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Editorial

As scientists, we like to think that if only we had all the information on any particular problem, then we would be able to solve it. This applies to small problems like why a piece of electrical equipment has stopped working, and to large problems like a cure for cancer. How else can we explain the apparent need to collate all possible information in specific areas of research by library searches that must be comprehensive? We must have an underlying belief that every scrap of knowledge will contribute to the solution. This thirst for comprehensive collection of published research ignores the possibility that some of it might be wrong, and until artificial intelligence programs are more advanced, then the scientist's ability to filter and assess the scientific literature is likely to remain more important than the impressive lists and tables the literature-searching computer can produce.

This is not to say that the all-too human scientist is not above ignoring information that is inconvenient, for all sorts of reasons. The brilliant steroid chemist Russell E. Marker, having pioneered optical rotation as a characterization tool in organic chemistry, fell out with his supervisor over the subject and never again published optical rotation data on newly synthesized or isolated compounds, leaving a large gap in subsequent steroid literature.

A noted example of scientists choosing to ignore a well-known but inconvenient fact, is in the treatment of drugs which can exist as enantiomers and are almost always being marketed as racemates. This will be especially true where the drug has been synthesized from non-chiral precursors; drugs such as steroids and β-lactam antibiotics which were derived from naturally occurring precursors escaped this fate. It is ten years since Ariens pointed out that such racemates may contain a 50% impurity as far as active drug was concerned. This caused some comment at the time, but little outrage; after all he was only pointing out what everyone knew (at least since the time of Pasteur) and there was no evidence that the so-called impurities had any clinical implications. Propranolol and ibuprofen are both racemates and are two of the most successful drugs of all time.

Part of this complacency was due to the lack of simple means of producing optically pure compounds, or in separating enantiomers either for preparative or analytical purposes. Even those methods that were available were extremely expensive or time-consuming and were not justified by contemporary views on the importance of single isomers as drugs.

However, Ariens' paper coincided with the emergence of the chiral chemist in the medicinal chemistry laboratory, and the development of chiral chromatography stationary phases. The former enabled the industry to see new ways of marketing old drugs (an optically pure version of a drug previously marketed as a racemate had a new patent life) and to exploit greater safety claims for new entities. The latter enabled the monitoring of the chemical synthesis or separation of bulk drug substance, and later the study of the pharmacokinetics and metabolism of separate enantiomers after administration of the racemate. These bioanalytical studies proved to be the real eye-opener and a greater spur to demands for optically pure drugs than had the warnings of Ariens on the 50% ballast. For example, the enantiomers of warfarin were shown to have different half-lives, so that any measurement of warfarin in blood without separating the isomers would give a biphasic decay which would be open to erroneous interpretation. Regulatory authorities took a greater interest at this stage, particularly where pharmacokinetic and clinical pharmacology studies were heavily reliant on such analyses. First, the industry had to begin to produce analytical methods for enantiomer separation, and then there was a move towards developments of single isomers only.

The argument for single-isomer products is not as clear-cut as might first appear. A rapid interconversion of isomers might take place (as apparently happens for ibuprofen). The enantiomers may have complementary pharmacological properties, unsuspected during the initial testing of a racemate, but fortuitously providing a drug with a desirable profile. Proponents of the single-isomer view will often quote the case of thalidomide, where, it is said, the teratogenic effect resided in one of the enantiomers and use of the other enantiomer would have precluded the tragedy of the early 1960s; however, animal evidence is inconclusive on this point and the hypothesis is untestable in man.

Nevertheless, all the signs are that future drugs with asymmetric centres will be developed and marketed as single isomers. The chemistry necessary to do this will become just another part of the process chemist's everyday problem. Chiral analysis will be common in the pharmaceutical analytical laboratory and preparative chiral chromatography may also become important.

Drug bioanalysis is difficult enough when one considers the ratio of analyte to everything else in the sample matrix; adding the problem of chiral separation is a further challenge. The bioanalyst has risen to this challenge with many ingenious systems to take advantage of the chiral properties of the analyte, stationary phases, mobile phases and derivatives. There is a certain irony in the developing situation, however; if indeed only pure isomers are the drugs of the future, then for pharmacokinetic studies of the unchanged drug, chiral separation will no longer be necessary. Metabolites, too, will be less likely to be chiral, as metabolizing enzymes, although introducing new asymmetric centres to non-chiral compounds, are likely to do this stereospecifically.

Thus, although life may be more difficult for the synthetic chemist and for the pharmaceutical analyst, for once, the bioanalyst may find new drug developments are in his favour.

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