Adverse Effects of Chemicals on Male Reproductive Function in Mammals

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1 INTRODUCTION

The two topics relating to male infertility caused by chemicals, namely:

(1) the effects of pharmacological and other chemical agents on the testis, male accessory organs, ejaculation and spermatozoa, and

(2) the criteria used in the evaluation of changes produced by these agents,

are described and discussed below in a general manner only. A more detailed account of current research aimed at solving the complex mechanisms which underlie the action of antifertility agents, and the means of quantitatively appraising the adverse effects, can be found in our recent monograph on Male Reproductive Function and Semen. Themes and Trends in Physiology, Biochemistry and Investigative Andrology (Mann and Lutwak-Mann, 1981) and in several review articles dealing with specific groups of chemicals (Thomas, 1975; Neumann et al., 1976; Gomes, 1977; Lucier et al., 1977; Thomas et al., 1977; Patanelli, 1978; Dixon and Lee, 1980; Dougherty et al., 1980; Davies, 1980; Amann, 1981).

2 EFFECTS ON TESTIS, ACCESSORY ORGANS, EJACULATION AND SPERMATOZOA

2.1 Hallucinogens, Opiates, Amphetamines, Cocaine and Alcohol

Sexual inadequacy has long been known to drive men to hallucinogens and psychedelic drugs, in hopes that they can thereby enhance their libido and sexual gratification. But it is equally recognized that addiction to substances such as the opiates, leads to an opposite effect, that is, an actual decrease in sexual desire and performance. On this subject there is a fast growing literature, and apart from opiates many other hallucinogenic agents, such as LSD (d-lysergic acid diethylamide), mescaline, psilocybin, cannabis derivatives and 'ayahuasca'
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among others, have been receiving increasing attention (Mann, 1968, 1970; Emboden, 1979). We have as yet much to learn about the mechanisms underlying the action of all these hallucinogens; concerning the last-mentioned ‘ayahuasca’ (Banisteria caapi), its hallucinogenic properties are supposedly derived from the presence of harmine and harmaline which by inhibiting monoamine oxidase, can lead to the accumulation of endogenously synthesized biogenic amines, such as epinephrine and norepinephrine. A direct inhibitory effect on monoamine oxidase is also at the basis of the action of some other potent pharmacological agents, and in particular certain psychopharmaceuticals such as phenelzine; by inhibiting monoamine oxidase, this drug interferes with the normal metabolism of biogenic amines, such as norepinephrine, dopamine, tryptamine and serotonin (5-hydroxytryptamine).

As in the case of narocotics and hallucinogens, there is evidence for the existence of a relationship between amphetamine dependence and sexual inadequacy (real or imaginary) in men. Though occasionally they stimulate libido, on the whole, amphetamine compounds tend to reduce the standard of the mating performance, and in this respect there is some, though admittedly not close, similarity between amphetamines and cocaine. The latter often enhances male sexual desire but at the same time reduces sexual power. It is important to bear in mind that men as well as animals exhibit a wide range of individual responses to drugs such as amphetamine, cocaine and morphine. This particularly applies to the action of these agents on the ejaculatory process. For example, in mice the extent to which morphine depresses contractions of the vas deferens and thereby inhibits the ejaculatory process is strain dependent; less morphine is required to suppress the contractions of the deferent duct in the TO, than in the C57/BL strain (Henderson and Hughes, 1976).

Excessive alcohol consumption by men is frequently associated with failure to achieve or maintain erection and a generally reduced sexual performance. The impotence pattern in the alcoholics has long been recognized by physicians and laymen, and it has been frequently expressed in the literature, as for example, in Macbeth, Act II, Scene III, where the porter thus answers Macduff’s enquiry about the effect of ‘drink’: ‘Lechery, sir, it provokes and it unprovokes; it provokes the desire, but it takes away the performance.’ Animals don’t seem to differ in this respect from man, and experiments on male rats inhaling alcohol or ether vapours have demonstrated clearly that erection, ejaculation and copulatory behaviour are all adversely affected. Moreover, there are indications that the deleterious effects express themselves in a reduced survival rate of progeny; in mice, progeny number and survival rate were shown to be distinctly lower in litters sired by ethanol-treated males than in controls (Badr and Badr, 1975; Anderson et al., 1978). A respectable amount of work has also been done on effects of alcohol on testosterone clearance; consumption of alcohol by men elevates the metabolic clearance rate of testosterone, concomitantly with increased activity of the enzymatic system responsible for the aromatization of
testosterone to oestradiol; hence the increased risk of gynaecomastia (Gordon et al., 1976). Testicular atrophy and a high percentage of sperm abnormalities in semen are another frequently encountered findings in chronic alcoholics (Van Thiel et al., 1979).

2.2 Industrial Chemicals

Among substances which influence adversely testicular function and the output of spermatozoa in semen, industrial and therapeutic chemicals rank high in importance. Many of them produce germinal aplasia, oligospermia, azoospermia and also a decrease in testosterone formation; they are furthermore responsible for failure of erection, ejaculatory disturbances and other symptoms of deficient male reproductive function.

Industrial chemicals with such properties include a wide range of insecticides, herbicides, fumigants and other pesticides, flame retardants and petrol additives. Some of them affect the testes and male accessory organs directly, some influence the metabolism of other organs as well, and as regards failure of erection and ejaculation, which has been reported for instance in agricultural workers handling herbicides and pesticides, these chemicals act on the parasympathetic and sympathetic nervous system and thereby influence the mechanism of central nervous transmission. Organochlorine and organobromine compounds constitute a particularly serious hazard to the male on account of their antifertility, mutagenic, carcinogenic and in some instances, oestrogenic properties, aggravated by easy absorption through the skin and accumulation in tissues. Polychlorinated biphenyls (PCB) which are employed in the manufacture of plastics, lubricants and flame-retardant synthetic fibres, quickly penetrate the workers’ protective clothing. High permeability of the skin and storage capacity in the tissues (fat in particular) are also characteristic of polybrominated biphenyls (PBBs), about which much has been heard since the Michigan incident in 1973 (Chen, 1979) when several thousand pounds of PBBs, inadvertently mixed into livestock feed, caused the death of large numbers of farm animals. An even more tragic event occurred in Italy, in 1976, when ‘dioxin’, another toxic chlorine compound, was accidentally discharged from the trichlorophenol reactor over a large populated area in Seveso, causing much hardship to adults and children, and necessitating prolonged large-scale evacuation of this region.

Arrest of spermatogenesis and severe degenerative changes in the testes are characteristic of the effects produced by a number of other chlorine and bromine organic industrial chemicals in men and animals. In this category are dibromochloropropane (soil fumigant against nematodes), dibromopropanol (the mutagenic derivative of Tris-BP) and dibromoethane (a petrol additive and a fumigant used in controlling grain insects and for disinfecting seed, tobacco and food in storage). Similarly dangerous are insecticides such as DDT (dichlorodiphenyl trichloroethane), and herbicides such as the defoliating tri-
chlorophenoxyacetic acid. Many other substances have also gained much attention in recent years as potential antifertility and mutagenic agents. Of special concern are in this respect Tris-BP (tris[2, 3-dibromopropyl]phosphate) and the chemically closely related tris[dichloropropyl]phosphate, since flame retardants speedily penetrate the skin of the human scrotum.

As regards insecticides, several organophosphorus compounds belonging to this group have been shown to be powerful inhibitors of choline esterase; and parathion, the extremely toxic phosphothioate analogue, was shown to be an effective inhibitor of testosterone metabolism in the liver. Testicular atrophy and in some instances involution of the male accessory organs have been observed in animals after the application of a good many other industrial chemicals, notably carbamate insecticides which inhibit choline esterase, paraquat and ethylene oxide cyclic tetramer (endowed with chelating properties).

2.3 Chemotherapeutic Drugs

Pronounced antifertility properties attributable to either spermatogenic failure or inhibition of steroidogenesis in the testis, are typical of a wide range of chemotherapeutic drugs. Niridazole, the schistosomicidal drug is a strong suppressor of the meiotic division of the spermatocytes. Cyclophosphamide, the cytostatic drug used effectively in the treatment of lymphoma, acute lymphocytic leukaemia and nephrotic syndrome, frequently produces germinal aplasia and azoospermia in patients on immunosuppressive therapy, especially when used in combination with other cytostatic agents. Cimetidine, which is widely used in the treatment of peptic ulcer disease, acts both as antiandrogen and antispermatic agent; it lowers the output of spermatozoa in the human ejaculate and in some cases produces impotence and gynaecomastia; in male rats it inhibits competitively the binding of dihydrotosterone to cytoplasmic receptors in the ventral prostate and seminal vesicle.

2.4 Psychopharmaceuticals

Among the antipsychotic, antianxiety and antidepressant drugs belonging to this group and available for the treatment of emotional disorders, there are several that affect male reproductive function. Thioridazine and chlorpromazine have been reported to interfere with ejaculation, to weaken erection and delay ejaculation in men. Reserpine, another antipsychotic drug, inhibits ejaculation, though by no means consistently. Men treated with reserpine frequently complain of loss of libido, and some also exhibit feminization symptoms, probably due to changes in the neuroendocrine activity of the brain (the hypothalamus in particular) and interference with the biosynthesis, storage and release of biogenic amines. As regards the antianxiety and antidepressant agents, failure of ejaculation has been described in men treated with chlordiazepoxide;
some of the hydrazide derivatives have also been shown to possess anti-ejaculatory properties.

2.5 Antispermaticogen, Antiandrogenic and Spermicidal Agents

Broadly speaking, antispermaticogen agents fall into three groups, namely those acting on the mitotic, meiotic and postmeiotic stage of sperm development, but on close examination some of these substances affect several stages, pending on dosage and conditions of treatment. Colchicine acts mainly on mitosis, whereas two-phase sterility is typical of certain alkylating agents such as tretamine (2, 4, 6-triethyleneiminotriazine). Nitrofurane derivatives ingested by mice or rats inhibit predominantly the primary spermatocyte stage of spermatogenesis, but they can also destroy spermatogonia. Nitropyroroles are capable of interfering with the primary spermatocyte stage and the spermatid transformation.

Testosterone itself, notwithstanding the fact that it is a normal product of the testis and essential for spermatogenesis and function of the male accessory organs, when administered in suitable doses, can successfully suppress spermatogenesis and thereby produce oligospermia or temporary azoospermia. It is because of this antispermaticogen activity that testosterone, along with certain other steroids such as danazol or various progestational steroids, has been considered for use as a male contraceptive (Patanelli, 1978). These suppressive effects on the testis are, however, not the result of a direct interaction with the testis, but the outcome of inhibitory influence on the gonadotrophic function of the pituitary gland. The same is true of certain oestrogens, steroidal and nonsteroidal (e.g. diethylstilboestrol) which act mainly via the pituitary gland. In this respect, however, there are notable exceptions, and oestrogens in particular can produce inhibitory effects by acting on the testis directly. The antispermaticogen action of methallibure is mediated by the pituitary gland, and the same applies to certain siloxanes and chlormadinone, as well as the new synthetic agonists of the hypothalamic gonadotropin-releasing hormone, which when injected in suitable doses over a period of several weeks, strongly inhibit spermatogenesis.

Quite distinct from the pituitary-mediated mechanism of action exerted by testosterone and other steroids on the testis, is the mode of action of the so-called antiandrogens. Cyproterone acetate, methyltestosterone and other antiandrogens act at the level of target organs, be it the testis, prostate, seminal vesicle or other organs. Their principal action depends on competing with testosterone and dihydrotestosterone for androgen receptors. By blocking access to testosterone and dihydrotestosterone, the antiandrogens prevent the Sertoli cells in the testis from forming normal secretory products such as the androgen-binding protein, and they prevent the male accessory organs from carrying out their normal secretory function, expressed in the formation of fructose, citric acid and other chemical constituents of the seminal plasma.

Concerning the mechanism of action of drugs which interact directly with
spermatozoa, distinction must be drawn between substances which, when acting on spermatozoa in vitro, immobilize them reversibly, that is temporarily, and can therefore be designated as spermiostatic, and other agents, more properly called spermicidal, which incapacitate the spermatozoa permanently (Mann, 1958, 1964). Enzyme inhibitors, such as sodium fluoride, are on the whole spermiostatic, provided that their contact with the sperm cell is not a prolonged one; when fluoride is removed from the spermatozoa in good time, motility recovers. Many thiol reagents and most detergents, on the other hand, particularly when applied in high concentrations, are spermicidal in the full sense of the term; the structural and biochemical changes which they induce, such as disruption of the sperm plasmalemma or the leakage of intracellular enzymes and coenzymes, cannot be reversed. But in some instances the adverse effects of these substances can be prevented by advanced application of certain protective agents. Thus, for example, the antiperoxidant factor which we detected in the seminal plasma, effectively protects the spermatozoa from the lethal effects of unsaturated fatty acid peroxides (Jones et al., 1979; Mann et al., 1980), and sulphhydryl-containing substances such as reduced glutathione, cysteine or ergothioneine can protect the spermatozoa from the spermicidal effect of certain heavy metals.

Among heavy metals, copper and mercury (inorganic and organically bound) have strong spermicidal properties. Systemically introduced cadmium also constitutes a hazard to testicular function as clearly demonstrated by Pařízek (1956, 1960), but the available evidence favours the view that the destructive influence of cadmium on the seminiferous epithelium is caused primarily by ischaemia and necrotic changes due to interference with testicular vascularization and breakdown of the blood–testis barrier. In line with this concept are some observations on the countereffects of selenium which protects the testis from the injurious effects of cadmium. Apart from the seminiferous tubules and spermatogenesis, cadmium damages also the interstitial tissue; in the hamster, a single injection of 1 mg CdCl₂ produces a marked reduction in the content of testosterone, dihydrotestosterone and other steroids in both the testis and the blood (Lau et al., 1978).

Of the many other substances with either antispermaticogenic or spermicidal properties, two have received exceptional attention in recent years. One is gossypol and the other α-chlorohydrin. As a result of extensive clinical trials, conducted mainly in China, gossypol, a disesquiterpene aldehydic constituent of cottonseed oil, has been recommended in that country as a male antifertility agent; after 20 mg/day, orally given for 2 months, most men had a sperm count below 4 million/ml or showed necropermia. The mechanism of the antispermaticogenic action of gossypol and the various general side effects resulting from its ingestion, are still under investigation; gossypol is also known to immobilize human spermatozoa in vitro, but at concentration levels (5–40 mg/ml) which are far in excess of doses effective in vivo (Waller et al., 1981). Chlorohydrin acts on the spermatozoa primarily in the epididymis, as shown by
experiments on rats; the toxicity of chlorohydrin precludes its testing in man. Two enzymatic reactions in the spermatozoa seem to be specially sensitive to chlorohydrin; one involving glycerol kinase, and the other glyceraldehyde-3-phosphate dehydrogenase. Other competitive inhibitors of sperm enzymes include a variety of antimetabolites, such as deoxyglucose and chlorinated sugars.

3 METHODOLOGICAL CRITERIA IN THE APPRAISAL OF DAMAGE INDUCED BY CHEMICALS IN THE MALE REPRODUCTIVE TRACT AND SEMEN

3.1 The in Vitro Fertilization Test

The ultimate test of male fertility is the ability of the spermatozoon to fertilize the egg cell and to produce healthy offspring. The quickest way to assess the fertilizing ability of the spermatozoon under laboratory conditions is to perform the fertilization test in vitro. This procedure is now extensively utilized in investigations with the gametes of laboratory animals, and it has been suggested that it may form a basis for exploring the effect of drugs that interfere with the process of sperm penetration and fertilization. For example, fertilization of a freshly procured mouse egg with zona pellucida intact, by a mouse spermatozoon, can be inhibited (in vitro) in a dose-dependent fashion by some cholinomimetic agents (Florman and Storey, 1981). However, a test of this kind could hardly be routinely applied to human eggs, not merely because they are not readily available, but also because their use for laboratory experiments may conflict with ethical views. It is noteworthy that in vitro human spermatozoa are capable of fusing with the vitelline membrane of zona-denuded hamster eggs and are subsequently capable of undergoing decondensation, and this observation gave rise to the suggestion that hamster eggs could be used for assaying the fertilizing potential of human spermatozoa (Barros et al., 1979); zona-free eggs of the hamster also fuse with spermatozoa of other animals, e.g. those of the guinea pig and boar, the latter being able to fuse only after they have undergone the acrosome reaction, which is a normal prerequisite of fertilization (Imai et al., 1980).

So far, the reproducibility of the hamster-egg in vitro test as a method of assaying fertility in individual men has been investigated only on a small scale (Bentwood et al., 1981), but its clinical practicability for drug screening certainly deserves further exploration.

3.2 Evaluation of Testicular Function

Testicular biopsy is not free of hazards. None the less, histological analysis of tissue specimens obtained by this method has been recognized for some time as a
helpful procedure for diagnosing spermatogenic failure and assessing the extent of damage inflicted upon the testis by antispermatogenic agents. The quantifiable histological techniques involving light microscopy are now being supplemented by electron microscopic assays. In addition, as a result of the perfection of chemical methods of androgen analysis (radioimmunoassay in particular), testicular biopsy specimens are increasingly used for determinations of testosterone and other testicular steroids, and also for exploring the ability of the testicular tissue to synthesize testosterone in vitro from added labelled precursors. Another frequently employed method of assessing the endocrine function of the testis, and the androgenic status of the male as a whole, depends on measuring testosterone in blood plasma. However, in view of the large fluctuations in the blood testosterone level of man and animals, sporadic analyses of blood plasma are of little value, since the results are strongly influenced by the episodic, circadian and seasonal variations in the pattern of testosterone release by the testis, also by the age of the individual, schedule of blood sampling, the amount of luteinizing hormone available to the testis around the time of blood sampling, and nutritional and environmental factors (the phototropic stimuli in particular). An additional factor that must be carefully considered in evaluating the results of androgen analysis in blood is that under normal conditions only a small proportion of testosterone is in a free, that is, active form, and the major part is protein bound.

A variety of testis-specific proteins and enzymes has been described in man and animals, and their appearance in the normally developing prepubescent testis has been shown to coincide with specific stages of spermatogenesis, that is, the appearance of primary spermatocytes, secondary spermatocytes, spermatids and testicular spermatozoa (still immotile and infertile). Enzymes in this category are the testis-specific LDH-X isozyme of lactate dehydrogenase, acid phosphatase, esterase, sorbitol dehydrogenase and various glycosidases, peptidases and proteases. These findings gave rise to the idea that enzymes of this kind could be used as biochemical markers or ‘fingerprints’ of particular steps in the spermatogenic process, not merely in the normal testis, but also in gonads with abnormal spermatogenesis. It remains to be seen how far enzymatic fingerprinting, along with other methods, such as histochemical and autoradiographic techniques, can be developed for assessing the adverse effects of chemicals on spermatogenesis.

For the moment, direct examination of the ejaculated semen provides the simplest and most reliable means of assessing the degree of damage inflicted by an antispermatogenic agent on testicular gametogenic function. The volume of the ejaculate, the concentration and total number of spermatozoa in that ejaculate, the relative proportion of motile and immotile spermatozoa and the ratio between live and dead sperm cells (assessed by live-dead differential staining procedures), the degree of motility (assessed microscopically or by physical means), and the type and percentage of abnormal spermatozoa, along
with related tests such as the cervical mucus penetration and postcoital tests, offer the best chance of evaluating the effects of drugs on gametogenic function, provided of course, that several factors are taken into account. Time interval since the previous emission of semen, frequency of ejaculation, microbial contamination of semen, and the method by means of which semen has been collected and stored prior to examination, all these and other factors have to be considered in the appraisal of semen quality. Above all, whilst considering the adverse effect of a drug on spermatogenesis, one must bear in mind the fact that the injury to the testis might have occurred as long as 2 months prior to the time of semen collection and examination, in view of the period of time required for completion of spermatogenesis in the testis and sperm passage (and maturation) in the epididymis.

It is possible that in the future hormone analyses in ejaculated semen will become part of the routine examination of semen for assessing defects in the androgenic status of the male. Testosterone, dihydrotestosterone, follicle-stimulating hormone, luteinizing hormone, a chorionic-gonadotrophin-like hormone, prolactin, these and other hormones occur in the seminal plasma of man and animals (for recent literature see Eiler and Graves, 1981; Mann and Lutwak-Mann, 1981; p. 135, this paper).

3.3 Evaluation of the Functional State of Male Accessory Organs

When semen is collected by the split-ejaculate method, it is frequently possible to obtain several fractions of the ejaculate, originating in different and distinct parts of the male reproductive tract, such as the epididymis, seminal vesicle, prostate, Cowper's gland and urethral glands. In man, the determination of the activity of acid phosphatase and the concentration of citric acid and zinc provides a sensitive criterion of the prostatic secretory activity, whilst that of fructose, lactoferrin and prostaglandins, among other substances, can serve as a criterion for assessing the secretory output of the seminal vesicles. Carnitine and glycercylphosphorylcholine are sometimes used for determining the contribution of the epididymal secretion, but in man the usefulness of glycercylphosphorylcholine as an indicator of the epididymal secretory function is limited by the occurrence of this substance also in the seminal vesicle secretion.

The secretory output of male accessory glands of reproduction and consequently the composition of the seminal plasma are both strictly dependent upon androgenic stimuli emanating from the testis, and therefore, chemical analyses of either whole semen or even more so, of a split ejaculate, can be used for diagnosing effects of androgen deficiency on male reproductive function in a number of species, amongst them the bull, boar, stallion, rabbit and deer. Chemical analyses of semen and seminal fractions can also serve to diagnose degenerative changes in distinct parts of the male reproductive tract, such as inborn occlusion of the ejaculatory duct and deferent duct in cases of cystic
fibrosis. Chemical methods of semen analyses also help to express in a
quantitative manner the effects of drugs on the output of individual male
accessory glands of reproduction, as demonstrated for example, by the
investigations of the action of pilocarpine and atropine (Mann and Lutwak-
Mann, 1976).

3.4 Drug-induced Disturbances in the Ejaculatory Process

Earlier on in our paper, examples were given of drugs which influence adversely
errection and ejaculation. Underlying this pathology are probably faults in the
autonomous nervous mechanism which controls the contractile pattern of the
male reproductive tract. Normally, ejaculation is initiated by strong contraction,
probably starting in the ductuli efferentes of the testis, and quickly spreading
along the entire length of the tract, when first the prostate, next the ampullae and
finally the seminal vesicles contract in an orderly fashion, thus predetermining
the chemical character of the various seminal fractions which constitute the split
ejaculate. In man, the secretion of Littré’s (urethral) and Cowper’s (bulbourethral)
glands precedes the ejection of the prostatic secretion, which is then followed
by the spermatozoa and finally, the seminal vesicle secretion. Chemical analysis
of the seminal fractions by the split-ejaculate method enables one to decide
whether the ejaculatory pattern is normal, slightly upset or seriously disturbed.
In extreme cases of ejaculatory sterility, semen is ejaculated into the bladder, and
this state of retrograde ejaculation is best diagnosed by urine analysis; collection
of spermatozoa from urine is sometimes useful in connection with artificial
insemination.

Ejaculation disturbances are also encountered in animals, as for example, in
the stallion, in which ejaculation is a fairly prolonged process, enabling one to
collect several distinct seminal fractions. Combined analyses of citric acid
(coming from the seminal vesicles) and ergothioneine (a secretory product of the
large ampullary glands) in split ejaculates of stallions with ejaculatory distur-
bances have shown that in some such animals the citric acid appears in the
ejaculate before instead of after the spermatozoa and ergothioneine (Mann,
1975).

3.5 Passage of Chemicals into Semen

Alcohol, salicylates and sulphonamides, to name but a few, pass after ingestion
into human and animal semen. The same is true of ampicillin, erythromycin and
other antibiotics, but it is possible that in some studies leading to the detection of
drugs in semen insufficient care may have been exercised to exclude con-
tamination of semen by traces of urine. Tetracycline and thalidomide together
with its metabolites, also readily find their way into semen; having passed into
the semen, thalidomide becomes firmly attached to the spermatozoa (Lutwak-Mann et al., 1967).

Methadone, phenytoin, valproic acid, tranexamic acid, urea and selenite provide further examples of substances capable of passing into semen. A recent addition to this list is tris[dichloropropyl]phosphate, above-mentioned as one of the flame retardants with mutagenic and antifertility properties (Hudec et al., 1981). Detection of unusual chemicals in semen is made easier nowadays by the perfection of sensitive chemical methods. Compounds that may have escaped detection, even by gas chromatography–mass spectrometry, can now be screened in human and animal seminal plasma by more sophisticated means. Negative-chemical-ionization mass spectral screening used in the detection of tris[dichloropropyl]phosphate in extracts of human seminal plasma, provides a good example of the advantages that modern analytical techniques offer in investigations of drug passage into the semen.

4 CONCLUDING REMARKS

As this brief survey indicates, the information available to date on the mechanisms underlying the adverse effects of chemicals on male reproductive function is patchy and in need of more thorough documentation. Equally, the methodological criteria for appraising the damage induced by chemicals in the male reproductive tract and semen are too few and imperfect. These particular aspects of andrological pharmacology and toxicology, while still underdeveloped, represent an eminently attractive area for future research.

5 REFERENCES


Adverse Effects of Chemicals on Male Reproductive Function


