

RACEMIC DRUGS AND ENANTIOMERS

Identifying the really useful innovations

Many drugs are available as **racemic mixtures** or 50:50 mixtures of two molecules (enantiomers) that are different merely by one being the non-superimposable mirror image of the other. There are normally two classifications used for enantiomers: the first one distinguishes the two molecules as a **dextrorotatory** and **levorotatory** enantiomer, the second one distinguishes them as an **R** and **S** enantiomer (see fly-leaf).

Almost all biological organisms produce only one of the 2 enantiomers, usually the levorotatory one. For this reason, production, experimentation and clinical use of **substances of natural origin** are suddenly directed towards single enantiomers (typical examples are levothyroxin and levodopa).

On the other hand, **enantiomers of non-natural origin**, before the decade of '80-90, had been predominantly marketed in the form of racemic mixtures. Some examples are ketoprofen, atenolol, warfarin, omeprazole, fluoxetine. In the last 20 years, technical innovations have made the synthesis of single enantiomers more feasible; the regulatory authorities have gradually made it a requirement that, when drugs at the development stage are made up of a racemic mixture, the producer must assess the efficacy of the single enantiomers and choose, giving reasons, which of the two to market. So, in the near future, there will have to be a gradual reduction in the marketing of **new drugs** made up of racemic mixtures.¹



Among the new drugs marketed from the outset as single enantiomers there are: simvastatin, atorvastatin, pravastatin, paroxetine, clopidogrel, fluticasone, salmeterol, valsartan, etc. (see table 1).

In some cases, the **enantiomers recently brought on to the market are not really new drugs**: they are simply the active enantiomer of racemic mixtures of proven clinical efficacy whose expiring patent reduces their commercial value.

In other cases, the enantiomer is a real improvement compared to the racemic mixture in terms of better effectiveness, less toxicity or more advantageous pharmacokinetic profile.

Finally, it has to be considered that the marketing of a single enantiomer, whose racemic mixture has already been licenced, may be approved on a basis of relatively limited evidence, with few new clinical trials.^{2,3}

In this Information Package, the effectiveness and tolerability of some recently marketed enantiomers will be analysed in comparison with the corresponding racemic mixture, with particular reference to the choices guided by predominantly commercial-type reasons.

	Racemic drugs	Corresponding single enantiomers
On the market in Italy	Omeprazole	Esomeprazole
	Cetirizine	Levocetirizine
	Ofloxacin	Levofloxacin
	Citalopram	Escitalopram
	Ketoprofen	Destroketoprofen
Not on the market in Italy	Ibuprofen	Destroibuprofen
Under study	Fluoxetine	Destrofluoxetine Levofluoxetine

Racemic drugs <i>the enantiomer is not marketed</i>	A large number of drugs on the market are racemic mixtures, eg: atenolol, warfarin, disopyramide, atropine, Ca-antagonists,...
Enantiomers <i>marketed only as single enantiomers</i>	Clopidogrel, atorvastatin, simvastatin, pravastatin, paroxetine, sertraline, fluticasone, salmeterol, valsartan,...

Table 1. Some examples of racemic mixtures and enantiomers of non-natural origin

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Racemic drugs, enantiomers & Co.
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fly-leaf

From ofloxacin to levofloxacin: the spectrum is changed

Ofloxacin is a fluoroquinolone, on the market since 1987 as a racemic mixture.

The antibacterial activity of the racemic drug ofloxacin is due mainly to its levorotatory enantiomer (levofloxacin)^{4,5}. From the microbiological point of view, in fact, levofloxacin is up to 128 times more effective than the dextrorotatory enantiomer and up to twice as effective than the racemic mixture according to the Gram positive and Gram negative bacterial stocks assayed.⁵

The pharmacokinetics of levofloxacin is similar to those of ofloxacin, but its greater microbiological efficacy (represented by lower MIC₉₀ for some pathogens) helps it to reach effective tissue concentrations that permit administration of a single daily dose.⁵

Of particular clinical interest is the extension of the spectrum with respect to *Streptococcus pneumoniae* (**pneumococcus**): in fact, the main guidelines on treatment of community acquired pneumonia mention levofloxacin (and not ofloxacin) among the fluoroquinolones with activity against pneumococcus.^{7,8}

With regard to tolerability, no clinically significant differences have been found between the racemic mixture and the pure enantiomer; it should, however, be remembered that a risk of tendinous lesioning/rupture is associated with the administration of fluoroquinolones.¹⁰

Levofloxacin = S (-) ofloxacin

Registered indications: substantially similar even if more detailed for levofloxacin.

Patents and marketing activities:

Ofloxacin: the patent expired in January, 2006.

Levofloxacin: it came on to the market in Italy in 1998.

IN PRATICE...

The introduction on the market of levofloxacin provided a therapeutic choice of greater efficacy compared with ofloxacin, in particular in the treatment of community acquired pneumonia. Tolerability seems to be substantially similar.

Levocetirizine: nothing new but the dose

Levocetirizine = R (-) cetirizine

Registered indications: similar.

Patents and marketing activities:

Cetirizine: the patent will expire in 2007.

Levocetirizine: it came on to the market in Italy in 2003.

Quite often in the history of antihistamines, it has been observed the replacement of old drugs - because of frequent (eg. sedation) or serious side effects (eg. death from arrhythmia) - with analogues, usually metabolites, that are better tolerated or less toxic: terfenadine - for example - was replaced by its active metabolite fexofenadine. This is not the case of levocetirizine, an active enantiomer of cetirizine.^{11,12}

Levocetirizine was compared with cetirizine only in healthy volunteers in order to assess its effective dose: 2.5 and 5 mg of pure enantiomer were as effective as 5 and 10 mg respectively of racemic mixture in reducing the response to intranasal¹¹ and cutaneous¹² administration of histamine.

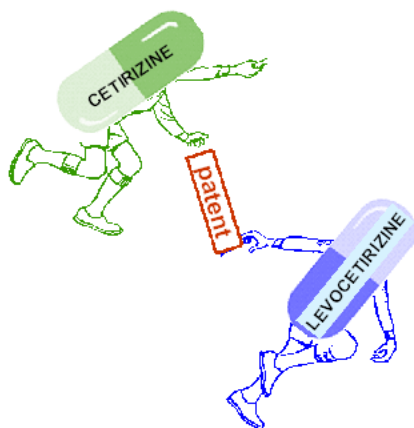
Clinical trials available

Seasonal or permanent allergic rhinitis. The clinical efficacy of levocetirizine (5 mg/day) was assessed in around 20 RCTs, none of which was versus cetirizine, most against placebo and some versus other antihistamines. In the comparisons available, levocetirizine was more effective than placebo but mostly as effective as the comparative antihistamines (fexofenadine 180 mg, loratadine 10 mg, desloratadine* 5 mg) in reducing the symptoms of rhinitis, measured with various scales. The larger published RCT versus another antihistamine,¹³ involved 373 patients treated for 2 days with levocetirizine (5mg/day), desloratadine* (5mg/day) or placebo: both antihistamines were shown to be more effective than placebo in reducing the symptoms (rhinorrhea, eye irritation, etc.).

*active metabolite of loratadine

Chronic idiopathic urticaria. In literature there are 7 RCTs (for a total of less than 200 subjects) of which 5 are on healthy volunteers and only 2 on patients. Of the latter two, the first one¹⁴ is in Chinese and cannot be found, the other is versus placebo and has shown the greater effectiveness of levocetirizine (5 mg/day) in reducing the symptoms of urticaria (measured as subjective symptoms, daily episodes, etc.).¹⁵

Tolerability. Data on tolerability of levocetirizine are no different from those of cetirizine, although with a decidedly lower observation time and number of patients treated.



IN PRATICE...

On the basis of studies available, levocetirizine does not appear to provide any advantage over cetirizine in terms of effectiveness and tolerability.

Esomeprazole: double dose in order to seem more effective

S (-) omeprazole (hence the name esomeprazole) is the levorotatory enantiomer of omeprazole, a 50:50 racemic mixture of levo and dextro (or R) omeprazole.

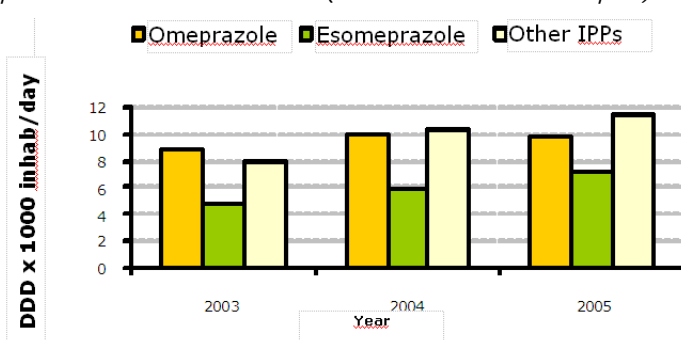
Both enantiomers are partially inactivated: S-omeprazole is inactivated to a lesser extent than R-omeprazole, thus reaching greater blood concentrations. At gastric cell level there occurs the transformation of both isomers in omeprazole-sulfenamide, the **active metabolite** on the proton pump.^{16,17}

As a result of the different inactivation of the two enantiomers, administration of 20 mg of esomeprazole makes it possible to obtain blood concentrations of the drug (evaluated as area under the curve or AUC) 70-90% higher than those obtained by administering 20 mg of the racemic drug.^{17,18} Due to the higher serum levels obtained, 20 mg of esomeprazole administered for 5 days cause 90% suppression of gastric acidity, higher than the 79% obtained with 20 mg of omeprazole¹⁹

On the basis of these figures, it can be said that **14-16 mg of esomeprazole are able to induce an increase in gastric pH similar to that produced by 20 mg of omeprazole.**

In a comparative trial on healthy volunteers, administration of 40 mg of esomeprazole for 5 days maintained gastric pH >4 for 14.0 hours: a higher effect if compared to the 12.1 hours obtained with rabeprazole (20 mg), 11.8 hours with omeprazole (20 mg), 11.5 hours with lansoprazole (30 mg) and 10.1 hours with pantoprazole (40 mg).²⁰ This superiority was not confirmed in a trial where healthy volunteers treated with 20 mg of esomeprazole for 5 days showed a less rapid and prolonged gastric pH control compared with 20 mg of rabeprazole.²¹

Figure 1. National prescription trend of esomeprazole, omeprazole and all the other PPIs (Source: 2005 OsMED Report)



IN PRATICE...

There are no figures showing the superiority of one PPI over the others if used at equivalent doses. The introduction of esomeprazole into clinical practice has not provided real advantages, but is an example of a commercial initiative designed to maintain a market share when the patent of drugs belonging to the same class expires.

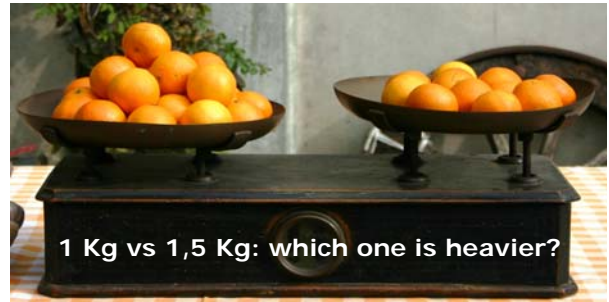
Esomeprazole = S (-) omeprazole

Registered indications: similar

Patents and marketing activities:

Omeprazole: it has been marketed as a generic drug since 2001 in the USA, since 2003 in the EU, but in Italy the validity of the patent was extended until 2008 (Supplementary Protection Certificate).

Esomeprazole: it came on to the market in Italy in 2002 with a mutual recognition procedure.



Clinical data: an uneven comparison

Despite the availability of basic pharmacological data, clinical trials were conducted using mainly 40 mg of esomeprazole: in practice **the choice was made to compare relatively higher doses of esomeprazole in relation to the standard doses of the other proton pump inhibitors (PPI).**

An example of this is the greater effectiveness in the treatment of reflux esophagitis found in a systematic review comparing esomeprazole with other PPIs²² attributable to the use of esomeprazole in higher doses than the standard doses of the other PPIs. After 8 weeks of treatment, 40 mg of esomeprazole achieved an endoscopic cure in 4% more patients (88% vs. 84%) compared to those treated with standard doses of the other PPIs.

IPP	Equivalent doses*	Doses on the market
Omeprazole	20 mg	10-20 mg
Lansoprazole	30 mg	15-30 mg
Pantoprazole	40 mg	20-40 mg
Rabeprazole	20 mg	10-20 mg
Esomeprazole	14 -16 mg	20-40 mg

Table 2. Equivalent doses and doses on the market for various PPIs. * Equivalence expressed on the basis of the ability to inhibit gastric acidity

What they write from abroad...



Esomeprazole does not provide advantages compared with equivalent doses of the other proton pump inhibitors.¹⁸



...Esomeprazole, promoted in order to replace omeprazole, does not really have any clinical advantage over it, either in terms of effectiveness or in terms of adverse side effects. Its raison d'être is purely commercial...²⁴

Escitalopram: are there major advantages over citalopram?

Escitalopram, a selective antidepressant inhibitor of the re-uptake of serotonin (SSRI), is the active enantiomer of the racemic mixture **citalopram**.

Escitalopram vs. Citalopram: the available evidence

The efficacy of escitalopram in the treatment of major depression, panic attacks and anxiety in adults was initially demonstrated - in the same way as that of the racemic mixture (citalopram) - in comparison with placebo.

RCTs were then carried out versus other antidepressants.

Major depression. There are only four RCTs published (found in PubMed) that have compared escitalopram (10- 20 mg/day) with citalopram (20-40 mg/day) in major depression. Three trials²⁵⁻²⁷ were over a short period of time (8 weeks) and had 280, 469 and 491 patients enrolled, respectively, whereas only one trial²⁸ on 357 patients had a clinically relevant follow-up period (24 weeks).

Three²⁶⁻²⁸ out of four of these RCTs showed no differences in the average score on the MADRS depression scale (main indicator). Only one RCT²⁵ lasting for 8 weeks showed a statistically significant difference on the MADRS scale in favour of escitalopram: the size of this difference is, however, **negligible from the clinical point of view** (2 points on a scale of 60).

In 3 RCTs^{25,26,28} escitalopram showed an improvement of some secondary indicators (percentages of patients responding to the treatment or patients in remission) compared with the racemic mixture; these results still need confirmation, considering the short study period and the limits of the statistical analyses made.²⁹

Panic attacks. One RCT only³⁰ compared the 2 drugs in the prevention of panic attacks, evaluating 366 patients over 10 weeks and not showing any differences.

Side effects: from the trials available, it is unclear whether there are differences in tolerability between the 2 drugs.

Conclusions

- Ever since the chemical synthesis of single enantiomers has been possible and economically sustainable, it has become increasingly frequent to see them being brought out on the market. This approach is currently required by international regulatory authorities for new drugs.
- The use of the pure enantiomer is not justified when there are on the market racemic mixtures of the same effectiveness and tolerability, shown by trials and prolonged clinical use.
- Of the examples given, levocetirizine, esomeprazole and escitalopram have similar effectiveness to the respective racemic compounds, and their marketing seems, above all, linked to economic reasons (expiry of racemic drug patent). On the other hand, compared with ofloxacin, levofloxacin has greater microbiological activity against some bacteria, in particular pneumococcus.

Escitalopram = S (+) citalopram

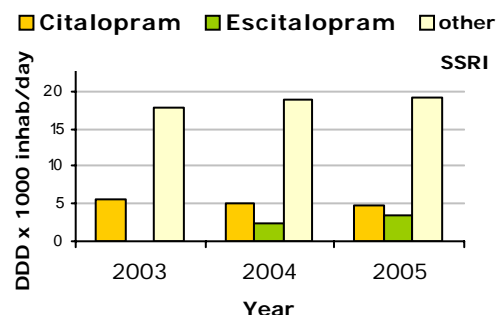
Registered indications: similar

Patents and marketing activities:

Citalopram: the patent expired in 2004 (the generic product is also available).

Escitalopram: it came on to the market in 2003.

Figure 2. Prescription trend of SSRI in Italy: the rise of escitalopram (Source: 2005 OsMED Report)²³



IN PRACTICE...

At present there is insufficient evidence that escitalopram is really an innovative drug compared to the racemic mixture citalopram.

Its introduction on the market seems to be linked to commercial reasons.

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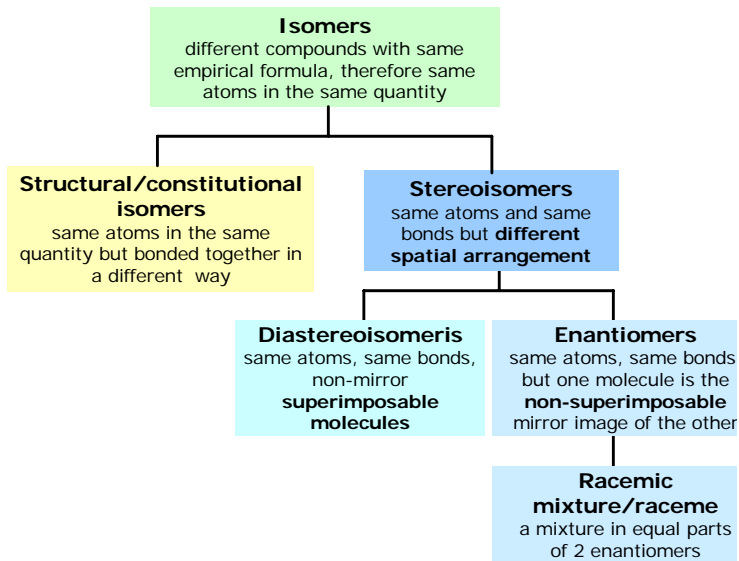
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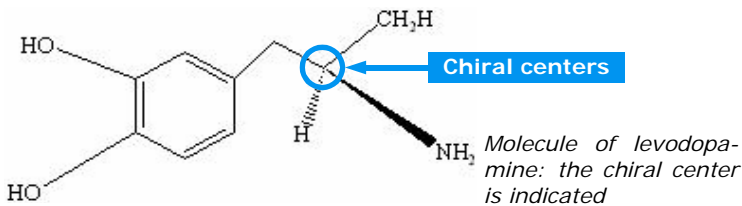
Racemic drugs, enantiomers, chiral centers & Co. How to find your way around the definitions



WHEN ARE TWO MOLECULES CHIRAL?

If 2 molecules have the same composition and the same type and quantity of bonds between atoms but are a **superimposable mirror image of each other** they are called **chiral** (from the Greek *chiròs*, hand).

These molecules contain one or more **chiral centers** or asymmetric atoms (usually of carbon) to which other atoms or groups of atoms, all different from each other, are bonded.



Chirality is a necessary condition for the existence of enantiomers: a compound whose molecule is chiral can exist in the form of enantiomers.

HOW ARE ENANTIOMERS INDICATED?

There are mainly 2 types of classification:

- the one that is based on the direction towards which they rotate a plane of polarized light: if to the right, the **enantiomer** will be **dextrorotatory** and will be indicated as (+); if to the left, it is **levorotatory** and will be indicated as (-);
- the one that refers to the spatial arrangement of the molecule in relation to the chiral center/s: if the arrangement of the atoms or groups of atoms (starting from the heaviest and going towards the lightest) goes clockwise it will be known as **enantiomer R** (from *rectus*); if anti-clockwise it will be known as **enantiomer S** (from *sinister*) (rule of Cahn, Ingold, Prelog).³¹

The 2 types of classification are independent of each other: it is impossible to know a priori whether the rotation (+) or (-) corresponds to the R or S configuration.

BIBLIOGRAPHY

1. Caner H, et al. Trends in the development of chiral drugs. *Drug Discov Today*. 2004;9: 105-10.
2. Fda's policy statement for the development of new stereoisomeric drugs <http://www.fda.gov/cder/guidance/stereo.htm>
3. Somogyi A, et al. Inside the isomers: the tale of chiral switches. *Aust Prescr*. 2004;27: 47-9
4. New drugs IV. *Therapeutics Letter*. 1998;26 <http://www.ti.ubc.ca/pages/letter26.htm#levofloxacin>
5. Hayakawa I, et al. Synthesis and antibacterial activities of optically active ofloxacin. *Antimicrob Agents Chemother*. 1986;29:163-4
6. Fish DN, Chow AT. The clinical pharmacokinetics of levofloxacin. *Clin Pharmacokinet*. 1997;32: 101-19
7. Guidelines for the Management of Adults with Community-acquired Pneumonia. *Thorax*. 2001;56:(suppl IV). <http://www.thoracic.org/sections/publications/statements/pages/mtpi/commacq1-25.html>
8. The British Thoracic Society. Pneumonia Guidelines. http://www.brit-thoracic.org.uk/iqs/sid.03471940206136091807508/bts_guidelines_pneumonia_html
9. Owens RC, Ambrose PG. Antimicrobial safety: focus on fluoroquinolones. *Clin Infect Dis*. 2005;41(Suppl 2):S144-57.
10. Ministero della Salute. Dear Doctor Letter 15/03/2002
11. Wang DY, et al. Effect of cetirizine, levocetirizine, and dextrocetirizine on histamine-induced nasal response in healthy adult volunteers. *Allergy*. 2001;56: 339-43
12. Devalia JL, et al. A randomized, double-blind, crossover comparison among cetirizine, levocetirizine, and ucb 28557 on histamine-induced cutaneous responses in healthy adult volunteers. *Allergy*. 2001; 56 :50-7
13. Day JH, et al. Comparative clinical efficacy, onset and duration of action of levocetirizine and desloratadine for symptoms of seasonal allergic rhinitis in subjects evaluated in the Environmental Exposure Unit (EEU). *Int J Clin Pract*. 2004;58: 109-18
14. Yun R, et al. A clinical trial of levocetirizine in the treatment of chronic idiopathic urticaria. *Journal of Clinical Dermatology*. 2003;32:477-8
15. Nettis E, et al. Levocetirizine in the treatment of chronic idiopathic urticaria: a randomized, double-blind, placebo-controlled study. *Br J Dermatol*. 2006; 154:533-8
16. Hassan-Alin M, et al. *Eur J Clin Pharmacol*. 2005; 60:779-84
17. Astra-Zeneca, report drawn up by M. Hassan-Alin, et al. *Eur J Clin Pharmacol*. 2005;60: 779-84
18. Do Single Stereoisomer Drugs Provide Value? *Therapeutics Letter*. 2002;45
19. Andersson T, et al. *Aliment Pharmacol Ther*. 2001;15:1563-9
20. Miner P Jr, et al. Acid Control With Esomeprazole Lansoprazole, Omeprazole, Pantoprazole, and Rabeprazole: A Five-Way Crossover Study. *Am J Gastroenterol*. 2003;98:2616-20
21. Warrington S, et al. Effects of rabeprazole 20 mg or esomeprazole 20 mg on 24-h intragastric pH and serum gastrin in healthy subjects. *Aliment Pharmacol Ther*. 2002;16: 1301-7
22. Edwards SJ et al. Systematic review: proton pump inhibitors for the healing of reflux oesophagitis - a comparison of esomeprazole with other PPIs. *Aliment Pharmacol Ther*. 2006;24: 743-50
23. The use of drugs in Italia. Rapporto OsMED 2005 <http://www.agenziafarmaco.it>
24. Redactional. Esoméprazole et oméprazole: bonnet blanc et blanc bonnet. *Prescrire*. 2002;227:248-50
25. Moore N, et al. Prospective, multicentre, randomized, double-blind study of the efficacy of escitalopram versus citalopram in outpatient treatment of major depressive disorder. *Int Clin Psychopharmacol*. 2005;20: 131-7
26. Lepola UM, et al. Escitalopram (10-20 mg/day) is effective and well tolerated in a placebo-controlled study in depression in primary care. *Int Clin Psychopharmacol*. 2003;18:211-7
27. Burke WJ, et al. Fixed-dose trial of the single isomer SSRI escitalopram in depressed outpatients. *J Clin Psychiatry*. 2002;63: 331-6
28. Colonna L, et al. A randomized, double-blind, 24-week study of escitalopram (10 mg/day) versus citalopram (20 mg/day) in primary care patients with major depressive disorder. *Curr Med Res Opin*. 2005;21:1659-68
29. Svensson S, Mansfield PR. Escitalopram: superior to citalopram or a chiral chimera? *Psychother Psychosom*. 2004;73: 10-6
30. Stahl SM, et al. Escitalopram in the treatment of panic disorder: a randomized, double-blind, placebo-controlled trial. *J Clin Psychiatry*. 2003;64:1322-7
31. Morrison RT, Boyd RN. Organic chemistry. *Ambrosiana Publishers Milan*. 5th edition, 1991