GENERAL REMARKS

Oestrogens and progestogens (progestins) and their medical uses for contraception and for post-menopausal hormonal therapy were considered by previous working groups, in 1974 (IARC, 1974), 1978 (IARC, 1979) and 1987 (IARC, 1987). The monographs included in this volume incorporate new data that have become available. They also reflect modifications to the Preamble to the *IARC Monographs* (IARC, 1991), which permit more explicit inclusion of information on mechanisms of carcinogenesis (Vainio *et al*., 1992) and of data on effects other than cancer in the evaluation process.

IARC Monographs Volume 21 (IARC, 1979) gives a general discussion of sex hormones and cancer, and the principles described in that volume remain applicable, especially in the section 'General Conclusions on Sex Hormones': 'Steroid hormones are essential for the growth, differentiation and function of many tissues in both animals and humans. It has been established by animal experimentation that modification of the hormonal environment by surgical removal of endocrine glands, by pregnancy or by exogenous administration of steroids can increase or decrease the spontaneous occurrence of tumours or the induction of tumours by applied carcinogenic agents …. The incidence of tumours in humans could be altered by exposure to various exogenous hormones, singly or in combination.' These statements underline the facts that oestrogens and progestogens occur naturally and that the hormonal milieu and dose are generally inextricably involved in the carcinogenic effects of oestrogens and progestogens.

Naturally occurring and synthetic oestrogens and progestogens are among the most widely used drugs in medicine; however, the use of specific agents, combinations and regimens for contraception and for post-menopausal hormonal therapy varies from one geographic region to another and among countries, and the use of oestrogens and progestogens in medical practice continues to evolve rapidly. Moreover, the doses prescribed have changed significantly since previous evaluations in the *IARC Monographs*. The drugs themselves are complex and often cannot be classified simply as oestrogens or progestogens; some have multiple endocrine actions that may vary from one tissue to another. Accordingly, the substances evaluated in these monographs may differ from those evaluated under the same names by previous working groups.

Hormonal contraceptives

Oral contraceptives allow effective, convenient family planning for women and couples worldwide, and they have revolutionized the reproductive lives of millions of women since their introduction in the 1960s. When combined oral contraceptives are used correctly, the pregnancy rate is 0.1 per 100 woman–years, while the pregnancy rate with use of progestogen-only pills is somewhat higher (0.5 per 100 woman–years). Combined

oral contraceptives prevent pregnancy primarily by inhibiting ovulation, while progestogen-only pills act mainly by altering the cervical mucus. Use of combined oral contraceptives leads to regular monthly bleeding in most women. Most of the studies of side-effects of hormonal contraceptives have been conducted with combined oral contraceptives; limited data are available for progestogen-only contraceptives, but they are generally regarded as safe.

In the 1960s, combined oral contraceptive preparations contained 100–150 μg ethinyloestradiol[1] and about 1–5 mg of a progestogen. The doses of both ethinyloestradiol and progestogens were successively lowered, and today preparations containing less than 50 μg ethinyloestradiol are generally used. The 'pill' most commonly used worldwide today contains 30 μg ethinyloestradiol and 150 μg levonorgestrel. New synthetic progestogens, i.e. desogestrel, gestodene and norgestimate, have been introduced. Combined oestrogen plus progestogen preparations are also available in injectable form, and progestogen-only preparations are available as tablets, injections, implants and intrauterine devices. Combined and progestogen-only tablets are used not only prophylactically but also as emergency contraceptives up to 72 h after intercourse.

The hormones that make up the various oral contraceptives affect not only the reproductive system but other bodily systems as well, and their effects on the prevalence and incidence of various diseases have been the subject of numerous studies over the past decades. Shortly after the introduction of combined oral contraceptives in about 1960, case reports were published of venous thrombolic disease, stroke and myocardial infarct in women using them. These reports spurred a large number of epidemiological studies of the cardiovascular effects of combined oral contraceptives. The relationship between use of combined oral contraceptives and acute myocardial infarct, stroke and venous thromboembolism has been reviewed (Chasan-Taber & Stampfer, 1998; WHO Scientific Group on Cardiovascular Disease and Steroid Hormone Contraception, 1998) and is summarized below.

The review of Chasan-Taber and Stampfer (1998) of 374 epidemiological studies led them to conclude that non-smoking women under 40 years of age who use oral contraceptives have little or no increase in their risk for myocardial infarct when compared with women who do not use these preparations. The WHO Scientific Group on Cardiovascular Disease and Steroid Hormone Contraception (1998) concluded that the risk for myocardial infarct is not increased by use of combined oral contraceptive by women who do not smoke, whose blood pressure is checked regularly and who do not have hypertension or diabetes, regardless of age; however, use of combined oral contraceptives increases the already elevated risk for myocardial infarct among women with cardiovascular risk factors, such as smoking and hypertension.

The risk for ischaemic stroke among women who do not smoke, have their blood pressure checked regularly and do not have hypertension is 1.5-fold higher for those who

[1] Throughout this volume, the term ethinyloestradiol is used for 17α-ethinyloestradiol.

currently use low-dose combined oral contraceptives than for those who do not (WHO Scientific Group on Cardiovascular Disease and Steroid Hormone Contraception, 1998). Combined oral contraceptives cause a small increase in blood pressure, even at low doses. A study in China showed an increase of 1.8–2.3 mm Hg (0.24–0.30 kPa) in diastolic pressure (Shen *et al*., 1994). Among women who use combined oral contraceptives, the risk for haemorrhagic stroke is not increased in those who do not smoke, are not hypertensive and are under the age of 35 years, but may be increased by twofold in women aged 35 years or older. In general, use of combined oral contraceptives by women with risk factors for stroke adversely modifies their already elevated baseline risk (WHO Scientific Group on Cardiovascular Disease and Steroid Hormone Contraception, 1998).

The WHO Scientific Group on Cardiovascular Disease and Steroid Hormone Contraception (1998) concluded that current users of combined oral contraceptives have a three- to sixfold increase in the risk for venous thromboembolism in comparison with non-users; the excess risk is probably highest during the first year of use and declines thereafter, but it persists until discontinuation. Combined oral contraceptives containing desogestrel or gestodene have been associated in some studies with a greater increase in risk for venous thromboembolic disease than that reported with combined oral contraceptives containing levonorgestrel, but other studies have not come to the same conclusion. Smoking and hypertension do not appear to elevate the risk for venous thromboembolism.

The risk for gall-bladder disease, including gallstones, has been associated with current use of combined oral contraceptives, which may enhance the development of symptoms of already existing gallstones, with or without enhancement of gallstone formation (Thijs & Knipschild, 1993). Low-dose oral contraceptives appear to confer a lower risk for gall-bladder disease than high-dose oral contraceptives (Strom *et al*., 1986; Vessey & Painter, 1994).

Use of combined oral contraceptives confers several benefits other than contraception. Their use has been associated with a reduced risk for benign breast disease, although it is not yet clear whether low-dose oral contraceptives have the same protective effect as high-dose preparations (McGonigle & Huggins, 1991). It has been reported that oral contraceptive users have a reduced risk for uterine myomas and for undergoing surgery for uterine myomas (Lumbagnon *et al*., 1996). Other non-contraceptive benefits of combined oral contraceptive use include a reduced risk for iron deficiency anaemia, because of decreased menstrual blood loss, and lower frequencies of dysmenorrhoea and functional ovarian cysts (Mehta, 1993; Mishell, 1993). Two reviews also indicate a lower risk for uterine salpingitis in women who have contracted a sexually transmitted disease (Mishell, 1993; Burkman, 1994).

The newer progestogens used in low-dose combined oral contraceptives, desogestrel and gestodene, have fewer androgenic effects than those used earlier. Patients with acne have shown improvement after treatment with pills containing desogestrel, gestodene or norgestimate in randomized controlled trials (Mango *et al*., 1996; Redmond *et al*., 1997).

Post-menopausal hormonal therapy

With improvements in health and longevity, an increasing proportion of women's lives is lived after the menopause. In developed countries, life expectancy is such that, on average, women are expected to live half of their adult lives after the menopause, with the associated reductions in the concentrations of endogenous oestrogen and progestogen.

Post-menopausal oestrogen therapy, introduced more than 50 years ago, was originally prescribed for the short-term relief of menopausal symptoms; interest in the risks and benefits of long-term therapy is relatively recent (see review by Ettinger, 1998). Studies of the health outcomes of oestrogen use after the menopause are heavily weighted by studies of oestrogens and of combined oestrogen and progestogen from the United States, where the oestrogens used are conjugated equine oestrogens and the progestogen is medroxyprogesterone acetate. The use of transdermal oestradiol[1] is relatively new, and few data on disease outcomes are available.

Post-menopausal oestrogen therapy is the most commonly prescribed medication in the United States. Nevertheless, even there, most post-menopausal women are not treated, and most of those who are prescribed oestrogen therapy discontinue it within a few years because of its side-effects or fear of cancer. Evidence of an increased risk for cancer is reviewed in this volume. The carcinogenic risks must be placed in the perspective of potential benefits (Grady *et al*., 1992). The best-established benefit is the prevention of osteoporotic fractures (Lufkin *et al*., 1992). Because coronary heart disease is the most common fatal disease among women in most developed countries, any significant reduction in risk for that outcome is important. As recently reviewed (Barrett-Connor & Grady, 1998), a meta-analysis of 25 studies of oestrogen therapy showed an overall relative risk for coronary heart disease of 0.70 (95% confidence interval [CI], 0.65–0.75), most of the use being of conjugated equine oestrogens alone, and seven studies of oestrogen plus a progestogen showed an overall relative risk of 0.66 (95% CI, 0.53–0.84). At present, the evidence that oestrogen prevents heart disease is consistent but circumstantial. The other most important postulated benefit of post-menopausal oestrogen therapy is the prevention of memory loss or dementia. As reviewed by Yaffe *et al*. (1998), a meta-analysis of 10 published studies showed a summary odds ratio of 0.71 (95% CI, 0.53–0.96) for the risk of developing dementia. The major well-documented non-cancer risks associated with post-menopausal oestrogen use are gall-bladder disease and deep-vein thrombosis or pulmonary embolism. In a large cohort study (Grodstein *et al*., 1994), a twofold increase in the risk for cholecystectomy (relative risk [RR], 2.1; 95% CI, 1.9–2.4) was seen among post-menopausal women using hormones. The first published data showing a two- to fourfold increase in the risk for venous thromboembolic disease was published in 1996 (Daly *et al*., 1996; Grodstein *et al*., 1996; Jick *et al*., 1996), and the results were confirmed in a randomized clinical trial (Grady *et al*., 1997).

[1] Throughout this volume, the term oestradiol is used for oestradiol-17β.

The favourable health profiles of women who use oestrogens undoubtedly have contributed to the apparent protective effect of these drugs against cardiovascular disease and memory loss or dementia.

Methodological considerations in the interpretation of epidemiological studies

All possible reasons for discrepancies in the results of epidemiological studies must be considered critically. Broadly, the roles of chance, bias, confounding and biological susceptibility should be weighed before a final interpretation is made.

Chance: Many of the studies summarized clearly suffer from small numbers, particularly in relevant potential high-risk strata, e.g., with long-term exposure. All of the studies include associations with 'ever-use', but such analyses are rather uninformative and probably misleading, since the results become incomparable due to variations in exposure. Only a minority of the studies were large enough and had meaningfully large numbers of subjects in the long-duration sub-categories (e.g., Brinton *et al*., 1986; Ewertz, 1988; Bergkvist *et al*., 1989; Colditz *et al*., 1995; Newcomb *et al*., 1995; Persson *et al*., 1997).

Five meta-analyses of the combined results from several (but different) sets of studies were conducted to improve the statistical power of subgroup analyses (Armstrong, 1988; Dupont & Page, 1991; Steinberg *et al*., 1991; Sillero-Arenas *et al*., 1992; Colditz *et al*., 1993). Even these analyses arrived at different results: two failed to demonstrate an association between increased risk for breast cancer and long-term exposure. A collaborative re-analysis of most of the epidemiological evidence (Collaborative Group on Hormonal Factors in Breast Cancer, 1997), which included more studies with greater statistical power, showed a slight but significant relation between current long-term pre-menopausal use of oestrogens and breast cancer risk. Nevertheless, there was insufficient power to examine the association for users of regimens with progestogens only and for women with long duration of treatment in the distant past.

Biases: Non-differential measurement errors, e.g. imprecise classification of exposure to hormones, would be expected to attenuate (bias towards the null) any true association with the risk for breast cancer. For instance, in the collaborative re-analysis (Collaborative Group on Hormonal Factors in Breast Cancer, 1997), information on the hormonal constituents of the consumed drugs was available for only 40% of the subjects, indicating that there may be important heterogeneity with regard to compound types, regimens and schedules of exposure. Studies that provide precise measurements of the particular post-menopausal hormonal therapy used should, if there is a true link, achieve the most valid estimates.

More serious are biases that could systematically distort the results. In cohort studies, there is a possibility of surveillance bias, e.g. that subjects prescribed post-menopausal hormonal therapy more often undergo mammography (Barrett-Connor, 1991). Differential use of mammography was addressed in previous studies (Colditz *et al*., 1995; Persson *et al*., 1997) and studies performed within breast screening programmes (Brinton *et al*., 1988; Schairer *et al*., 1994; Persson *et al*., 1997), and a positive risk relationship

was seen. An additional complexity with regard to detection is the possibility that post-menopausal hormonal regimens enhance the density of the mammogram, depending on the treatment regimen (Persson *et al*., 1997), and reduce the sensitivity of mammography to detect small tumours (Laya *et al.*, 1996).

In case–control studies, a general concern is recall bias, meaning that affected women report exposure more accurately than do controls; however, there is some empirical evidence that differential misclassification by case–control status is not a problem (Goodman *et al.*, 1990). Bias in the selection of controls is another possibility in many of the cited studies. Hospital-based studies (e.g. Harris *et al*., 1992; La Vecchia *et al*., 1995; Levi *et al*., 1996; Tavani *et al*., 1997) may be inherently biased, since hospitalized control subjects may have conditions related to exposure to hormones (e.g. fracture cases would be expected to have less exposure to hormones). Valid selection of controls should follow the study base principle, i.e. that controls are randomly sampled from the population and time that generated the cases. Even when population-based controls are used, as in the random-digit dialling procedure (Wingo *et al*., 1987; Stanford *et al*., 1995), there may be selection of subjects with regard to exposure variables (Olson *et al*., 1992).

Confounding: It is clear that women taking post-menopausal hormonal therapy have anamnestic or behavioural features that may correlate with the risk for breast cancer (Barrett-Connor, 1991). Ethnicity and socioeconomic status are possible confounders. Obesity, linked to less use of hormones and to increased risk for post-menopausal breast cancer, and alcohol consumption (Rosenberg *et al*., 1993) are examples of life-style factors that could be confounders. Time of natural or surgical menopause (oophorectomy) is a particularly important determinant of breast cancer risk and also of use of post-menopausal hormonal therapy (Colditz, 1996). The type and time of menopause and reproductive factors are crucial possible confounders.

The approaches used to deal with confounding have varied, particularly with regard to the variables of menopause (Pike *et al*., 1998). One difficulty is classification of the menopausal status and age of women who have had a hysterectomy (without oophorectomy) or who started hormone use before the cessation of natural menses. In the collaborative analysis (Collaborative Group on Hormonal Factors in Breast Cancer, 1997), women of unknown age at menopause were excluded (18% of all subjects), implying that a substantial number of women who used bleeding-provoking oestrogen–progestogen regimens were not included in the analyses. Confounding by indication—the reason for treatment—is difficult to rule out; however, it is reasonable to believe that menopausal symptoms or osteoporosis would be associated with low levels of endogenous oestrogens.

All of these issues relate to the validity of the results of the individual studies. The approaches used to deal with aspects of validity vary among the studies, and this heterogeneity may be an important explanation for the inconsistencies among studies. A critical evaluation of validity is therefore basic to an interpretation of the results of any study.

Biological interpretation: As mentioned above, one reason for differences among the results may be the lack of sufficiently large numbers of women exposed for long enough

sufficiently long ago, i.e. effects of both duration and latency. Even the collaborative analysis (Collaborative Group on Hormonal Factors in Breast Cancer, 1997) suggests that the number of women with such exposure is insufficient.

Even if issues of validity are properly addressed and the risk relationships are analysed in comparable ways, there may still be true differences in the effects of hormones on breast cancer development, due to differences in susceptibility factors. A number of such factors are considered in the monographs, e.g. obesity, ovarian status, age at diagnosis, use of combined oral contraceptives, reproductive factors, alcohol consumption, cigarette smoking, benign breast disease and family history. The only factor shown in several studies to modify the effects of hormones on the risk for breast and endometrial cancer is body mass (Brinton, 1997; Collaborative Group on Hormonal Factors in Breast Cancer, 1997). Hypothetically, differences in the degree of obesity in some study populations in the United States (Colditz *et al*., 1995; Newcomb *et al*., 1995; Stanford *et al*., 1995), as compared with those in European studies (Ewertz, 1988; Bergkvist *et al*., 1989; Persson *et al*., 1997), could explain the inconsistent results. A definite difficulty in most studies of interactive effects is lack of power due to small numbers within subgroups.

New, very large, rigorously designed studies are needed. The underlying hypothesis should be supported by the results of clinical or basic research on hormonal pathways and mechanisms.

Studies in experimental animals

The results of studies in experimental animals (mice, rats, dogs and monkeys) are a fundamental component of the evaluation of agents for carcinogenicity. The results of whole-animal bioassays ideally provide data on tumour incidence, type and multiplicity in relevant tissues and organs and potential mechanisms of carcinogenesis. The use of rodents (rats and mice) allows the formation of test groups comprised of sufficient numbers of animals to provide statistically meaningful comparisons among groups, multiple groups exposed to agents at different doses and testing of both males and females. A major additional advantage of animal bioassays is that individual compounds or combinations of specific compounds can be tested for carcinogenicity, which is not possible in most epidemiological studies.

In practice, however, for several reasons, there are limitations to the data. Thus, while experimental animals provide the advantages mentioned above, depending on the agents being tested, they may not be an appropriate surrogate for human exposure because of fundamental pharmacokinetic and/or toxicokinetic differences. In addition, there are no appropriate animal models of menopause; the only approach available, ovariectomized animals, is likely to be biologically different from spontaneous menopause. The manner in which humans and test animals are exposed could lead to significant differences in carcinogenic effects. For example, test animals are generally exposed in the diet at constant doses. With sex hormones in particular, humans may be exposed to oestrogen–progestogen combinations in ratios that vary at different times during the month. Such a pattern of exposure is not generally used in bioassays. In addition, the doses used are

generally high, and non-physiological metabolism of such high doses raises concern about potential toxicity that may compromise the responses.

In these monographs, only results available in the public domain, principally the peer-reviewed literature, are used in the evaluations. Published studies were not necessarily designed for the purpose of providing a comprehensive bioassay: frequently dose–response data were not obtained, the group sizes were not optimal and not all tissues were evaluated for the presence of tumours, thus reducing the sensitivity of the study. Furthermore, the final evaluations and classifications of carcinogenicity require that such agents produce malignant tumours in at least two species and/or each sex and/or more than one tissue/organ system. Because of these considerations, the Working Group tried to be as selective as practical in choosing studies for evaluating the carcinogenicity of oestrogens and progestogens.

Hormonal activitivy in relation to human carcinogenesis

The two main categories of compounds in oral contraceptives and post-menopausal hormonal therapy have either oestrogenic or progestogenic effects: in some cases, overlap of biological activities occurs. The relevance of the effects of oestrogens and progestogens to carcinogenic effects in humans varies with the target tissue. The main human tissues affected are breast, endometrium, cervix and ovary, with minor effects on the liver and colon. Only in the endometrium is there a clear-cut hypothesis about the molecular events that cause oestrogens to increase cancer risk and progestogens to antagonize the effects of oestrogens. These changes can be modelled in terms of receptor-mediated hormone effects on cell proliferation (King, 1997), but the genotoxic effects of oestrogen metabolites may also be important (Yager & Liehr, 1996). In the breast, it is clear that exposure to oestrogens increases cancer incidence, but whether progestogens have a stimulatory, inhibitory or benign role is unclear (Key & Pike, 1988; King, 1993). In the ovary, some of the effects may be indirect, acting by altering ovulation rates. In the cervix, the mechanisms are more obscure: human papillomavirus (see IARC, 1995), an important contributory agent to cervical cancer, has a weak glucocorticoid or progestogen response element in its DNA which indicates a possible stimulatory mechanism (Villa, 1997). In the liver, the relation with infection by hepatitis viruses B and C (see IARC, 1994) has been little studied.

The majority of the above responses can be explained by oestrogen and progestogen receptor mechanisms (King, 1991), but non-receptor processes may also exist (Duval *et al*., 1983; Yager & Liehr, 1996). Cell proliferation may be the most important receptor-mediated mechanism by which hormonally active compounds act in carcinogenesis at hormone-sensitive target tissues. Cell proliferation is fundamental to the process of carcinogenesis; it is an essential (co)factor and enhances cancer incidence (i.e. tumour promoting) by preferentially stimulating the growth of genetically altered and preneoplastic cells (Preston-Martin *et al*., 1990). Most if not all steroid hormonal stimulation of cell proliferation involves autocrine and paracrine events secondary to the steroid–hormone receptor complex interaction with hormone-response elements in the promoter region of relevant genes; this has been shown for breast and endometrial epithelium (Boyd, 1996; Snedeker

& Diaugustine, 1996). Exposure to certain hormones can result in the production of reactive intermediates which, either *per se* or via secondary generation of reactive oxygen species, can cause genetic damage in some tissues under certain conditions (Yager & Liehr, 1996). The significance of this property is not clear. The following approximations indicate how the doses of hormones used in experimental studies relate both to receptor and non-receptor mechanisms and to the doses achieved *in vivo* with oral contraceptives or post-menopausal hormonal therapy. In humans, the doses of hormones in oral contraceptives and post-menopausal hormonal therapy are usually in the low range of micrograms per kilogram body weight per day, which generate plasma hormone levels of nanograms (progestogens) or picograms (oestrogens) per litre (Orme *et al*., 1983; Barnes & Lobo, 1987). These are the concentrations at which receptor-mediated events can be saturated *in vitro*. At appreciably higher concentrations, non-receptor mechanisms, such as induction of genetic damage, become detectable. It should be borne in mind that at concentrations of micrograms per millilitre, these compounds can have surfactant effects (Duval *et al*., 1983). As stated earlier, the significance of these non-receptor-mediated mechanisms is not clear; however, genetic and related effects in experimental systems have been reported by Vickers *et al*. (1989) (ethinyloestradiol plus a potent carcinogen) and Topinka *et al*. (1993) (cyproterone acetate) with doses relevant to use of oral contraceptives or post-menopausal hormonal therapy. In addition, Ghosh and Ghosh (1988), Pinto (1986) and Olsson *et al*. (1991a,b) observed genetic damage in women taking contraceptives or post-menopausal oestrogen therapy. Other factors involved in the carcinogenic process may also be involved in carcinogenic responses to hormones (Barrett & Tsutsui, 1996).

The changes made in the composition and mode of delivery of contraceptives were driven primarily by requirements for adequate contraception and minimization of side-effects, including those involving cardiovascular function. Effects on cancer development have not been a major consideration, especially as observations of effects may require extended use. For this reason, it is unclear how recent modifications in the composition and mode of use of contraceptives will affect cancer incidence. It is reasonable to expect that, because of these changes, the effects of contraceptives and post-menopausal hormonal therapy will have to be reviewed again in the future.

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