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## “Where name and image meet”—the argument for “adrenaline”

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Their white epinephrin, my crimes

Aldous Huxley, *Island*

Assuming that you don't want to call it dihydroxyphenylmethylaminoethanol, which name should you use—adrenaline or epinephrine? All the arguments and evidence suggest that you should prefer adrenaline.

### Naming names

All drugs have at least three different names.<sup>1</sup>

- *The chemical name*—whose form generally follows the rules issued by the International Union of Pure and Applied Chemistry—for example, (*R*)-1-(3,4-dihydroxyphenyl)-2-methylaminoethanol.
- *The approved (official or generic) name*—which is usually the World Health Organisation's recommended international non-proprietary name (rINN). However, it may be some locally approved name—for example, the British approved name (BAN), dénomination commune française (DCF), Japanese accepted name (JAN), or United States adopted name (USAN). The monster substance mentioned above is better known as adrenaline (British approved name) or epinephrine (recommended international non-proprietary name).
- *The proprietary (brand or trade) name*—which is the name given by a pharmaceutical manufacturer. For example, adrenaline is marketed in Britain as Epipen for intramuscular injection and as Eppy or Simplex eyedrops.

The chemical name is an unambiguous description of a drug's structure, but it is cumbersome and irrelevant to practical prescribing. As for brand names, pharmaceutical manufacturers make their own choices, although to avoid confusion between similar names of different drugs or formulations, these are subject to some restrictions.<sup>2</sup> But the existence of different approved names in different countries is unnecessary and potentially confusing. The European Community therefore issued a directive in 1992, decreeing that in member countries the recommended international non-proprietary name should be used exclusively.<sup>3</sup>

### Summary points

A European Commission directive requiring member states to use recommended international non-proprietary names for all drugs is soon to be implemented

For most drug names there will be little or no change

For around two dozen drugs the changes are more important; these will be dual labelled during the five year changeover period

It is intended that adrenaline (British approved name) will be changed to epinephrine (recommended international non-proprietary name)

The strong arguments for persuading the European Union to resist this particular change are based on usage, history, etymology, and, most importantly, risk of clinical errors

### The practicalities

Three cases arise in following this directive.

- In most cases, the British approved name and other national names are the same as the recommended non-proprietary names, and no changes are required.
- In many other cases, the British approved names and recommended international non-proprietary name are similar, and the changes are trivial (for example, we shall prescribe amoxicillin, not amoxycillin). A list of these names is given as “List 2” in the *British National Formulary*.<sup>4</sup>
- In a few cases (although a much longer list has been proposed<sup>5</sup>), the Medicines Control Agency considers that the change of name constitutes a high public health risk.<sup>6</sup> In the United Kingdom these names will change over at least five years, and there will be dual labelling of medicines during that time. For instance, frusemide will eventually be called furosemide, bendrofluazide will become bendroflumethiazide, and

lignocaine will become lidocaine—but during the transition period both names will be printed on labels and in information leaflets for patients. A list of these drugs (“List 1”) is given in the *British National Formulary*.<sup>1</sup> Other versions of this list<sup>7 8</sup> do not tally exactly with that in the *British National Formulary*, but the drugs number roughly two dozen.

In 1995 the Medicines Control Agency announced its intention to implement the changes required by the 1992 directive.<sup>9 10</sup> Full implementation was planned for 1998, but it was subsequently estimated that the necessary statutory instrument would not be published before the middle of 1999 at the earliest.<sup>11</sup> At the time of writing (July 1999) it was not in force.

## Opposition

Some people in the United Kingdom will deplore these changes,<sup>12</sup> partly because they will regard them as a wholesale abandonment of British approved names in favour of American ones. But they will be wrong. Although some of the recommended international non-proprietary names that replace current British approved names also happen to be United States adopted names, there are many opposite cases (table 1).

The change to recommended international non-proprietary names is rational and we should not resist it chauvinistically. However, there is one change that we should resist—the switch from adrenaline and nor-adrenaline (British approved names) to epinephrine and norepinephrine (recommended international non-proprietary names).

## The risk argument

The most important argument for using “adrenaline” as the recommended international non-proprietary name is that the adoption of “epinephrine” will increase the risk of accidental misuse of the drug in the

**Table 1** Some recommended international non-proprietary names that are British approved names, not United States adopted names

| British approved name (and recommended international non-proprietary name) | United States adopted name |
|--|----------------------------|
| Glibenclamide  | Glyburide                  |
| Isoprenaline   | Isoproterenol              |
| Moricizine   | Moricizine                 |
| Orciprenaline  | Metaproterenol             |
| Paracetamol  | Acetaminophen              |
| Pethidine  | Meperidine                 |
| Rifampicin   | Rifampin                   |
| Salbutamol   | Albuterol                  |
| Torsemide  | Torseamide                 |

many countries (see below) in which “adrenaline” is preferred. Errors in medication, which are not uncommon, are more likely to occur in emergencies, when there is little time to attend to the nuances of nomenclature and other details, as anyone who has attended a cardiac arrest will testify.<sup>13</sup>

Some studies have illustrated these risks:

- Only nine of 30 anaesthesiologists managed a simulated cardiac arrest according to the US advanced cardiac life support guidelines<sup>14</sup>
- Nineteen residents made major management errors in 58% of cases when faced with five types of simulated critical incidents, including cardiac arrest<sup>15</sup>
- In prehospital treatment for arrhythmias associated with cardiac arrest, treatment errors were made in managing 46% of 263 consecutive patients.<sup>16</sup>

Imagine looking desperately for adrenaline while treating a patient with a cardiac arrest, finding an ampoule labelled ephedrine, and mistaking it for epinephrine. Since the European Community directive was issued,<sup>3</sup> errors arising from confusion between ephedrine and epinephrine have been reported.<sup>17 18</sup> Major underreporting of mistakes over medication<sup>19</sup> means that many unreported errors have probably also occurred.

## The usage argument

If the name adrenaline were used in only a few countries, the risk argument, although important locally, would not be particularly strong in an international context. However, the name adrenaline is preferred to epinephrine in most parts of the world, as a frequency analysis of the use of the two names in the titles and abstracts of bioscientific publications shows (table 2). Although these data do not distinguish the extent to which preferences are those of editors rather than authors, I believe that they reflect a true worldwide preference for the name adrenaline—North America and Japan apart. This preference is also reflected in the terms used in national pharmacopoeias (table 2).

Not only is adrenaline the preferred technical term in most countries in the world, it is also the non-technical term for what people think of as the substance that surges through your body when you are on a high ... even in America. No one anywhere ever talks about a surge of epinephrine.



Jokichi Takamine patented the pure extract of the active principle from the adrenal gland in 1901

**Table 2** Pharmacopoeial names and the number (percentage) of times the names adrenaline and epinephrine have been used in bioscience titles or abstracts since 1965, by country of publication\*

| Country of publication                                      | Name in national pharmacopoeia or equivalent | Instances of "adrenalin(e)" | Instances of "epinephrin(e)" |
|---|--|-----------------------------|------------------------------|
| Australia   | Adrenaline                                   | 159 (85.0)                  | 28 (15.0)                    |
| United Kingdom (England, Northern Ireland, Scotland, Wales) | Adrenaline                                   | 3573 (73.6)                 | 1 282 (26.4)                 |
| France  | Adrenaline                                   | 453 (69.3)                  | 201 (30.7)                   |
| Scandinavia (Denmark, Finland, Norway, Sweden)              | Adrenalin†                                   | 710 (68.5)                  | 327 (31.5)                   |
| Spain   | Epinefrina                                   | 75 (65.2)                   | 40 (34.8)                    |
| Italy   | Adrenalina                                   | 233 (59.4)                  | 159 (40.6)                   |
| Germany   | Adrenalinum‡                                 | 1485 (58.3)                 | 1 062 (41.7)                 |
| Rest of the world   | —  | 3372 (55.4)                 | 2 214 (36.4)                 |
| Japan   | Epinephrine                                  | 441 (38.1)                  | 715 (61.9)                   |
| Canada  | Epinephrine                                  | 121 (28.7)                  | 301 (71.3)                   |
| United States   | Epinephrine                                  | 1157 (9.8)                  | 10 609 (90.1)                |

\*Papers (accessed on Medline) that used both adrenalin(e) and epinephrin(e) were excluded (they comprised under 1% of the total); the Medline records for 1965 are incomplete.

†No Nordic pharmacopoeia; Scandinavia follows the *European Pharmacopoeia*.

‡*Deutsches Arzneibuch*.

## The historical argument

That the adrenal (or suprarenal) glands contained a substance with dramatic pharmacological effects was first shown in 1893 by George Oliver, a Harrogate physician, and Edward Schäfer, professor of physiology at University College London.<sup>20</sup> However, a name was not coined for the substance until John Abel in the United States prepared crude adrenal extracts in 1897 and called them epinephrin. He was acting, he said, "on Hyrtl's suggestion that *epinephris* would be the best name for the suprarenal capsule."<sup>21</sup> Josef Hyrtl (1810-94), professor of anatomy at Vienna, preferred Greek to Latin, quoting Molière: "Parce qu'avec du grec on a toujours raison."<sup>22</sup>

However, none of Abel's epinephrin extracts behaved physiologically like adrenaline does. Then, in 1901, after having visited Abel, Jokichi Takamine prepared a pure extract of the active principle from the adrenal gland and patented it. Parke, Davis & Co marketed his extract, and because they used the proprietary name Adrenalin,<sup>23</sup> epinephrine became the generic name in America, on the incorrect assumption that Abel's extract was the same as



Henry Dale insisted in 1906 on using the name adrenaline in his publications

Takamine's adrenaline. It was, in fact, an inactive benzoylated derivative.<sup>24</sup>

In the United Kingdom, however, where Adrenalin was not marketed, adrenaline became adopted as the generic name. This was because Henry Dale, working in the Wellcome Physiological Research Laboratories, insisted in 1906 on using the name adrenaline in his publications, arguing that the term epinephrine had been used to describe extracts that were not physiologically the same as extracts called adrenaline. Dale disputed this with Henry Wellcome, who preferred the name epinephrine. Wellcome was keen not to infringe the brand name that Parke, Davis & Co had registered in America, remembering the problems that he had had in protecting his own brand name Tabloid.<sup>25</sup> However, Wellcome was eventually convinced by Dale's physiological arguments, in the face of counter arguments by Wellcome's chemists.<sup>26</sup> Particularly convincing was Dale's assertion that "In physiological literature the terminology is settled by those who describe the physiological action... [No] physiologists owed anything to Abel's work or could make use of his inactive substances."<sup>26</sup>

As a result of Dale's firm stand in the face of stiff opposition and Wellcome's final acceptance of his arguments, the name adrenaline (or adrenalin) became widely used. By 1908 it was noted in *The Practitioner* that "the active principle from the medulla of the suprarenal capsule is now generally known as *adrenalin*, though other terms have been applied, such as suprarenin, epinephrin."<sup>27</sup> The name suprarenin was coined by Otto von Fürth of Strasbourg, who made a crude extract similar to that of Abel at about the same time.<sup>28</sup> Fränkel had called another extract sphygmogenin,<sup>29</sup> and Schäfer had suggested the name adrenin.<sup>30</sup> But adrenaline prevailed.

As this brief account shows, there is no historical justification for the use of the term epinephrine. Indeed, the evidence clearly shows that it is the wrong name to use.

## The etymological argument

Other words use the stems adren(o)- or -enine rather than epinephr(o)- or -ephine.

- The gland is the adrenal gland, not the epinephric gland, and the operation to remove it is adrenalectomy. Other derivatives include adrenochrome, adrenocortical, adrenocorticotrop(h)ic, adrenogenital, and adrenolytic; none has a counterpart with the stem epinephro-
- Neurones with adrenaline and noradrenaline as neurotransmitters are called adrenergic and noradrenergic neurones; although the terms epinephrinergic and norepinephrinergic exist, their use is rare. A search of Medline showed that since 1965 they have been used in only 39 papers, whereas adrenergic or noradrenergic have been used 86 101 times
- The receptors on which adrenaline and noradrenaline act are classified internationally as adrenoceptors<sup>31</sup>
- The recommended international non-proprietary name for the noradrenaline derivative isopropylnoradrenaline is isoprenaline; its analogue 1-(3,5-dihydroxyphenyl)-2-isopropylaminoethanol is orciprenaline

- The proposed international non-proprietary name for the  $\beta$  keto derivative of adrenaline is adrenalone, which is also the United States adopted name; there is no epinephrone.

## Conclusion

When the legislation is promulgated, the two dozen or so drugs that the Medicines Control Agency in Britain has identified as having a problematic recommended international non-proprietary name will be labelled with both names.<sup>4 7 8</sup> Dual labelling has already been adopted in the *British Pharmacopoeia* for 16 of those drugs.<sup>32</sup> There the recommended international non-proprietary name is given first, except, crucially, in the case of adrenaline and noradrenaline, for which the British approved name is given first. Dual labelling will pose some problems for pharmacists,<sup>33</sup> but they are not major ones, and we shall eventually get used to the new names, without (one hopes) serious errors. We shall, if we must, even get used to epinephrine ... eventually. But the dangers in changing the name from adrenaline to epinephrine will far outweigh any other problems during the lengthy changeover period.

Use of the term epinephrine will increase the risk of serious errors in administering adrenaline in the many countries in which the term adrenaline is currently preferred. There is, furthermore, clear historical and etymological evidence that epinephrine is an inappropriate name to use. We should urge the World Health Organisation to change the recommended international non-proprietary name epinephrine to adrenaline (and norepinephrine to noradrenaline). If the existence of Adrenalin as a brand name in some countries militates against this, the European Union should allow adrenaline to be an exception to the rule that all names should be recommended international non-proprietary names. After all, the title of the relevant monograph in the *European Pharmacopoeia* is—yes—“Adrenaline.”

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Competing interests: JKA is a member of the British Pharmacopoeia Commission's nomenclature committee, but

the views expressed here do not necessarily reflect those of other members of that committee or of the British Pharmacopoeia Commission itself.

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## One hundred years ago The Royal Academy Exhibition

General art criticism of a comprehensive and sweeping nature hardly comes within our journalistic limits, but without stepping very far from beyond our proper sphere, we may cordially congratulate the Academy on the undoubted success of their annual show. For once there is a practical agreement between experts and the man in the street, that Burlington House is well worth a visit, and that the 2,057 products of British brushes and chisels have attained a standard of excellence which make this a remarkable if not a record year. Some of the older men who seemed disposed to rest with middle-aged complacency on the

easy couch of past laurels have sprung once more to their feet and asserted their position in the foremost rank, and their junior competitors are pressing on briskly from behind. Old Sidney Cooper will not yield an inch of the vantage ground which he has gained during his 97 years of active and successful life, and the vigour and firmness of his work lead us to hope that we may yet have the pleasure of congratulating the Royal Academy on including a centenarian among the number of its elect.

(*BMJ* 1900;i:1179.)