arrangement are discussed in Lip-3.13. Hyphens replace left-to-right arrows (see Section 3.4 of ref.[13]).
[b] Name of glycolipid is formed by converting ending -ose to -osyl, followed by -ceramide, without space; e.g., globotriaosylceramide.
[c] Should be followed by Cer for the glycolipid, without space; e.g., $McOse_3Cer$, Mc_4Cer (see Lip-3.13).
[d] The short form should be used only in situations of limited space or in case of frequent repetition.

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APPENDIX A.

Names of and symbols for higher fatty acids.

Numerical symbol	*Structure* $H_3C\text{-}[R]\text{-}CO_2H$	*Stems of*		*"Name" symbol*
		Systematic names[a]	*Trivial names*[b]	
1. 10:0	$-[CH_2]_8-$	Decano-	Capr-[c]	Dec
2. 12:0	$-[CH_2]_{10}-$	Dodecano-	Laur-	Lau
3. 14:0	$-[CH_2]_{12}-$	Tetradecano-	Myrist-	Myr
4. 16:0	$-[CH_2]_{14}-$	Hexadecano-	Palmit-	Pam
5. 16:1	$-[CH_2]_5CH{=}CH[CH_2]_7-$	9-Hexadeceno-	Palmitole-	ΔPam
6. 18:0	$-[CH_2]_{16}-$	Octadecano-	Stear-	Ste
7. 18:1(9)	$-[CH_2]_7CH{=}CH[CH_2]_7-$	*cis*-9-Octadeceno-	Ole-	Ole
8. 18:1(11)	$-[CH_2]_5CH{=}CH[CH_2]_9-$	11-Octadeceno-	Vaccen-	Vac
9. 18:2(9,12)	$-[CH_2]_3[CH_2CH{=}CH]_2[CH_2]_7-$	*cis,cis*-9,12-Octadecadieno-	Linole-	Lin
10. 18:3(9,12,15)	$-[CH_2CH{=}CH]_3[CH_2]_7-$	9,12,15-Octadecatrieno-	(9,12,15)-Linolen-	αLnn
11. 18:3(6,9,12)	$-[CH_2]_3[CH_2CH{=}CH]_3[CH_2]_4-$	6,9,12-Octadecatrieno-	(6,9,12)-Linolen-	γLnn
12. 18:3(9,11,13)	$-[CH_2]_3[CH{=}CH]_3[CH_2]_7-$	9,11,13-Octadecatrieno-	Eleostear-	eSte
13. 20:0	$-[CH_2]_{18}-$	Icosano-[d]	Arachid-	Ach
14. 20:2(8,11)	$-[CH_2]_6[CH_2CH{=}CH]_2[CH_2]_6-$	8,11-Icosadieno-[d]		Δ_2Ach
15. 20:3(5,8,11)	$-[CH_2]_6[CH_2CH{=}CH]_3[CH_2]_3-$	5,8,11-Icosatrieno-[d]		Δ_3Ach
16. 20:4(5,8,11,14)	$-[CH_2]_3[CH_2CH{=}CH]_4[CH_2]_3-$	5,8,11,14-Icosatetraeno-[d]	Arachidon-	Δ_4Ach
17. 22:0	$-[CH_2]_{20}-$	Docosano-	Behen-	Beh
18. 24:0	$-[CH_2]_{22}-$	Tetracosano-	Lignocer-	Lig
19. 24:1	$-[CH_2]_7CH{=}CH[CH_2]_{13}-$	*cis*-15-Tetracoseno-	Nervon-	Ner
20. 26:0	$-[CH_2]_{24}-$	Hexacosano-	Cerot-	Crt
21. 28:0	$-[CH_2]_{26}-$	Octacosano-	Montan-	Mon

[a] Ending in -ic acid, -ate, -yl, for acid, salt or ester, acyl radical, respectively.
[b] Ending in -ic acid, -ate, -oyl for acid, salt or ester, or acyl radical, respectively.
[c] Not recommended because of confusion with caproic (hexanoic) and caprylic (octanoic) acids. Decanoic is preferred.
[d] Formerly "eicosa-" (changed by IUPAC Commission on Nomenclature of Organic Chemistry, 1975.)

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APPENDIX B.

Symbols recommended for various constituents of lipids.

Name	*Symbol*[a]
For alkyl radicals[b] Methyl, Ethyl, . . . Dodecyl	R Me, Et, Pr, Bu, Pe, Hx, Hp, Oc, Nn, Dec, Und, Dod
For aliphatic carboxylic acids[b] Formyl, Acetyl, Glycoloyl, Propionyl, Butyryl, Valeryl, Hexanoyl, Heptanoyl, Octanoyl Nonanoyl, Decanoyl, Undecanoyl, Lauroyl, Myristoyl, Palmitoyl, Stearoyl, Eicostearoyl, Linoleoyl, Arachidonoyl	acyl (not abbreviated), RCO- Fo (or HCO), Ac, Gc, Pp, Bt, Vl, Hxo, Hpo, Oco, Nno, Dco, Udo, Lau, Myr, Pam, Ste, eSte, Lin, Δ_4Ach
For glycerol and its oxidation products[c] Glycerol, Glyceraldehyde, Glycerone, Glyceric acid	Gro, Gra, Grn, Gri
For "glycosyl" Glucose, Galactose, Fucose, . . . Gluconic acid, Glucuronic acid Glucosamine[f], *N*-Acetylglucosamine Neuraminic, Sialic, Muramic acids *N*-Acetylneuraminic acid, *N*-Glycoloylneuraminic acid Deoxy	Ose Glc[d], Gal, Fuc, . . . GlcA, GlcU[e] GlcN, GlcNAc Neu, Sia, Mur NeuAc or AcNeu[g], NeuGc or GcNeu d
Miscellaneous Ceramide, Choline, Ethanolamine, Inositol, Serine, Phosphatidyl, Sphingosine, Sphingoid, Phosphoric residue	Cer, Cho, Etn[h], Ins, Ser, Ptd, Sph, Spd, *P*

[a] These symbols are constructed in analogy to those already in use for amino acids and saccharides[11,13]; they may assist the abbreviated representation of more complex lipids in a way similar to the peptides and polysaccharides. Prefixes such as iso, tert, cyclo are specified in the symbols by lower-case superscripts (Pr^i, Bu^t, Hx^c) or lower-case prefixes (iPr, tBu, cHx), unsaturation by e.g., Δ^3 for a 3,4 double bond, $\blacktriangle^3$ for a 3,4 triple bond (cf. Proteins, Vol. I, pp. 96 - 108, in *Handbook of Biochemistry*, 3rd edition, G. Fasman, ed., CRC Press, Cleveland, Ohio, 1976). Many of these symbols are drawn from previously published recommendations (refs.[11,12]). See also Appendix A.

[b] Systematic and recommended trivial names of unbranched, acyclic compounds only (cf. Appendix A). Other forms are created by prefixes (e.g., iso, tert, cyclo). See also Appendix A.

[c] These symbols form a self-consistent series for a group of closely related compounds. It is recognized that other abbreviations (but no symbols) are currently in use. (See Lip-2.12.).

[d] Not Glu (glutamic acid) or C (nonspecific).

[e] Recommended in place of GlcUA, the "A" being unnecessary.

[f] Approved trivial name for 2-amino-2-deoxyglucose; similarly for galactose (GalNAc), etc.

[g] AcNeu was recommended earlier (ref.[11]). When it is necessary to differentiate between *N*-acetyl and *O*-acetyl derivatives, Neu*N*Ac and Neu*O*Ac (italicized locants, in contradistinction to GalNAc, etc.) may be employed.

[h] May take the form OEtN< if substitution on the nitrogen atom is to be indicated.

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APPENDIX C.

Abbreviated representation of gangliosides.

Designation according to			
	Lipid document[a]	*Wiegandt*[b]	*Svennerholm*[c]
1.	I^3NeuAc-GalCer	G_{Gal} 1 NeuAc	–
2.	II^3NeuAc-LacCer	G_{Lac} 1 NeuAc	G_{M3}
3.	II^3NeuGc-LacCer	G_{Lac} 1 NeuNGl	–
4.	$II^3(NeuAc)_2$-LacCer	G_{Lac} 2 NeuAc	G_{D3}
5.	II^3NeuAc/NeuGc-LacCer	G_{Lac} 2 NeuAc/NeuNgl	–
6.	II^3NeuGc-LacCer	G_{Lac} 2 NeuNGl	–
7.	II^3NeuAc-GgOse$_3$Cer	G_{Gtri} 1 NeuAc	G_{M2}
8.	II^3NeuAc-GgOse$_4$Cer	G_{Gtet} 1 NeuAc	G_{M1}
9.	IV^3NeuAc-nLcOse$_4$Cer	G_{Lntet} 1a NeuAc	G_{M1}-GlcNAc
10.	IV^6NeuAc-nLcOse$_4$Cer	G_{Lntet} 1b NeuAc	–
11.	IV^2Fuc,II^3NeuAc-GgOse$_4$Cer	G_{Gfpt} 1 NeuAc	–
12.	IV^3NeuAc-nLcOse$_4$Cer	–	–
13.	$II^3(NeuAc)_2$-GgOse$_4$Cer	G_{Gtet} 2b NeuAc	G_{D1b}
14.	IV^3NeuAc,II^3NeuAc-GgOse$_4$Cer	G_{Gtet} 2a NeuAc	G_{D1a}
15.	$II^3(NeuAc)_3$-GgOse$_4$Cer	G_{Gtet} 3b NeuAc	–
16.	IV^3NeuAc,$II^3(NeuAc)_2$-GgOse$_4$Cer	G_{Gtet} 3a NeuAc	–
17.	IV^3NeuAc,$II^3(NeuAc)_3$-GgOse$_4$Cer	G_{Gtet} 4b NeuAc	–
18.	$IV^3(NeuAc)_2$,$II^3(NeuAc)_3$-GgOse$_4$Cer	G_{Gtet} 5 NeuAc	–
19.	IV^3NeuAc,II^3NeuAc-GgOse$_5$Cer	G_{Gpt} 2a NeuAc	–

[a] To indicate linkage points and anomeric form: Fuc should be written (←1αFuc); NeuAc should be written (←2αNeuAc); $(NeuAc)_2$ should be written $(\leftarrow 2\alpha NeuAc8)_2$; etc. If these features are assumed or defined, the short form used in this column is more convenient for use in texts and tables.

[b] The subscripts to G (for ganglioside), from 7 on, have the meanings: Gtri = gangliotriose, Gtet = gangliotetraose, Litet = lactoisotetraose, Gpt = gangliopentaose [= GalNAc(β1→4)Gal(β1→3)GalNAc(β1→4)Gal(β1→4)GlcCer], Gfpt = gangliofucopentaose[14].

[c] G = ganglioside, M = monosialo, D = disialo, T = trisialo. Arabic numerals indicate sequence of migration in thin-layer chromatograms[15].

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Dietary Fat and Health: The Evidence and the Politics of Prevention

Careful Use of Dietary Fats Can Improve Life and Prevent Disease

WILLIAM E.M. LANDS

ABSTRACT: **Every year, more young people start the slow progressive injury that eventually becomes cardiovascular disease and death. It could be prevented with nutrition education, but medical efforts focus more on treatments for older people than on preventing primary causes of disease in young people. Two avoidable risks are prevented by simple dietary interventions: (1) Eat more omega-3 and less omega-6 fats, so tissues have less intense n-6 eicosanoid action, and (2) eat less food per meal to lower vascular postprandial oxidant stress. An empirical diet–tissue relationship was developed and put into an interactive personalized software program to aid informed food choices.**

KEYWORDS: **essential fatty acids; omega-3; omega-6; polyunsaturated fatty acids (PUFAs); highly unsaturated fatty acids (HUFAs); eicosanoids; thrombosis; inflammation; atherosclerosis; prenylated proteins; platelet activating factor (PAF); oxidized LDL**

Much of this chapter echoes talks given 10, 20 and 30 years ago,[1–3] presenting information which failed to percolate effectively into clinical practice or preventive nutrition. As a result, I continue trying to find different methods of effective education so that chronic diseases may be prevented in the elderly. Recent efforts involve two distance-learning web sites with useful "homework" for everyone who wants to learn. One site, for education about essential fatty acids[a] has many details to help people understand the effects of nutritionally essential fatty acids. The other[b] has been hosted by the Office of Dietary Supplements for almost four years, and was upgraded recently with additional background information on how diet affects eicosanoids and how eicosanoids affect health and life.

[a]http://efaeducation.nih.gov/
[b]http://ods.od.nih.gov/eicosanoids/

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The death rate from heart attacks in the United States is among some of the worst in the world.[4] FIGURE 1 demonstrates that death, not life, begins at 40. That is the age at which people begin to lose colleagues and become aware of death. Students feel invulnerable, because not many 30-year-olds die. However, among my peers in their 70s, 1 or 2 per 100 are likely to die of ischemic heart disease in any year.[1] Clinicians say that arterial damage and calcium deposition is just a matter of aging, and that nothing can be done about that. I don't believe that a bit. In Japan, age-specific death rates for coronary heart disease are much lower.[5] However, an apparent inevitability about this is rooted in American lifestyles, all the way back to childhood.

FIGURE 1, presented in 1993,[1] has results added from the PDAY (Pathological Determinants of Atherosclerosis in Youth) study,[6-8] which documented this problem definitively. The problem became apparent 50 years ago, when young soldiers were being killed in Korea. Autopsies showed coronary artery damage in 20-year-old Americans, but not in native Koreans.[9]

Results from the PDAY study[6-8] show that effective primary prevention of atherosclerosis needs to begin with adolescents. FIGURE 1 suggests that by the time American men are 55 years old, most already have inflammatory

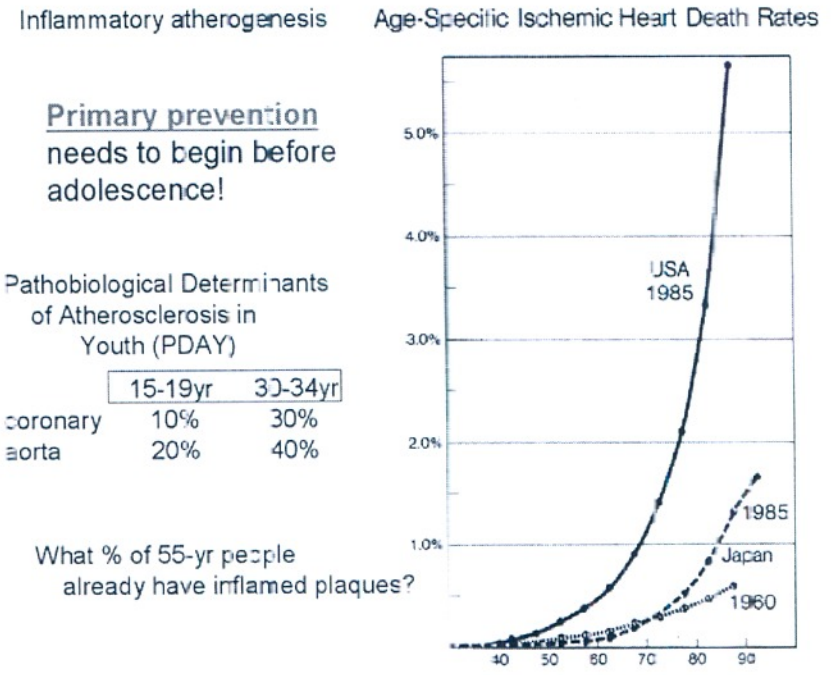


FIGURE 1. Inflammatory atherosclerosis begins developing before adolescence. (Presented in 1993;[1] results added from the PDAY study.[6-8]

plaques in their arteries. Intervention then is really secondary prevention.[10] The effective new technique of electron beam computerized tomography is maturing into a wonderful diagnostic tool.[11] Unfortunately, knowing that you have a lot of calcium in your arteries doesn't tell you how to get rid of it or how to prevent it from accumulating further. We still have a lot of biochemical work to perform.

Real primary prevention doesn't fit programs or goals of pharmaceutical companies, because they cannot make money by preventing the diseases they treat.[10] They work with treatment-oriented groups who aren't interested in educating people about specific dietary interventions that prevent causes of risk. One avoidable risk, an imbalance between intake and expenditure of energy, has received a lot of attention in the last two years. There is a need for further discussion about how it affects vascular inflammation and oxidant stress.

One solution is to eat foods that provide less energy per meal, as noted later in this chapter (FIG. 3). A second avoidable risk is the current severe imbalance between omega-3 and omega-6 nutrients. Most people are completely oblivious to it, but that imbalance is easily corrected by adjusting dietary intakes to more omega-3 and less omega-6 fats. The current imbalance in America is just a happenstance of food marketing.[12] Unfortunately, priorities of corporate health groups will favor the status quo over any action that prevents disease and suffering without adding to corporate profits.[10, 12]

FIGURE 2 shows the consequence of this imbalance. The horizontal axis shows that apparently healthy normal people around the world have different balances of omega 6 and omega 3 in their HUFAs (highly unsaturated fatty acids) because of the different foods they eat.[13,14] The HUFAs are pivotal in the body's healthy self-healing actions. Epidemiology shows that when HUFAs in the body are 70 or 80% omega 6, coronary heart disease rates are around 200 per 100,000.[4] In contrast, people in Spain or Italy have HUFAs containing about 60% omega 6 and 40% omega 3,[10] and their CHD mortality rate is around 120 per 100,000. In Japan, the traditional proportions of HUFAs are about 35–40% omega 6 and 60–65% omega 3, and the heart attack rate in Japan is about one-fourth to one-fifth that in the United States.[5] In Greenland, coronary heart disease is almost undetectable.

Many investigators do not like transnational epidemiology, claiming that genetic diversity impairs interpretation. However, genetic diversity within the United States is probably greater than the mean genetic difference between the United States and Japan. Now we have data from three groups in Quebec, within the same province of the same country on the same continent with the USA. There are urban Quebecois who eat foods that generate HUFA proportions similar to those of people in Chicago and Detroit and New York.[15] On the other hand, in villages north of Quebec City, there are Quebec Cree Indians with different ethnic food habits that give them a different HUFA pattern and mortality rate.[16] Further north in Quebec, Inuits have a lower average n-6

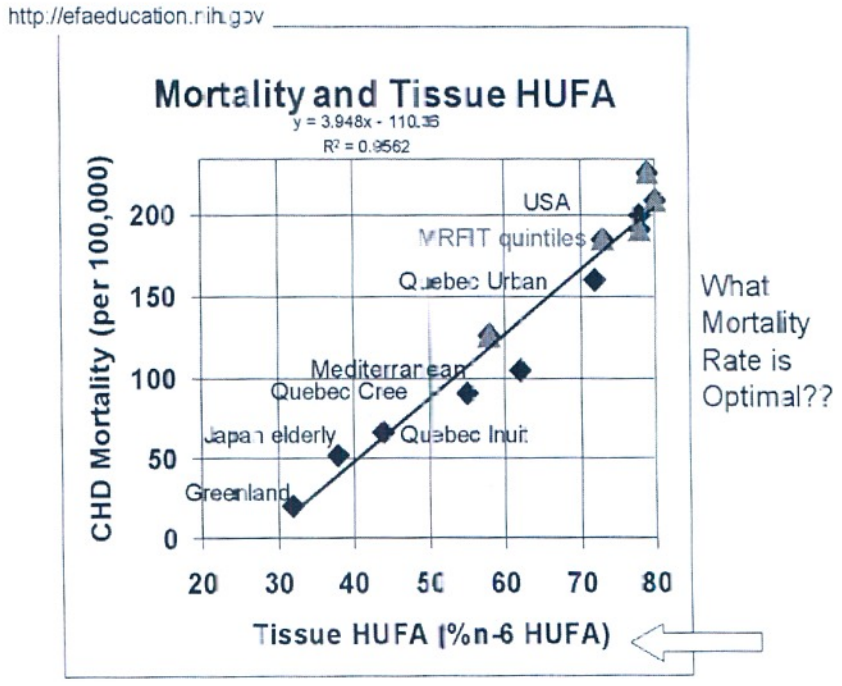


FIGURE 2. Coronary heart disease mortality is proportional to n-6 HUFA in plasma HUFA. Available at <http://efaeducation.nih.gov/sig/personal.html> .

HUFA composition and a lower mortality rate.[17] The trend is clear, even though the Inuit diet has changed tremendously during the last 40 years and is now far more heterogeneous. Indeed dietary heterogeneity worldwide is the important variable for preventive intervention, more so than genetic variability. Environmental food variability is driving variability in CHD mortality.

Essential fatty acids are polyunsaturated fatty acids (PUFAs) required by all mammals. Like vitamins, these are not produced within the body and must come from the diet. They are of two types, n-3 and n-6. Linoleic is a n-6 PUFA (18:2n-6) and alpha-linolenic is the n-3 PUFA (18:3n-3). When we eat those acids, our body converts them into longer chain-length, highly unsaturated fatty acids (HUFAs).[c]

What people eat in their diet determines the proportions of HUFAs in their tissue membrane phospholipids. In my first 15 years of academic life, I worked on lipid metabolism[18] and was highly cited on that topic. In 1964, when researchers in Stockholm reported that the n-6 HUFA, arachidonic

[c]http://efaeducation.nih.gov/sig/overviews.html

acid, was converted to the potent hormone, prostaglandin,[19] I hypothesized that HUFA for these hormones comes from the 2 position of the phospholipids in human tissues. But is HUFA converted to eicosanoids on the phospholipids and stored, or is it first hydrolyzed before the free hormone is synthesized? Collaborating with the researchers in Stockholm, I found that the HUFAs in phospholipids were hydrolyzed and then converted to eicosanoids. The hormone then acts at a receptor and generates a signal, which is usually a transient, reversible event that returns to basal state.[20,21]

By the late 1960s, we knew that omega-6 eicosanoids and omega-3 eicosanoids were involved in inflammatory processes. Later, I studied the mechanism by which fatty acid oxygenases act. This requires lipid hydroperoxide activators.[20] Eliminating the peroxides eliminates the ability to make a prostaglandin. Peroxides are also required to activate ribonucleotide reductase, and the free radical is essential to make deoxyribonucleotides for new DNA. The eicosanoids, and the peroxide tone that regulates them, are usually under tight control.[22]

For 15 years I studied aspirin-like non-steroidal anti-inflammatory drugs (NSAIDs),[23,24] working with drug companies to develop new patented drugs for treatment. During the 70s, dozens of eicosanoids were isolated.[21] Nearly all healthy human tissues use eicosanoid modulations of physiologic responses in a rapid transient manner.[20] However, uncontrolled excessive production of omega-6 eicosanoids over prolonged periods of time is associated with heart attacks, thrombotic stroke, arrhythmia, arthritis, asthma, headaches, dysmenorrhea (menstrual cramps), inflammation, tumor metastases and osteoporosis.[21,25] We had been looking at essential vitamin-like fatty acids as "angels" but in excessive amounts they turn into devils. When the body goes out of control, something must be done, and it became my goal to prevent this loss of control.

Two brief narrated presentations covering these general issues are available on the Internet.[d] The distance-learning site for the Office of Dietary Supplements has a section on dietary reference intakes[e] with a graph and citations.[f] These show that most people are eating on the order of 20 times more of the essential vitamin-like n-6 linoleic acid than they need. As with vitamin A and vitamin D, from which the body makes potent hormone-like compounds, there is a probable risk in excessive intakes. The website notes evidence for requiring these substances in amounts on the order of 0.5% of calories or less, but a day's menu in the United States far exceeds that.

To design an effective prevention strategy, one needs to identify causal mechanisms by asking how people die. From this point of view, the role of cholesterol[26, 27] has been portrayed in a misleading fashion for 25 years. Al-

[d]http://efaeducation.nih.gov/sig/beginners.html
[e]http://efaeducation.nih.gov/sig/dietary2.html
[f]http://efaeducation.nih.gov/sig/dri.html

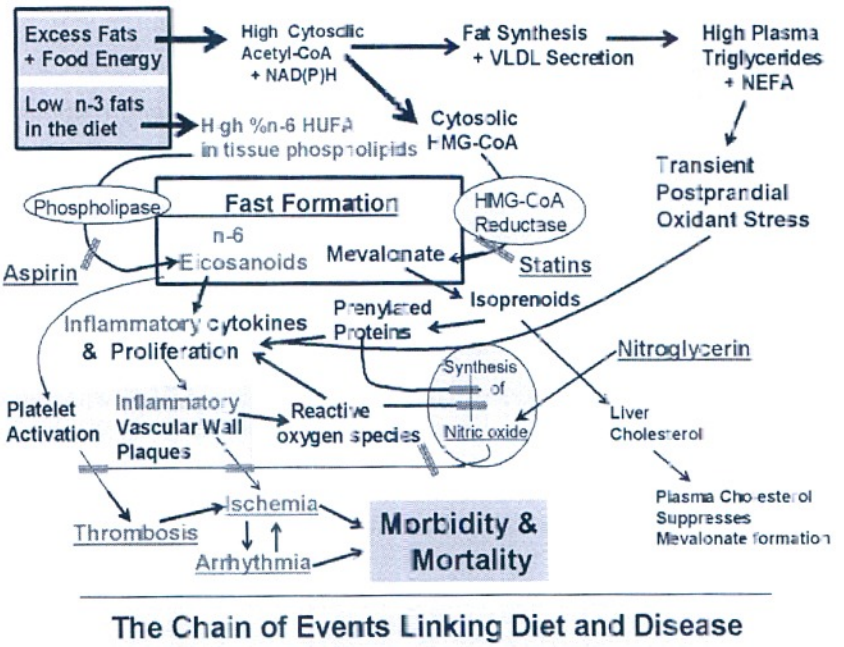


FIGURE 3. Two primary imbalances link diets to disease and death. Modified from an earlier figure[1] at <http://efaeducation.nih.gov/sig/dietdisease.html>.

though some lipoproteins may increase death, cholesterol itself was never proven to kill anyone. However, those who market anti-cholesterol drugs will never mention that fact. To consider primary prevention of heart attacks, we worked backward with the diet–disease concepts shown in FIGURE 3, by stating that a death from heart attack is a death from ischemia, which is exacerbated by arrhythmia, and from thrombosis, which was brought on by a predisposition to inflammatory plaques in the arteries. All three of these processes are exacerbated by n-6 eicosanoids (FIGURE 3). The release of inflammatory cytokines and cell proliferation are enhanced by omega-6 eicosanoids formed from dietary fats.

Inflammatory vascular wall plaques cause ischemia and stimulate thrombosis. Thrombosis is driven by thromboxane, one of the major eicosanoids discovered 29 years ago.[28] Thromboxane causes platelets to clump, causes calcium movement, and causes thrombosis. The omega-6 derivative (TX_{A2}) has the same effect; the omega 3 (TX_{A3}) also has that effect, but to a limited degree.

Aspirin, statins, and nitroglycerin are used widely to diminish the processes set in motion by the two nutritional imbalances shown in the upper left of FIGURE 3. In 1979, when I lectured[2] about these issues in Switzerland and the

Netherlands, the socialized medicine systems in those countries were paying for expensive coronary bypass surgery, and governments were considering preventive nutrition as an economic measure. However, proponents of medications and surgery were not interested in what they regarded as nutritional behavior modification. I scorned the clinicians' disinterest in nutrition at the time, but now I see they may be right. Often it is easier to persuade people to have surgery than to persuade them to change their ideas about what to eat.

What can we do to change people's behavior? Our responsibility is to inform people properly, and their responsibility is to learn what we are trying to teach. The two dietary interventions that people need to learn are shown in the upper left-hand corner of FIGURE 3. Eat more omega-3 and less omega-6 fats to have less-intense n-6 eicosanoid actions. Also, eat less high-energy food per meal to cut transient postprandial oxidant stress three times a day, a thousand times a year. Even when it's 99.9% reversible, the remaining one-tenth of a percent creates another irreversible inflammatory locus every year. By the time people are in their 70s, and the postprandial stress has excess n-6 HUFA and pro-inflammatory eicosanoids, then their condition is seen to move downward in FIGURE 3 and upward in FIGURE 1.

Low-density lipoprotein (LDL) and its phospholipids have some effect on events in FIGURE 3. When inflammatory sites oxidize those phospholipids, they create a platelet activating factor (PAF) agonist that binds the PAF receptor, causing calcium influx plus a stronger inflammatory response. That process has been understood, published, and well accepted for a decade. PAF and PAF mimics are potent calcium ionophores and inflammatory agents in mammalian tissue.[10] Electron beam computerized tomography, described in this volume by Dr. Harvey Hecht,[11] gives a good measure of atherosclerosis by measuring calcium accumulation. We need to learn more about what causes calcium to accumulate and how to prevent it and reverse the effect. Like LDL, high-density lipoprotein (HDL) is an aggregation of proteins, some of which are anti-inflammatory enzymes that destroy PAF and the oxidized phospholipid, preventing them from causing calcium entry and inflammation.[10]

Membrane phospholipids are limited in abundance, and the HUFAs compete for the limited space. If you eat a lot of n-6 fat, it displaces n-3 HUFAs and enhances n-6 eicosanoid formation (FIG. 3). If you eat a lot of n-3 fat, it displaces n-6 HUFAs. The enzymes are promiscuous and don't discriminate much between n-3 and n-6 HUFAs, which means that what you eat can change your body tissue.[13,14]

In the mid-80s, after a Nobel Prize had been awarded for discovery of eicosanoids and their physiology and I had done years of research on lipid metabolism and on NSAID mechanisms, it was well-know that n-6 thromboxane caused heart attacks and n-6 prostaglandins caused inflammation.[25] Pfizer gave me a grant to study the relationship between dietary n-6 and n-3 fats and the proportions of n-6 HUFA in body tissues. I developed and published an empirical predictive equation.[13,29]

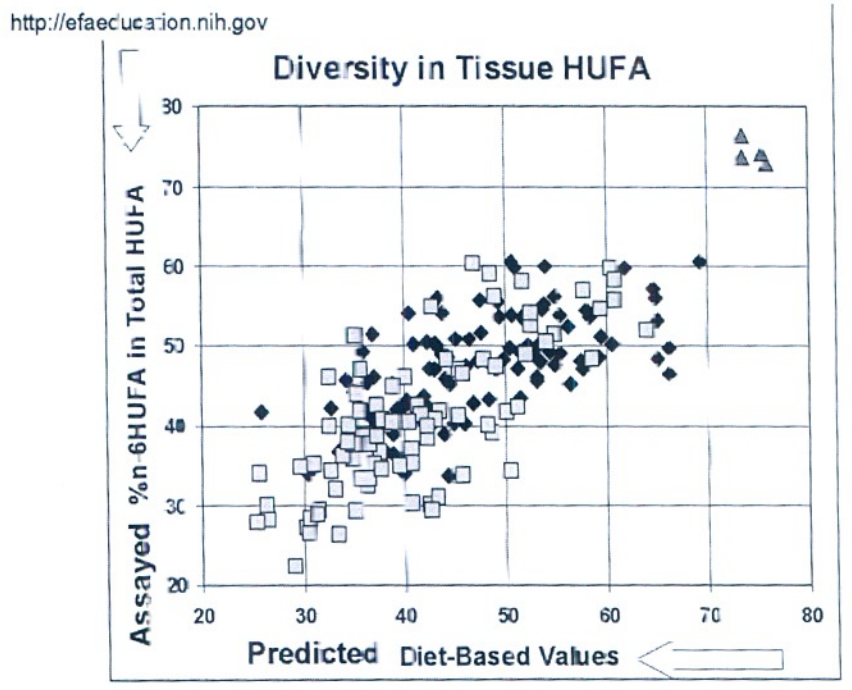


FIGURE 4. Predicted proportions of HUFA fit observed proportions. Previously presented[5] in 2003.

Sadly, I don't think many people read those papers, and I don't think anyone used the equation.[g] I then put it into a spreadsheet so people are not required to do any algebra. They can simply put numbers into a table and let the spreadsheet calculate the likely outcome.[h] FIGURE 4 shows that the equation predicts outcome with a correlation coefficient greater than 0.95. Dietitians carefully monitored the food that people ate, and that information inserted into the equation predicted values of the percentage of n-6 HUFAs in the total HUFA value. There is a good fit between predicted HUFA proportions and those observed by gas chromatographic analysis.[5]

The vertical scatter may be due to proteomics and genomics, whereas horizontal scatter is likely due to imprecise interviews. The group of people represented in the upper right hand in FIGURE 4 were 35-year-old Chicago women. The diamonds represent a group of 45-year-old dietitians in the cities of Japan, and the squares show 55-year-old rural Japanese men. They are all healthy people eating what they choose. The mean value for all people in ei-

[g]http://efaeducation.nih.gov/sig/hufacalc.html
[h]http://efaeducation.nih.gov/sig/dietbalance.html

ther FIGURE 4 or FIGURE 1 would not reveal much about any individual value or the risk of any individual in the group. Those who ate more dietary n-6 as linoleic acid (of which Americans eat a lot) acquired predictably higher proportions of n-6 HUFAs.[13,30]

I used the Pfizer grant to develop a diet–tissue relationship because people doing clinical interventions were making ineffective changes in the diet, too little and too late. Now you can sit down and plan effectively with a little "pocket calculator" at the learning site.[j] The outcome depends on four kinds of dietary essential fatty acid: the 18 carbon n-3 and n-6 and the long-chain n-3 and n-6 HUFA. Diet–tissue calculations can now be handled in a simple spreadsheet, using no algebra or arithmetic.

To illustrate the diet–tissue relationship, the family of curves in FIGURE 5 indicate how different mixtures of n-6 linoleate and n-3 HUFA in daily food create tissue HUFA proportions. Four different ethnic groups are shown as ovals. We still have a long way to go from the HUFA status for average Americans (200 deaths per 100,000 people) to where we might like to be. One cannot choose one's parents or one's genetics, but one can choose the food one puts in one's mouth.[30] It's a simple intervention for someone who is properly informed.

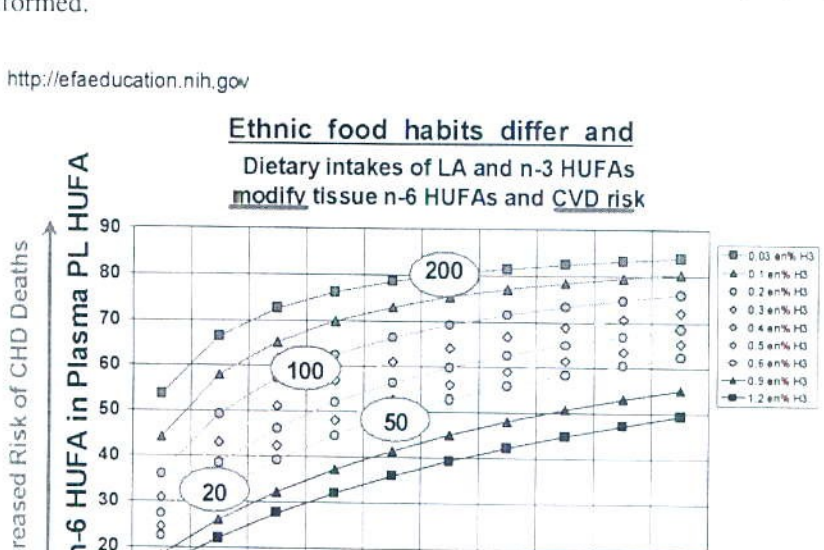


FIGURE 5. Diet–tissue relationship predicts the tissue proportions of n-6 HUFA in tissue HUFA. Available at <http://efaeducation.nih.gov/sig/food2.html>.

[j]http://efaeducation.nih.gov/sig/dietbalance.html

The HUFA proportions for 3,000 Quebec residents ranged from 15 to 91% n-6 HUFA. From FIGURE 2, people can choose their comfort level: what HUFA value they would like to have, and what heart attack risk they would accept. Many people don't want to choose; they want to be told the optimum value. FIGURE 2 makes it obvious that there is no optimum. As you go to higher proportions of n-6 HUFA, the risk grows worse.

Others can see the relationship and risk, but they want to be told which foods are best to eat. Although the distance-learning sites provide a great deal of background information, I decided to use the USDA data base of 6,000 different foods, more than 12,000 servings of food, to create an interactive, computerized, personalized, daily menu-planning program that can be downloaded free.[k] The program allows users to choose foods they want to eat, and it keeps the data managed to let them see whether the daily totals meet their personal goals of cardiovascular risk. The food software takes lifestyle information and tells users what their recommended daily energy allowance is (a value that most sedentary Americans exceed).[31] It also gives some background concepts of risk, and then asks users to choose their risk level and begin choosing foods. Once they look at specific foods, they can begin to see where the omega 6 is entering their diet. For example, the software tells users that the USDA describes a serving of applesauce as having 583 milligrams of 18-carbon omega-6 and only 48 milligrams of omega-3 with no long-chain HUFAs. You can't find any food that doesn't have quite a few milligrams of n-6 linoleate. People producing foods put in n-6-rich oils and raise the level even higher; some breads and muffins have huge amounts. The interactive software shows details and gives the bottom line—total daily total calories and the likely surrogate outcome of HUFA proportions. It also gives a few other dietary facts that dietitians are concerned about and want to convey.

What people really need to know is that their caloric intake is correct and their proportions of eicosanoid precursors are where they want them to be. The nature of a mealtime is that people eat more than they need at that moment and then have transient excess. That excess and its transient postprandial oxidant stress is the beginning of a problem.

If people ate only one meal a day, they would have a large bolus of carbons and electrons entering metabolic pathways. The liver would to make free radicals (and also make cholesterol) and the endothelial cells would respond with oxidant stress due to that postprandial bolus. If people ate smaller meals, five times a day, they would have smaller and more reversible oxidant stress; it would be still lower, with more n-3 and less n-6 HUFAs in the tissues. To take in less energy per meal, people should eat several small meals or snacks if they want. One of the underlying rules is to eat no more than you need.

The top predicted causes of death and disability[32] worldwide for 2020 (ischemic heart disease and unipolar major depression), and three top causes

[k]http://efaeducation.nih.gov/sig/kim.html

in developed regions (ischemic heart disease, cerebrovascular disease, and unipolar major depression) all seem linked to imbalanced omega-3 and omega-6 actions in tissues. We knew about n-6 eicosanoid mechanisms for thrombosis and inflammation 25 to 30 years ago. In the past five years, increasing evidence suggests that major depression, post-partum depression, and behavior disorders also relate to imbalances in omega-3 and omega-6 dietary intakes. Additional evidence showed important actions of n-3 HUFAs in brain function,[33] and the American Heart Association recently urged putting more n-3 HUFAs into daily diets.[34] The growing awareness of the importance of balancing n-3 and n-6 fats is evident from the single major personal health change recommended recently by the health and nutrition division members of the American Oil Chemists' Society: to eat more fish and take an omega-3 supplement.[35] Also, their most frequent advice to other people was to eat more seafood and fish.

In this volume, Dr. Richard Cutler[36] has given us a philosophical view of these issues. We tend to simplify matters that are complex. We use words like "gene" or "the genome" or "inflammation" or "aging," as if these phenomena were a single entity when, in fact, they are a mass of ill-defined parts. On the other hand, some things that are actually simple seem complex. FIGURE 3 outlines the chain of events that lead from food choices to morbidity and mortality. Three types of medication (aspirin, nitroglycerin, and statins) are noted, to show the step in the process at which these familiar drugs intervene. However, when we recognize the initial imbalances in our nutrition that cause cardiovascular death, we can design more effective primary prevention and better nutrition education for the public.

Inflammation was always important in vascular disease, and it was driven by excessive n-6 eicosanoid actions amplifying results of excessive food energy, producing more carbon and electrons than the body could deal with at any given moment. That led to increased cytosolic acetyl-CoA and HMG-CoA, which led to more mevalonate and prenylated proteins (FIG. 3) which are having effects that we didn't recognize 20 years ago. Some prenylated proteins block synthesis of nitric oxide and enhance inflammation. They come about because HMG-CoA reductase is pushed into making more mevalonate than necessary. We knew 25 years ago that plasma cholesterol gave negative feedback that suppressed cholesterol biosynthesis. We subsequently learned that plasma cholesterol suppresses the proteolysis of sterol regulatory element-binding protein, slowing activation of genes expressing fat-forming enzymes. The misimpression that cholesterol (a marker of excessive HMG-CoA reductase action) has been killing people, when the killers are actually vascular inflammation, thrombosis and arrhythmia, is one of the tragedies of biomedical science.[26,27]

The discussion in FIGURE 3 notes that lipoprotein (LDL) has phospholipids that form highly potent inflammatory agents on oxidation, regardless of cholesterol. Phospholipids in the LDL may be deadly. HDL may have cholesterol

(and it has phospholipids), but it has enzymes that neutralize inflammatory oxidized phospholipid PAF mimics and PAF.[37] So HDL is beneficial and LDL is harmful, but it's absurd to talk about "bad cholesterol" and "good cholesterol." We can hope that the tragic detour that delayed understanding of nutritional causes and preventive interventions is nearly over, and that the organizations that could provide the necessary information will do so. Then a new day will dawn for the young people in whom every successive year perpetuates the slow progressive injury that leads to cardiovascular disease and death.

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*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	698959273	13/10/2015	4.224.000.00

*** Conceptos Pagados ***

CANT.	RENTISTICO	CONCEPTO	Vr.UNDITARIO	Vr.CONCEPTO
1	50005-01-03 CAMBIO DE MODALIDAD Y MODIFICACIONES	NES N.CREACION CORRECCION A SOLICITUD EN TRAMITE / MODOFICA	132.000.00	132.000.00
				$132.000.00

SON: **CIENTO TREINTA Y DOS MIL PESOS MONEDA CORRIENTE***

Responsable: _____
-****-

Recibo de Caja Aplicado al Expediente No. _____

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