

PRESCRIBING OF DRUGS REPORTED TO CAUSE ADVERSE REACTIONS

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The way in which data on the prescribing of drugs by doctors in Northern Ireland has been collected and analysed with the aid of electronic data processing equipment which was first installed in 1966 has been described by Wade and Hood (1972). The present paper describes changes in Northern Ireland in the prescribing of chloramphenicol, amphetamines, and bronchodilator aerosols, all of which are preparations which in recent years have been found to have serious adverse reactions.

CHLORAMPHENICOL

Chloramphenicol was first marketed in 1949. It is a broad-spectrum antibiotic of special value in typhoid fever but effective in many other infections. In 1951 Max Wintrobe and Philip Sturgeon each encountered a few patients with aplastic anaemia who had previously received chloramphenicol (personal communication). Evidence from other haematologists and a review of papers published in the United States, France, and Australia led to a warning by the American Medical Association to doctors in the USA of the hazard of aplastic anaemia if chloramphenicol was administered (Editorial, 1952). Later, after the establishment of a Registry of Blood Dyscrasias, there was further confirmation that chloramphenicol could occasionally cause marrow damage and this hazard was widely discussed in the world literature (Wade, 1970).

EARLY STUDIES IN NORTHERN IRELAND

The prescribing of chloramphenicol by general practitioners in Northern Ireland was first examined in December 1962 (Wade, 1966). During the month 3,123 prescriptions for chloramphenicol were written, 1,141 for capsules and 1,982 for syrup. Of the 756 doctors working in general practice at that time 513 wrote no prescriptions for either preparation and 243 wrote between one and four prescriptions. There were a few doctors who prescribed the drug more frequently. Indeed, one quarter of all the chloramphenicol used during the month was

prescribed by 10 doctors. A further study was made in February 1964. The use of chloramphenicol was found to have decreased, the total number of prescriptions written being 1,648. The pattern of prescribing had, however, remained, and in many instances the high prescribers of 1962 were still the high prescribers of 1964.

PRESENT INVESTIGATION

By the use of the data processing equipment the number of prescriptions written for capsules and for syrup of chloramphenicol has been monitored each month from April 1966 to December 1970 (Figure 1). In 1966 and 1967 a marked seasonal variation was apparent. The highest level of prescribing recorded during this period occurred in January 1967 when 1,104 prescriptions were written. In February 1967 the Committee on Safety of Drugs, which had been concerned at the extent of the continued use of chloramphenicol in Great Britain, issued a warning to all doctors with the suggestion that the use of chloramphenicol was justifiable only for patients with typhoid fever, meningitis due to *Haemophilus influenzae*, or infections with organisms on which sensitivity tests had clearly indicated that chloramphenicol was the

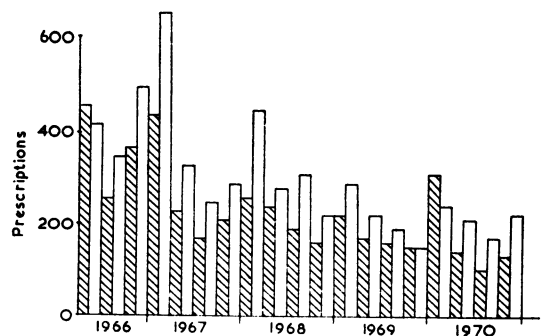


FIG. 1. Number of prescriptions for capsules (shaded) and syrup of chloramphenicol written by general practitioners in Northern Ireland in the first month of each quarter, April 1966—December 1970. A warning by the Committee on Safety of Drugs was issued in February 1967.

antibiotic of choice. The prescribing of chloramphenicol in Northern Ireland decreased by about half immediately after the issue of this warning and it has continued at between 300 and 500 prescriptions a month between 1966 and 1970. In 1968 chloramphenicol comprised 0.6% of all antibiotic prescribing in Northern Ireland, in marked contrast to West Germany where chloramphenicol accounted for approximately 25% of all antibiotics prescribed that year (Engels and Siderius, 1968).

AMPHETAMINES

Benzedrine was first prepared in 1887 (Edeleano, 1887) and was introduced to clinical medicine in the early 1930s, first as an inhalant to reduce nasal congestion and then for the treatment of narcolepsy (Prinzmetal and Bloomberg, 1935). During the war amphetamines were used in the armed Forces as an antidote to fatigue (Cuthbertson and Knox, 1947) and later became widely used in the treatment of depression and obesity.

The first observation of addiction to amphetamines was reported by Waud (1938), and after the war there were reports of psychotic states occurring in patients addicted to them (Norman and Shea, 1945; Knapp, 1952). Masaki (1956) reported the serious situation which had arisen in Japan where he estimated that at least 500,000 persons, mainly between the ages of 16 and 30, were misusing amphetamines. The Japanese Pharmacists' Association believed his estimate to be far too small and claimed that 1,500,000 people were misusing the drugs. In Sweden there was also a serious problem of amphetamine addiction; it was estimated that in a total population of 7,000,000 persons there were 7,000 amphetamine addicts. In Australia, Bell and Trethowan (1961) were also concerned about amphetamine addiction.

But in Britain the danger of addiction to amphetamines was still being authoritatively denied by Bett, Howells, and Macdonald in 1955, and its use in competitive sport, if not being encouraged, was being defended (Abrahams, 1958). In 1958 Connell published a comprehensive study of amphetamine misuse from the Maudsley Hospital, London, and over the next few years there was wide publicity in both the medical and the lay press in Britain of the extensive misuse of anti-obesity remedies by middle-aged women and the craze among adolescents for purple heart tablets (Drinamyl), a combination of dexamphetamine and amylobarbitone. Because of the wide illicit use of Drinamyl, the manufacturers, Smith, Kline, and French, sent a circular to all medical practitioners in July 1964

informing them that the characteristic and easily recognizable purple heart shaped tablet was being withdrawn and that in future Drinamyl would be marketed as a blue tablet. Despite this, leaders in the *Lancet* (1964 and 1965) still acquiesced with the view expressed by the Ministry of Health Interdepartmental Committee on Drug Addiction (1961) that amphetamine addiction was not a serious problem, although Gibson and Wade (1964) were of the opinion that at that time Drinamyl misuse represented the most serious drug addiction problem in the United Kingdom, and the United Nations Commission on Narcotic Drugs (1965) had recommended all member States to take steps to control the misuse of amphetamines.

PRESCRIBING OF AMPHETAMINES IN NORTHERN IRELAND

The first investigation of the use of amphetamines by doctors in general practice in Northern Ireland was reported by Moorehead (1968). He found a three-fold increase in the sales of amphetamines by wholesalers to pharmacies between 1963 and 1966. This was in sharp contrast to the hospital services of the Province where the prescribing of amphetamine had at this time become negligible.

Hood and Wade (1968) made a detailed analysis of the prescribing of amphetamines over the three-month period April-June 1966. In order to compare the use of the 11 preparations of amphetamine and of phenmetrazine which were being prescribed in Northern Ireland at that time, and which were of different doses and different composition, a 'unit' of amphetamine was defined as the equivalent of 5 mg of amphetamine (Table I). In the three-month period of the survey, 11,400 prescriptions were written for almost a million units of amphetamine. There were great differences in the 444 practices

TABLE I
PREPARATIONS OF AMPHETAMINE INCLUDED IN THE SURVEY AND THEIR CONVERSION TO ARBITRARY UNITS

Preparation	Dose	Units
Amphetamine sulphate	5 mg tablets	1
Benzedrine	5 mg "	1
Dextroamphetamine ..	5 mg "	1
Methedrine	5 mg "	1
Preludin	25 mg "	1
Dexedrine	5 mg "	1
	10 mg spansules	2
	15 mg "	3
	25 mg "	2
Dexten resinate	25 mg "	2.5
Durophet	7.5 mg tablets	1.5
	12.5 mg "	2.5
	20 mg "	4

TABLE II
PREScribing OF AMPHETAMINES, APRIL—JUNE 1966

Units Prescribed /1,000 List Patients	Practices Prescribing Amphetamines		Units of Amphetamine Prescribed	
	No.	%	No.	%
0	56	12.6		
1—999	293	66.0	302,794	31.7
1000—1999	48	10.8	210,175	22.0
2000—2999	28	6.3	226,066	23.7
3000—3999	6	1.4	53,594	5.6
4000—4999	7	1.6	78,675	8.2
5000—5999	3	0.7	26,671	2.8
6000—6999	1	0.2	20,089	2.1
7000—7999	—	—	—	—
8000—8999	1	0.2	9,745	1.0
9000—9999	1	0.2	27,582	2.9
Total	444	100	955,391	100

in the prescribing of these preparations (Table II). There were 56 practices (12% of all practices) in which no amphetamines were prescribed. In the majority of practices, between 1 and 2,999 units per 1,000 patients per three months were prescribed. There were 18 practices in which between 3,000 and 10,000 units per 1,000 patients per three months were prescribed, and these 18 practices (4% of all practices) were responsible for 20% of

the total prescribing of amphetamines in the Province.

The prescribing of amphetamines was much greater in the east of the Province than in the west (Figure 2), and in Belfast the number of units prescribed per 1,000 patients was 10 times more than in Co. Fermanagh (Table III). There were three small towns on the east coast where more than 2,000 units per 1,000 patients were prescribed in the three-month period, and two areas in Co. Fermanagh where none at all was prescribed.

TABLE III
DISTRIBUTION OF PREScribing OF AMPHETAMINES APRIL—JUNE 1966

	List Patients		Units of Amphetamine		Units/1,000 in County
	No.	%	No.	%	
Belfast ..	513,958	36	548,601	57	1,067
Co. Antrim ..	238,849	17	137,019	14	574
Co. Armagh ..	107,663	7	35,005	4	326
Co. Down ..	223,870	16	152,345	16	681
Co. Fermanagh ..	38,397	3	4,178	1	109
Co. Londonderry ..	168,566	12	45,344	5	269
Co. Tyrone ..	135,847	9	32,899	3	242
Whole Province ..	1,427,150	100	955,391	100	669

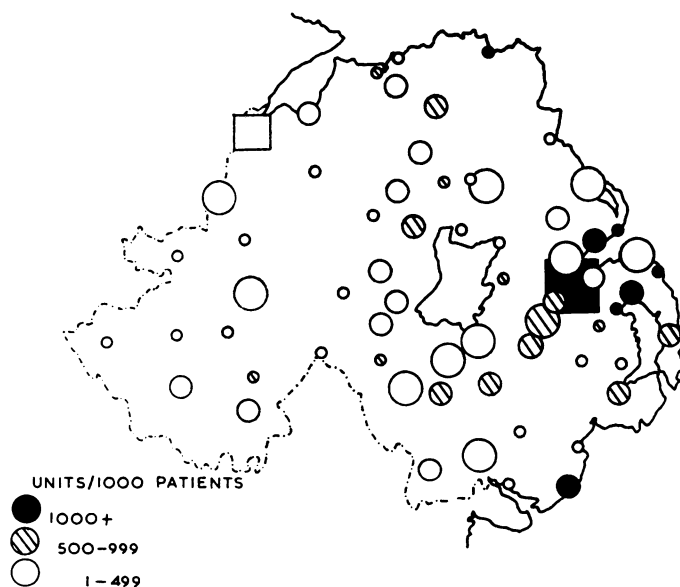


FIG. 2. Geographical distribution of the rate of prescribing of amphetamines in Northern Ireland, April—June 1966. The size of the circles or squares represents the numbers of patients on doctors' lists in the different areas.

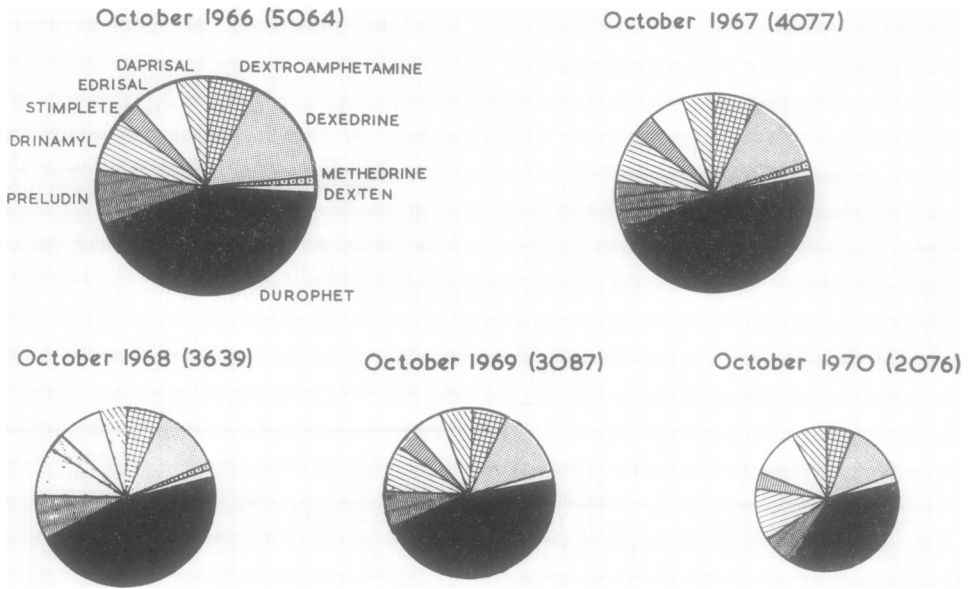


FIG. 3. Changes in prescribing of amphetamines in the month of October each year 1966-70. Total prescriptions for each month in parentheses.

After this survey the prescribing of amphetamines was kept under continuous monthly surveillance. Figure 3 shows the number of prescriptions written each October from 1966 to 1970, inclusive. There was a steady decrease in the number of prescriptions written each October until in 1970 it was less than half the 1966 figure. The prescribing of methylamphetamine (Methedrine) was restricted to hospital use on 2 October 1968.

A repeat survey of amphetamine prescribing for the second quarter of 1971 showed that the prescribing of amphetamines has decreased by almost three-quarters since the same period in 1966 (Table IV). The decrease was, for the most part, evenly spread across the Province but was greatest in Co. Londonderry (87%), probably due to general practitioners in the city of Londonderry having agreed not to prescribe these drugs. The proportion of all amphetamine prescriptions written by doctors in Belfast remained considerably above the proportion of the population resident there. Prescribing in the individual practices of Northern Ireland showed a marked overall decrease; 41% of practices prescribed no amphetamines and a further 55% prescribed less than 1,000 units per thousand patients. The amount of amphetamine prescribed in practices was found to have increased between the two survey periods in only a very few cases. Only two practices prescribed more than 4,000 units per thousand patients in 1971 whereas 12

practices prescribed this level in 1966 and one practice prescribed more than 8,000 units per thousand in that year.

BRONCHODILATOR AEROSOLS

Sympathomimetic amines are effective bronchodilators, relieving the bronchospasm and dyspnoea of asthma, but when given systemically they often cause an increase in heart rate and palpitations which patients may find unpleasant. In 1959 pressurized aerosols of isoprenaline were marketed. These allowed the inhalation of small metered doses which usually gave effective relief of bronchospasm and did not affect the heart rate. Pressurized aerosol preparations are convenient, effective, and

TABLE IV
DISTRIBUTION OF PRESCRIBING OF AMPHETAMINES
APRIL—JUNE 1971

	List Patients		Units of Amphetamine		Units/1,000 in County
	No.	%	No.	%	
Belfast ..	504,441	34	151,082	58	300
Co. Antrim ..	271,518	18	27,655	10	102
Co. Armagh ..	116,507	8	10,769	4	92
Co. Down ..	248,157	16	51,342	20	207
Co. Fermanagh ..	41,614	3	1,321	0.5	32
Co. Londonderry ..	180,257	12	6,444	2.5	36
Co. Tyrone ..	132,740	9	12,461	5	94
Whole Province ..	1,495,234	100	261,074	100	175

popular with patients, and by 1966 about 750,000 aerosol containers a year were being prescribed or sold over the counter in England and Wales.

It was in that year that Beryl Corner reported to a meeting of chest physicians her observation that there had been an increase in the Bristol area of deaths of children from asthma (Smith, 1966). Speizer, Doll, and Heaf (1968) examined the data of the Registrar General and confirmed that in England and Wales there had been a considerable increase in deaths from asthma between 1960 and 1965. It was especially marked in young persons aged 10-14 and in many instances the circumstances of death strongly suggested that the patient had taken an overdose of bronchodilator aerosols. As a result of these investigations the Committee on Safety of Drugs issued a statement in June 1967 to all doctors advising that patients be warned of the dangers of excessive use of pressurized aerosols. At the same time manufacturers began to print a warning against excess use on all containers and the Poisons Board limited the sale of these aerosols so that they could be obtained only by a doctor's prescription. The institution of these measures was followed over the next two years by a fall in the mortality due to asthma to its pre-1960 level. Inman and Adelstein (1969) estimated that between 1961 and 1967 3,500 more deaths from asthma occurred than had occurred in the previous seven years.

The hazards of the use of aerosols containing sympathomimetic amines were widely discussed in both the medical and the lay press after the statement by the Committee on Safety of Drugs was issued, but the mechanism by which the increase in mortality came about is still the subject of controversy.

It was assumed that the sudden deaths were due to the action of the β -adrenergic stimulant drugs on the heart, and for this reason orciprenaline (Alupent) and salbutamol (Ventolin), drugs which have less action on the β -adrenergic receptors of heart muscle than adrenaline or isoprenaline, were welcomed when they became available in 1968 and 1969, respectively.

The data processing equipment became available in Northern Ireland just at the time when these hazards of the bronchodilator aerosols were being recognized, and the prescribing of the pressurized aerosols has been monitored since April 1966.

PRESCRIBING OF BRONCHODILATOR AEROSOLS IN NORTHERN IRELAND

In the month of October 1966, 3,956 prescriptions were written for bronchodilator aerosols. Four preparations were prescribed: P.I.B. (isoprenaline),

Medihaler Iso Forte (isoprenaline), and Medihaler Epi (adrenaline and other drugs) were all equally and widely prescribed. There was a small number of prescriptions for P.I.B. Forte.

Between 1966 and 1971 (Figure 4) the number of different preparations available increased and in October 1971, 7,351 prescriptions for 12 preparations were written. More than half these prescriptions, however, were either for the sympathicomimetic amines orciprenaline (Alupent) and salbutamol (Ventolin), which were believed to be safer than isoprenaline, or for disodium cromoglycate (Intal) which was introduced in 1968; this is not a sympathicomimetic drug and is believed to act by interfering with the release of histamine or histamine-like substances when allergic reactions occur. The promotion of all these three preparations has stressed their freedom from cardiac toxicity.

Although in 1970 the total number of prescriptions had almost doubled compared with 1966, the prescribing of aerosols containing isoprenaline or adrenaline was less than it was in 1966.

DISCUSSION

The first investigation of the prescribing of chloramphenicol in Northern Ireland was made in 1962, 13 years after the introduction of the drug and 11 years after the first reports of its hazards which were widely discussed in the intervening years in the world's medical journals. It is unfortunate that there are no data available for the prescribing of chloramphenicol in the early 1950s. It is reasonable to presume that the highest level of prescribing occurred in those years and that by 1962 it had already fallen very considerably. It was a surprise to find in 1962 that it was still so widely used and its continued and seemingly unjustified wide use led the Dunlop Committee to issue its warning in 1967. Even that warning reduced the use by only half. These findings and the evidence that heavy prescribing was confined to a very few doctors suggest that even though there is wide publicity in medical journals about the adverse reactions of a drug, the prescribing habits of some doctors do not change, and even the warnings of the Dunlop Committee do not reach or do not carry weight with some practitioners.

The slow response of doctors in general practice to reports of adverse reactions of amphetamines was shown by Moorehead (1968). Between 1963 and 1966 he found a great increase in the prescribing of amphetamines at a time when there was much concern expressed in both the medical and the lay press about the misuse of the drugs and when hospital doctors had almost ceased to prescribe

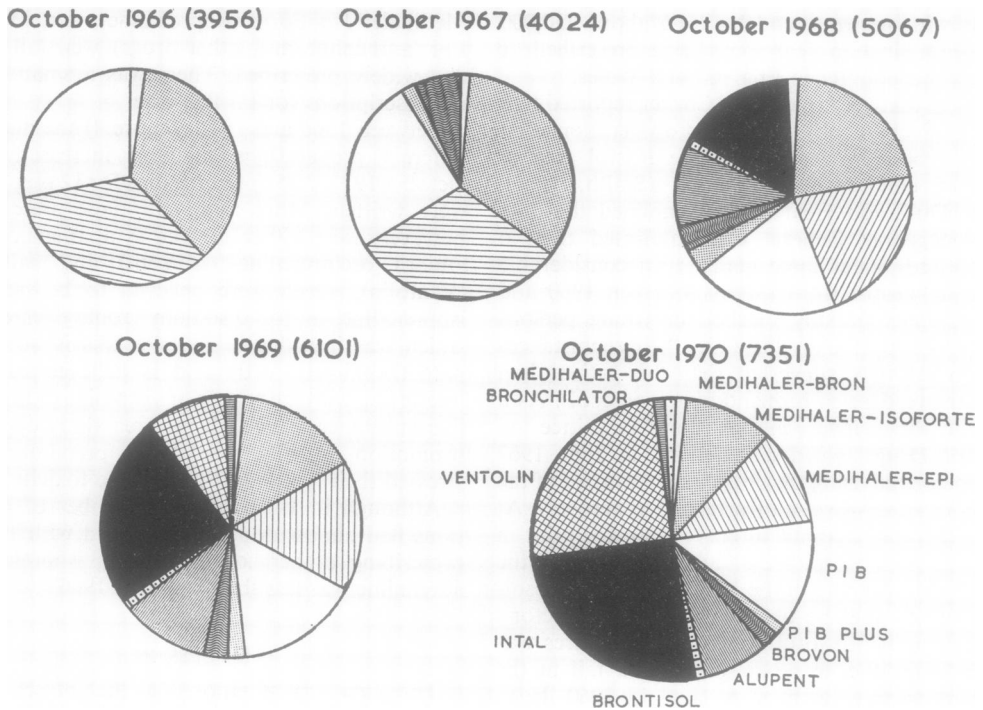


FIG. 4. Changes in prescribing of bronchodilator aerosols in the month of October each year 1966-70. Total prescriptions for each month in parentheses.

them. The fall in the prescribing of amphetamines since 1966 is encouraging. It suggests, however, that there is a considerable time lag between the recognition of an adverse effect of drugs and any change in prescribing habits. The decrease in prescribing of these drugs may have been accelerated by the British Medical Association which appointed a Working Party on amphetamines in 1967. The report of the Working Party (British Medical Association, 1968) emphatically stated that the amphetamines had been discredited as anti-obesity agents and superseded by more effective drugs in the treatment of psychiatric illness.

Nevertheless, the prescribing of amphetamines was still remarkably high in 1970. It would appear that some doctors either do not keep themselves acquainted with current views on drug prescribing or, perhaps in this instance, have difficulty in persuading their patients to accept withdrawal of their medication.

It is interesting to see the very rapid reduction in the excess death rate from asthma which was attributed to the use of pressurized aerosols of sympathicomimetic drugs. This suggests that the warnings about the very serious hazard of sudden death due to misuse of aerosols were successfully

conveyed to both patients and doctors. Yet, despite this, the prescribing of aerosols containing isoprenaline and adrenaline decreased only slightly over the five-year period 1966-70. Over this time there was a great increase in the overall number of aerosol preparations prescribed. But this increase appears to have been mainly of orciprenaline (Alupent), salbutamol (Ventolin), and disodium cromoglycate (Intal), all of which are thought to be less hazardous than isoprenaline. In this instance the rapid change in the pattern of prescribing may be due not only to appreciation by doctors of the hazards of isoprenaline but also to the appearance of new and apparently safer drugs on the market and their vigorous presentation by their manufacturers.

No doubt some general practitioners keep a close watch on contemporary information on drugs and their adverse reactions and change their prescribing habits appropriately. But it would seem from these studies that the prescribing habits of most doctors are firmly fixed and that changes in their habits occur slowly and only after a long time lag. There are some doctors whose response seems to be very slow. This would suggest that considerable weight should be given in postgraduate teaching to the discipline of clinical pharmacology and more

thought should be applied to the dissemination of unbiased information about drugs. Perhaps the torrent of drug promotional literature is a factor in diverting the attention of doctors from more important information about drugs which they require if their patients are to be treated as effectively and safely as possible.

SUMMARY

The prescribing by general practitioners of chloramphenicol, the amphetamines, and the pressurized aerosols of bronchodilator drugs has been studied in Northern Ireland. All these preparations have been associated with serious adverse reactions, aplastic anaemia, addiction, and sudden death. Even so the prescribing of these drugs by doctors changed only slowly over the years of investigation and the studies suggest that more thought is needed on the dissemination of unbiased information about drugs.

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