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RECENT ADVANCES IN DOPING ANALYSIS (4)

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DOPING CONTROL IN FLANDERS : FACTS, RESULTS AND STATISTICS[1]

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ABSTRACT

Since the application of the Flemish Antidoping Decree in 1987 nearly 14.400 athletes were unannouncedly controlled. 14.144 urine samples were analysed, the percentage of positive cases decreased from 7.2% in 1987 towards 4.5% in 1995. Most positive cases were found in cyclism and bodybuilding. The incidence of doping in other sports including soccer, volleyball, basketball and athletics was very low.

The statistical evaluation (1993-1995) of the hCG concentration in sportsmen and theophylline levels in athletes is used to establish a threshold value for these substances.

[1] This study was undertaken with the financial support of the Flemish Ministery of Health.

INTRODUCTION

Doping control in the Flemish region of Belgium is regulated by Decrees of the Flemish Government passed in 1987 and 1991 (1).
All athletes regardless of their nationality, preparing for or participating in a sport competition in Flanders are subjected to unannounced doping tests. The list of prohibited substances consists of seven classes including stimulants, narcotics, anabolic steroids, corticosteroids, beta blockers, diuretics and peptide hormones (and analogues). In any class each drug is specified, the list of forbidden stimulants e.g. contains 137 substances and 57 anabolic steroids are classified as forbidden compounds. The sentence "and related substances" from the IOC list is replaced by an additional paragraph in the Decree stating that the use of any substance in order to artificially increase the performance of the athlete and that could be harmful to his (her) physical or psychological integrity is not allowed.
In an attempt to harmonise the Flemish Antidoping Decree with IOC regulations, members of the Doping Commission regularly revise the list of forbidden substances resulting e.g. in removal of diphenoxylate and codeine in 1992. However there are still some differences between both lists. The testosterone-epitestosterone ratio e.g. is still limited to 6, but practically the Disciplinary Committee insists on the follow-up for T/E cases between 6 and 10. Another major difference is noticed for theophylline, a stimulant forbidden by the Flemish Antidoping Decree but allowed by the IOC.

Belgium is a federal country and the southern part also established an antidoping program. Unfortunately the practical application of this Decree is still not effective. One of the results of this discrepancy is that in 1995 major bodybuilder competitions moved from Flanders to the Walloon provinces and even some miles across the northern border in the Netherlands.

Nearly 85 physicians accredited by the Flemish Government are responsible for urine collection. Athletes are obliged to deliver at least 60 ml of urine. The sample is split, coded and sealed in the presence of the sportsman (woman). The A- and B-samples and the medication form are sent to the lab and 8 working days are allowed for reporting the results. When appropriate the athlete can ask for a confirmation test either in Gent or in Köln (Germany). A Disciplinary Committee decides on the penalties after hearing the dependant. An athlete found guilty of infringement of the doping control regulations is deemed ineligible for participation in all sports in Belgium for a period of 18-24 months. These penalties relate to the abuse of stimulants and anabolic steroids while the (first) use of ephedrines e.g. generally leads to less severe punishments.

RESULTS AND DISCUSSION

The numbers of samples analysed and the percentage of positive case in human sports during the period 1973-1995 are summarised in Table 1. From 1973 till 1986 the laboratory had a contract with the Belgian Cyclist Federation. The results during this period therefore mainly concern cyclists. Although widespread in sports and even for recreational use doping has always been associated with cyclism. Fatal cases due to the abuse of amphetamine in cyclists forced several European governments including France, Italy and Belgium to pass an antidoping act in 1965 afterwards resulting in the detection of the abuse of mainly amphetamine and metamphetamine in cyclists.

In the 1970's the medical or pseudo-medical environment of cyclists was very inventive in attempts to circumvent positive doping tests till the elaboration of a detection method for methylphenidate and phacetoperan (2) resulting in the first reports world-wide of positive cases for these drugs during several classical races in Belgium in 1974. The incidence of positive cases therefore increased from 1.7% in 1973 towards 7.5% in 1974.

Afterwards, professional cyclists, apparently medically informed, started to abuse the rumouredly undetectable stimulant pemoline. However the applications of a confirmation method for pemoline (3) again resulted in several positive cases firstly reported by our lab in 1977. Afterwards the percentage of positive cases varied between 2 and 3% (cyclists) till the application of the Flemish Antidoping Decree in 1987 when 7% positive cases were found (all sports). Obviously the reason for this increase was unannounced doping control. Most positive cases were detected in cyclism and bodybuilding.

The number of controlled bodybuilders and the percentage of positive cases is summarised in Table 2. Doping is prevalent in bodybuilders and probably reflects the pattern internationally. Percentage positive cases of respectively 90% and 100% in 1990 and 1991 in amateur federations are demonstrative. Moreover several athletes belonging to an association (NCOB) claiming to be free of anabolics were found positive.

From Table 3 it appeared that nandrolone, metenolone, testosterone and stanozolol were very popular steroids among bodybuilders. In particular metenolone has become one of the most popular anabolics, perhaps in an attempt to overcome detection or it has become known by word-of-mouth to be particularly effective. It also seemed that the pattern of misuse has to be traced to magazines as drostanolone and mesterolone are steroids with no obvious anabolic properties. As some of the abused steroids including methandienone, formebolone and oxandrolone are not marketed in Belgium and others like boldenone and trenbolone are not approved for human use, the existence of a black market trade should not be excluded.

Polysteroid abuse is common practice in bodybuilding with an actually provisional maximum of 7 different substances in a single urine sample (Table 4). Central stimulants with anorexic characteristics including fenfluramine, amphetamine, phentermine and amfepramone were also detected (Table 5). Diuretics are used by bodybuilders to achieve greater muscle definition by antagonising the subcutaneous water retention which is sometimes seen as a side effect of anabolic steroid use. Furosemide, hydrochlorthiazide and canrenone (spironolactone) seemed to be the most popular diuretics. During the last years the ß-agonist clenbuterol was found 35 urine samples from bodybuilders. Analysis of legally expired B-samples from the last quarter of 1991 revealed the presence of clenbuterol in the urine of several bodybuilders, one year before this repartitioner became notorious.

In Table 6 it is demonstrated that doping in Flanders is not widespread in volleyball, basketball, athleticism, soccer, handball, boxing and swimming. However, cyclism, the most favourite sport in this country, still suffers from the doping plague. Nearly 38 % of 5133 cyclists controlled during the period 1987-1995 belonged to the Official Belgian Cyclist Federation (Table 7). Generally forbidden substances were found in the urine of 7.2 % of the tested cyclists. This percentage is second to and far below the number found in bodybuilders but regardless disqualification, fines and suspensions, it is only slightly decreasing during the last years.
Although most of the positive samples were collected from athletes belonging to amateur federations, the discrepancy in percentage of positives between official and amateur federations was small when the number of fraudulent cases or refusals was taken into account.

From Table 8 it seems that the misuse of amphetamine and ephedrines is pronounced while prolintane, codeine and anabolic steroids were often detected.
The abuse of nandrolone is decreasing since 1991, the incidence of testosterone positives however is slightly higher after 1991. Contrary to what was found in bodybuilders, longacting anabolic steroids apparently are not popular among cyclists.
Polydrug abuse is also well known in cyclists as indicated in Table 9. Amphetamines in combination with anabolic steroids were found several times while polydrug abuse with pemoline and prolintane was also detected. However ephedrine and norephedrine alone or in combination with other doping substances were obviously popular among cyclists as they could be very helpful during the final stage of a race. Regardless their stimulant properties and irrespective the specific gravity and pH of the urine, threshold levels for ephedrine, pseudoephedrine and norephedrine were introduced by the International Cyclist Union. Neither pharmacokinetic nor pharmacodynamic evidence has been given to allow for urinary cut-off levels for ephedrines in athletes. Moreover it is well known that the excretion of basic drugs depends on the urinary pH (4) and the influence of the intake of large amounts of mineral water on the excretion of ephedrines has been well documented (5).

From Tables 8 and 9 it appeared that clenbuterol is not abused by or was not detected in cyclists. However the use of salbutamol, another ß-agonist increased during the last years. The Medical Commissions of IOC, UCI and also the Flemish Antidoping Decree tolerate the therapeutic use of this drug as an inhalator. Up to now no scientific studies allow to discriminate between the use of salbutamol by inhalation or by other administration routes. Anyway, salbutamol threshold levels have to be related to the analysis procedure. Indeed, nearly 50% of salbutamol is excreted as the sulphate conjugate and the concentration obtained using the mixed enzyme preparation SHP will substantially differ from the values found after hydrolysis with ß-glucuronidase. This argues for the necessity of standardising rigorously the analytical conditions before establishing an official salbutamol threshold.

Human chorionic gonadotropin is a glycoprotein that may be misused by athletes to stimulate endogenous testosterone production (6,7). It is rumouredly abused by bodybuilders at the end of their stacking regimen in order to counteract the feedback effect related to the abuse of anabolic steroids.

Based on hCG concentrations in urine samples from 1400 men, Laidler at al. (8) demonstrated that > 5.0 mIU/ml hCG in the urine of a male athlete is abnormal and they proposed a threshold level of 10 mIU/ml in nonconcentrated ultrafiltered samples.

From 1993 on using ABBOTT TDX equipment the hCG concentration (free and whole molecule-associated β - subunit) was screened for in 3805 male urine samples. It is well known that assay values from direct measurements of the urine specimens may result either from hCG or from non-specific interferences. However we found that potential contaminants can be easily removed by short centrifugation. In 1995 this procedure was for all samples with initial values > 2 mIU/ml. In that way 76 out of 90 urine samples with initial values > 2 mIU/ml appeared to contain less than 0.5 mIU/ml. However the values of positive hCG assays (55, 25 and 23 mIU/ml) did not significantly change after short centrifugation.

The distribution of the hCG values in 3805 urine samples is shown in fig. 1. Assay values ranged from 0 to 55 mIU/ml, the median was 0.48 mIU/ml. The distribution was non-gaussian, skewed to the left and only four of the data points had values > 5mIU/ml. A logaritmic transformation did not allow for useful satistical interpretation. However in applying a nonparametric form of analysis and ranking the results numerically the interquartile range (IQR) and the "far outside" value defined as [(3xIQR) + Q3] where Q3 is the third quartile line, i.e 75th percentile, were calculated to be 2.55 mIU/ml. The dispersal of the $\sqrt{x}$ values approached a gaussian distribution. The mean value was 0.5 mIU/ml. Adding 4 S.D. resulted in a threshold level of 4.72 mIU/ml. Obviously if we should have applied the short centrifugation step for the 1993 and 1994 samples even a lower value would be obtained.

Based on 1400 assays Laidler et al. (8) concluded that values greater than 5 mIU/ml were extremely unusual and proposed a decision limit of 10 mIU/ml. From our results based on

3805 determinations and using the same statistical evaluation a "far outside" level of 2.55 was calculated. A decision level of 5 mIU/ml therefore ensures with the greatest possible degree of certainty that no false positive result is reported.

Caffeine, theophylline and theobromine share in common several pharmacological actiona of therapeutic interest. They relax smooth bronchial muscle, stimulate the central nervous system, stimulate cardiac muscle and produce diuresis. Traditionally caffeine has been considered the most potent of the methylxanthines. However theophylline produces more profound and potentially more dangerous CNS stimulation than does caffeine. It is therefore surprising that Medical Commissions are reluctant to consider this drug as a forbidden substance. Anyway, theophylline is not allowed in sports in Flanders.

Based on a sedentary population of 200 subjects and 545 samples collected for doping analysis a threshold levels of 5 mg/ml was proposed two years ago (9). In the same study the proportion theophylline-paraxanthine (TP/PX) as an indicator for the intake of non-dietary theophylline appeared to be more reliable, the cut-off ratio was 0.3 .

The distribution of the concentration of theophylline in 3885 urine samples from controlled athletes is shown in fig 2. Theophylline levels above 0.25 µg/ml (LOQ) were found in only 1539 samples. A non parametic analysis of these values results in a " far outside value" of 2.25 µg/ml.

Taking into account that nearly 60 % of the 3885 samples did not contain theophylline or had a level below the detection limit for quantitation, a decision level of 5 µg/ml will certainly ensure that no false positive results are reported.

Statistical evaluation of the TP/PX ratio revealed a far outside value of 0.2.

A decision limit of 0.5 for TP/PX is therefore proposed.

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TABLE 1 : NUMBER OF SAMPLES ANALYSED AND PERCENTAGE POSITIVE CASES IN HUMAN SPORTS DURING THE PERIOD 1973 - 1995

Year	N	% positive	Year	N	% positive
1973	471	1.7	1985	945	2.1
1974	619	7.1	1986	134	2.2
1975	1149	3.5	1987	1048	7.2
1976	911	3.6	1988	1520	6.1
1977	1003	2.6	1989	1525	4.3
1978	916	1.3	1990	1629	6.1
1979	1013	2.7	1991	1733	6.3
1980	954	1.8	1992	1589	5.7
1981	859	1.6	1993	2018	6.6
1982	929	3.0	1994	1924	5.2
1983	923	2.4	1995	2038	4.5
1984	867	2.1			

TABLE 2 : NUMBER OF CONTROLLED BODYBUILDERS AND PERCENTAGE OF POSITIVE CASES (1988-1995)

	FEDERATION							
Year	IFBB		NABBA		WABBA		NCOB[b]	
1988	32	(22)a	-		-		-	
1989	16	(13)	-		-		-	
1990	16	(56)	6	(100)	20	(70)	-	
1991	20	(35)	28	(25)	21	(90)	30	(7)
1992	27	(52)	12	(92)	39	(41)	4	(0)
1993	51	(46)	48	(63)	46	(57)	15	(7)
1994	42	(36)	33	(39)	33	(61)	17	(18)
1995	30	(43)	5	(0)	14	(0)	19	(5)
Total	234	(38)	132	(51)	173	(55)	85	(8)

(a) the numbers between brackets stand for the percentage of positive cases

(b) federation founded in 1991

TABLE 3 : INCIDENCE OF DETECTED ANABOLIC STEROIDS IN URINE OF BODYBUILDERS DURING THE PERIOD 1988-1995

	YEAR								
Anabolic steroid	1988	1989	1990	1991	1992	1993	1994	1995	Total
Nandrolone	6	-	16	21	17	37	20	6	123
Metenolone	-	-	18	19	22	29	12	4	104
Testosterone	2	1	5	6	8	12	14	6	54
Stanozolol	-	-	-	7	4	8	14	5	38
Drostanolone	*	-	4	-	8	6	8	2	28
Oxymetholone	-	-	1	1	2	5	1	1	11
Mesterolone	-	-	2	1	1	2	2	1	9
Methandienone	-	-	2	-	-	4	2	-	8
Methyltestosterone	-	-	2	-	2	3	-	-	7
Oxandrolone	-	-	1	-	-	2	2	-	5
Formebolone	*	-	2	-	-	1	1	1	5
Boldenone	*	-	-	-	-	1	1	1	3
Trenbolone	*	*	*	*	1	-	-	-	1
Clostebol	-	-	-	-	-	1	-	-	1

* not screened for at that time

TABLE 4 : COMBINATIONS OF AT LEAST 4 ANABOLIC STEROIDS DETECTED IN URINE OF BODYBUILDERS (1990-1995)

Number of steroids	Combinations	
4	Metenolone - Testosterone - Methyltestosterone - Methandienone	(1)
	Metenolone - Nandrolone - Mesterolone - Drostanolone	(1)
	Metenolone - Nandrolone - Testosterone - Oxymetholone	(1) a
	Metenolone - Nandrolone - Drostanolone - Stanozolol	(2)
	Metenolone - Nandrolone - Drostanolone - Testosterone	(2)
	Metenolone - Nandrolone - Testosterone - Stanozolol	(1)
	Metenolone - Nandrolone - Testosterone - Oxandrolone	(1)
	Nandrolone - Testosterone - Drostanolone - Stanozolol	(1) b
	Nandrolone - Drostanolone - Stanozolol - Mesterolone	(1)
	Nandrolone - Testosterone - Methandienone - Stanozolol	(1)
5	Metenolone - Testosterone - Methyltestosterone - Oxymetholone - Formebolone	(1)
	Metenolone - Nandrolone- Testosterone - Stanozolol - Trenbolone	(1) b
	Metenolone - Nandrolone- Mesterolone - Stanozolol - Drostanolone	(1)
	Metenolone - Nandrolone- Drostanolone - Stanozolol - Testosterone	(1)
	Testosterone - Metenolone - Drostanolone - Stanozolol - Oxymetholone	(1)
	Testosterone - Nandrolone - Metenolone - Stanozolol - Formebolone	(1)
6	Metenolone - Nandrolone- Stanozolol - Testosterone - Boldenone - Oxandrolone	(1)
	Methandienone - Testosterone - Metenolone - Methyltestosterone - Oxymetholone - Mesterolone	(1)
7	Metenolone - Nandrolone - Stanozolol - Testosterone - Formebolone - Oxandrolone Methandienone	(1)

Figures between brackets refer to the number of such urine samples.

a in combination with clenbuterol, fenfluramine and canrenone

b in combination with clenbuterol

TABLE 5 : INCIDENCE OF DRUGS (OTHER THAN ANABOLIC STEROIDS) IN URINE SAMPLES OF CONTROLLED BODYBUILDERS (1990-1995)

	1990	1991	1992	1993	1994	1995	TOTAL
Clenbuterol	?	?	5	15	9	6	35
Canrenone [a]	-	2	6	2	7	-	17
Phentermine	-	3	5	4	-	2	14
Furosemide	-	2	3	3	4	-	12
Hydrochlorthiazide	-	2	4	2	-	1	9
Amphetamine	1	1	2	2	1	-	7
Amfepramone	1	2	-	3	-	1	7
Fenfluramine	-	1	1	3	1	-	6
Probenicid	-	-	-	1	1	-	2
Pemoline	-	-	-	-	-	1	1
Propranolol	-	-	-	-	-	1	1
Bumetanide	-	-	-	1	-	-	1

a Canrenone or spironolactone as the latter drug is completely metabolised and canrenone is found in the urine

TABLE 6 : NUMBER OF CONTROLLED ATHLETES AND POSITIVES IN DIFFERENT SPORTS IN FLANDERS (1987-1995).

Year	Athletism	Basketball	Boxing	Handball	Soccer	Swimming	Volleyball
1987	127(4)	60(3)	28 (3)	34 (0)	126(7)	65(0)	38(1)
1988	154(1)	72(3)	44 (0)	44 (0)	120(1)	23(0)	92(2)
1989	120(1)	36(3)	54 (2)	18 (0)	123(2)	60(1)	38(0)
1990	104(1)	32(3)	41 (2)	36 (1)	124(5)	43(0)	58(2)
1991	115(6)	34(3)	35 (2)	44 (1)	144(2)	61(3)	44(0)
1992	134(1)	16(3)	24 (0)	24 (0)	129(1)	49(0)	36(0)
1993	113(3)	40(3)	30 (0)	30 (0)	244(4)	50(1)	58(0)
1994	106(2)	100(3)	18 (4)	34 (2)	196(3)	38(0)	112(0)
1995	64(0)	71(3)	28 (4)	50 (2)	318(4)	45(1)	138(3)
1987-1995	1037(19)	461(17)	302(17)	314(6)	1524(29)	434(6)	614(8)

(a) number of positives between brackets

TABLE 7 : NUMBER OF SAMPLES COLLECTED, POSITIVE CASES AND REFUSAL OR FRAUD IN UNANNOUNCED DOPING CONTROL IN CYCLISTS (1987-1995).

Year	N samples		N (%) positives		N fraud/refusal		Total Positives (%)	
	a	b	a	b	a	b	a	b
1987	208	22	23 (11.1)	7 (31.8)	0	0	23 (11.1)	7 (31.8)
1988	231	233	19 (8.2)	48 (20.6)	1	2	20 (8.7)	50 (21.5)
1989	202	348	11 (5.4)	35 (10.1)	2	6	13 (6.4)	41 (11.8)
1990	194	456	10 (5.2)	32 (7.0)	2	6	12 (6.2)	38 (8.3)
1991	185	402	9 (4.9)	35 (8.7)	5	8	14 (7.6)	43 (10.7)
1992	213	387	13 (6.1)	19 (4.9)	2	5	15 (7.0)	24 (6.2)
1993	150	487	3 (2.0)	45 (9.2)	7	6	10 (6.7)	51 (10.5)
1994	233	423	11 (4.7)	24 (5.7)	3	2	14 (6.0)	26 (6.1)
1995	336	423	15 (4.5)	15 (3.6)	5	3	20 (6.0)	18 (4.3)
Total	1952	3181	109(5.6)	260(8.2)	17(0.9)	16(0.5)	141(7.2)	306(9.6)
	5133		369(7.2)		33(0.6)		447(8.7)	

a : official federation, b : amateur federations

figures between brackets refer to percentage

TABLE 8 : INCIDENCE OF SOME DOPING SUBSTANCES IN CYCLISTS (1987-1995).

	1987	1988	1989	1990	1991	1992	1993	1994	1995	Total
Ephedrine	6	18	21	20	22	13	15	10	5	130
Norephedrine	5	26	8	14	20	7	10	7	2	99
Nandrolone	15	29	8	13	12	4	6	6	6	99
Amphetamine	8	18	13	10	11	11	9	8	5	93
Prolintane	2	5	1	1	3	3	6	2	1	24
Pseudoephedrine	0	1	2	2	3	1	6	2	2	19
Testosterone	1	1	2	0	0	3	4	3	6	20
Pemoline	0	4	2	2	0	2	3	0	5	18
Codeine	0	0	0	0	0	6	6	a	a	12
Fencamfamine	-	3	3	1	2	-	0	0	-	9
Amfepramone	0	0	0	0	0	3	0	2	3	8
hCG	nd	nd	nd	nd	nd	nd	0	2	7	9
Theophylline	nd	nd	nd	nd	nd	nd	nd	2	5	5
Morphine	-	-	-	-	-	-	-	-	5	5

a: allowed since 1994

nd : not determined

TABLE 9 : INCIDENCE OF POLYDRUG ABUSE IN CYCLISTS (1992-1995).

Amphetamine + Ephedrine : 7
Amphetamine (Fenethylline) + Ephedrine + Nandrolone : 5
Pemoline + Ephedrine : 1
Prolintane + Norephedrine : 1
Amphetamine + Norephedrine : 1
Amphetamine + Metenolone + Norephedrine : 1
Amphetamine + Pemoline + Ephedrine + Prolintane : 1
Amphetamine + Pemoline + Ephedrine + Amfepramone + Codeine : 1

Amphetamine + Nandrolone : 2
Amphetamine + Testosterone : 1
Amphetamine + Testosterone + Prolintane : 1
Nandrolone + Pemoline + Morphine : 2
Nandrolone + Pemoline : 1
Nandrolone + Ephedrine : 1
Prolintane + Testosterone : 1
Amfepramone + Testosterone : 1
Fenfluramine + Amfepramone : 2
Prolintane + Pemoline : 1
Prolintane + Codeine : 1
Prolintane + Prethcamide : 1
Ephedrine + Pseudoephedrine + Codeine : 1

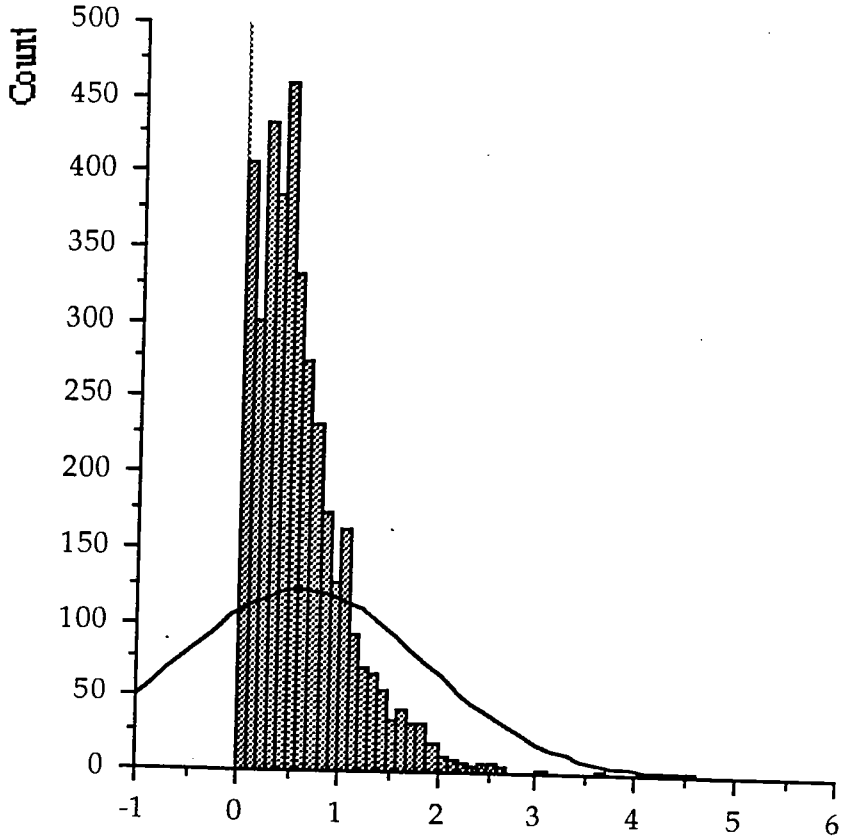

Fig 1: Distribution of hCG concentration (mIU/ml) in 3805 male athletes

The intervals specified do not contain the entire range of the data.

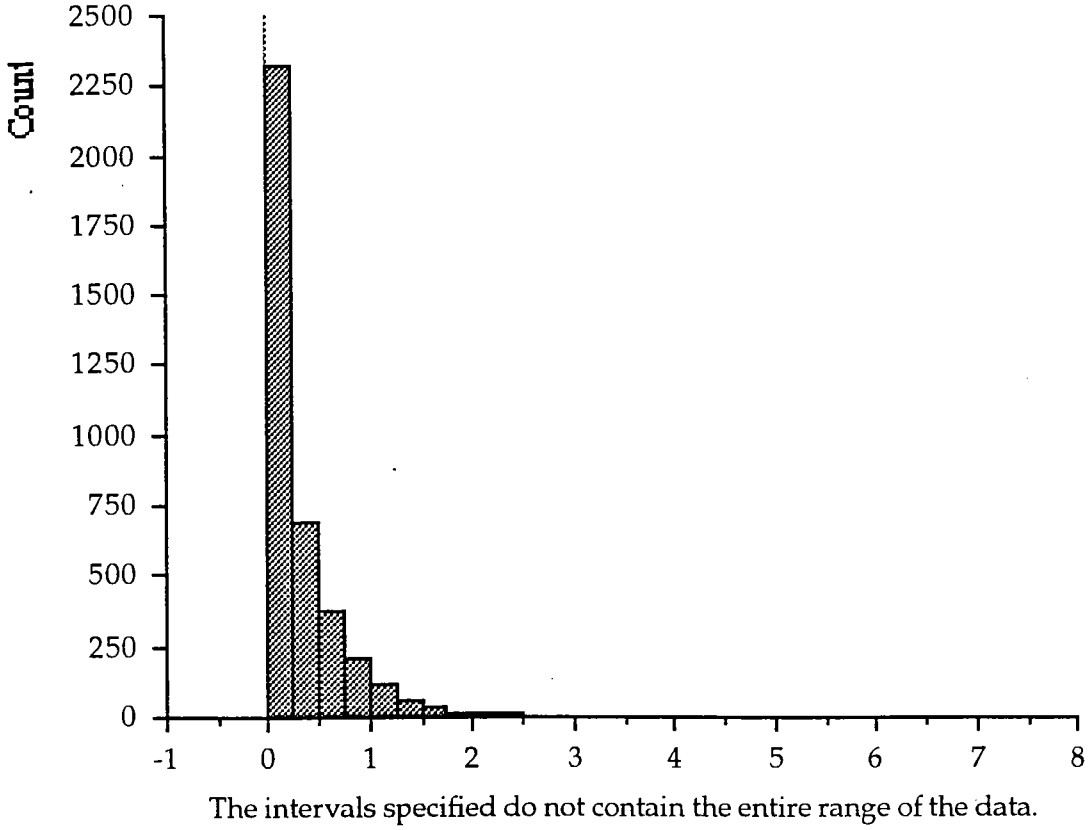

Fig 2 : Theophylline concentration (ppm) in 3885 athletes