Despite the richness of concepts contained within the many Main Headings (Descriptors, MeSH terms) that comprise the Chemicals and Drugs Category of MeSH, the rapid expansion of knowledge about chemicals and proteins requires a correspondingly rapid-changing supplementary vocabulary. Main Headings are updated annually; Supplementary Concept Records, discussed below, are updated on a daily basis.

Supplementary Concept Records (Substance Names)

The many substances that are described in the literature need to be named with a controlled vocabulary. Some of them, like ASPIRIN or LISINOPRIL, are MeSH terms. But most substances are not part of the MeSH trees of inter-related MeSH terms. Instead, these substances are part of a separate controlled vocabulary called "supplementary concepts," which are mainly chemical and protein concepts. Each of these "supplementary concepts" or "substance names" is described in a "Supplementary Concept Record," of which there are more than 150,000. These include the substance name itself, corresponding registry number (from Chemical Abstracts Service or Enzyme Commission Nomenclature number), entry terms (including synonyms, closely related names, trade names, and lab numbers) that map to the substance name, pharmacological action, date of introduction, and related MeSH terms.

Like MeSH terms, substance names can be used for searching. When you find a substance name in the Entrez MeSH Database, it will be marked as such. For example, using "Lipitor" as an entry term, we see "atorvastatin [Substance Name]." Subheadings and other MeSH features are not available within Substance Names.

Pharmacological Action [PA] Category of MeSH

Following a procedure that began in 1996, articles about the action of a drug or chemical are indexed both under the MeSH term for the drug or chemical and that for the pharmacologic action being

studied. Thus, a paper about aspirin's ability to prevent the clumping of platelets would be indexed under both ASPIRIN and PLATELET AGGREGATION INHIBITORS. Similarly, a paper about aspirin's anti-inflammatory effects would be indexed under both ASPIRIN and ANTI-INFLAMMATORY AGENTS, NON-STEROIDAL. Likewise, a paper about simvastatin's ability to block the synthesis of cholesterol by inhibiting the enzyme HMG-CoA reductase would be indexed both under SIMVASTATIN and HYDROXYMETHYLGLUTARYL-CoA REDUCTASE INHIBITORS. In each of these examples, we see a drug name that is a MeSH term and a particular type of pharmacologic action. All of the terms mentioned in this paragraph fall under the Chemicals and Drugs Category of MeSH (see Tables 3-1 and 3-4). If you look in the Entrez MeSH Database or NLM's MeSH Browser for PLATELET AGGREGATION INHIBITORS, or for ANTI-INFLAMMATORY AGENTS, NON-STEROIDAL, or for HYDROXYMETHYLGLUTARYL-CoA REDUCTASE INHIBITORS, to see where they fall in the hierarchy of MeSH terms, you will see that they are usually the last branch. The hierarchy cannot be used to view a list of all PLATELET AGGREGATION INHIBITORS, or of any other specific pharmacologic action.

To solve this problem a new MeSH category, *Pharmacological Action [PA],* was created in 2003. Each *Pharmacological Action* includes (ORs together) all of the MeSH terms and substance names thought to share that effect. The criterion for inclusion is that at least 20 papers have found an association with the particular pharmacological action. Thus, the Pharmacological Action category "Platelet Aggregation Inhibitors" includes a long list of substance names (such as 1,2-benzisothiazoline-3-one) and several MeSH terms (such as ASPIRIN). When you look in the Entrez MeSH Database for "statins," you will see two entries for HMG-CoA reductase inhibitors:

> 1: Hydroxymethylglutaryl-CoA Reductase Inhibitors
> Compounds that inhibit HMG-CoA reductases. They have been shown to directly lower cholesterol synthesis.

Year introduced: 1998

2: Hydroxymethylglutaryl-CoA Reductase Inhibitors [Pharmacological Action]

The full display for the first entry looks like that for any MeSH term. The full display for the second entry [Pharmacological Action] is different, in that there are no check boxes for subheadings or for anything else, no placing of the term within the MeSH trees. Instead, we find a list of drugs (both substance names and MeSH terms) that share this pharmacological action. The *Pharmacological Action* entry, which can be sent to the search box for a PubMed search, or is directly searchable in PubMed with the entry tag [PA] or [Pharmacological Action] rather than [MH] or [MeSH], is broader. It captures articles that are indexed under a particular branch of PHARMACOLOGIC ACTIONS, as well as all the substances that have that pharmacologic action. For example, here are two searches for papers about skeletal muscle damage (RHABDOMYOLYSIS) associated with the use of statins:

Search Strategy with MeSH Term:

- Searching for HYDROXYMETHYLGLUTARYL-COA REDUCTASE INHIBITORS [MeSH] found 5,520 citations.
- Limiting these 5,520 citations to articles also indexed under RHABDOMYOLYSIS found 171 citations.

Search Strategy with Pharmacological Action:

- On the other hand, searching for *hydroxymethylglutaryl-CoA reductase inhibitors* [Pharmacological Action] found 9,795 CITATIONS.
- Limiting these 9,795 citations to articles also indexed under RHABDOMYOLYSIS found 269 citations.

Which strategy should be used? It depends on what you are trying to accomplish. For most searches, the first search strategy

would be most useful. Essentially, it asks, "What articles report on an association between the use of HYDROXYMETHYLGLUTARYL-CoA REDUCTASE INHIBITORS (compounds have been shown to decrease cholesterol synthesis by inhibiting HMG-CoA reductases) and RHABDOMYOLYSIS (necrosis or disintegration of skeletal muscle often followed by myoglobinuria)?" This strategy will capture the main reports on this adverse effect. The second strategy casts a broader net. It ORs together all of the substances with this shared pharmacological action. It captures a case report—missed by the first strategy—of a patient with mild chronic renal failure who developed severe RHABDOMYOLYSIS after combined exposure to SIMVASTATIN and COLCHICINE (Baker 2004). The second strategy increases recall (pages 33-34). It says, "Many substances are hydroxymethylglutaryl-CoA reductase inhibitors. Show me all the articles that associate the use of any of these substances with RHABDOMYOLYSIS."

MeSH vs. Major MeSH

When the indexers at the National Library of Medicine assign the dozen or so MeSH terms that characterize the concepts contained in articles, they identify a few of them as central concepts. (See for example, the starred entries on pages 27-28.) These *Major MeSH* entries for each article are the same as those that appeared in the printed *Index Medicus*—until the end of 2004, when its publication ceased, having been fully eclipsed by the free world-wide availability of more complete, current, and easily searched Web versions. Remember (from Chapter 1), a printed index must limit the number of subject headings used to characterize each article; otherwise, it would become much too large. Therefore, only the MeSH terms of major importance to an article ended up in the printed *Index Medicus*. MEDLINE can be searched by designating a MeSH term as being one of these "Major Topic headings" or "Major MeSH." The MeSH term itself is the same, but the search strategy takes advantage of the context in which the MeSH term was applied during indexing. For example, when a search for IBUPROFEN was