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MITOTIC DISTURBANCES INDUCED BY THE DRUG "NOVALGIN" IN **ALLIUM CEPA** ROOT TIPS

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ABSTRACT

Growing root tips of *Allium cepa* are treated with seven concentrations of Novalgin ranging from 2.81×10^{-4} M to 1.5×10^{-4} M for 4, 8, 24, 48 and 72 hours.

The frequency of mitotic phases in the treated roots varies according to the concentration applied and period of treatment. Novalgin reduces the mitotic activity with the increase of concentration applied.

Novalgin induces a wide range of mitotic abnormalities, their frequencies vary according to the concentration and period of treatment. These abnormalities include c-metaphase, chromosome stickiness, c-anaphase, tripolar groups, chromosome bridges, lagging of chromosomes at anaphase, micronuclei and multinuclei at the interphase stage.

The most conspicuous type of abnormality is the ability of Novalgin to cause chromosome breakage which is noticed at different periods of treatment and at different concentrations applied, specially at low concentrations. The number of breaks varies from a single break to many at metaphase and acentric fragments at anaphase.

A test for recovery is carried out by treating roots for 8 hours then fixing after 4, 24 and 48 hours. The roots start to restore normal activity after 48 hours recovery interval but a number of abnormalities are still seen.

INTRODUCTION

Recent cytological studies have pointed out the dangers of many medical drugs used by man on the genetic machinery. They showed that many of these drugs could lead to major changes involving both mitosis and meiosis. Such cytological variations could lead to large numbers of mutations. For example, different types of antibiotics induced different types of chromosomal abnormalities in human, animal and plant cells (Obe 1970, Subramanyan and Reddy 1975,

Cilievici *et al* 1978, Mana 1978, Mercykutty and Stephen 1980). Similarly, a number of antituberculosis drugs caused the appearance of chromosomal aberrations (Roman and Georgian 1977). Other drugs also found to cause mitotic disturbances include different types of narcotics (Kabarity *et al* 1974, 1976 and El-Bayoumi *et al* 1977), different analgesic drugs (Mazrooei and Kabarity 1984), anticonvulsant drugs (Roman and Georgian 1978) and tranquillizers such as phenobarbitone and Valium (El-Bayoumi *et al* 1979, 1980).

The aim of the present study is to investigate the cytological effect of one of the drugs commonly and widely used by man, namely, "Novalgin". It is available for oral use in the form of tablets or syrup or for injection. Novalgin has analgesic, antispasmodic, antipyretic and antirheumatic properties.

MATERIALS AND METHODS

The experimental plant used in this investigation is *Allium cepa* bulb variety Giza. The test chemical is the drug "Novalgin". Its chemical formula is 1-phenyl — 2,3 dimethyl — 5 pyrazolon — 4 methylamino methane sulphonate sodium. Root tips while intact on the bulb are placed in a vial containing the test chemical Novalgin. The lethal concentrations and the threshold are first determined and a number of concentrations intermediate between these two limiting doses are selected for the different experiments. The selected concentrations used range from 2.81×10^{-4} to 0.001×10^{-4} M. Roots are treated for 4, 8, 24, 48 and 72 hours. A recovery test is carried out by treating the roots with different concentrations of Novalgin for 8 hours and fixing after transferring them in water for 4, 24 and 48 hours. The roots are fixed in Carnoy solution (3 absolute alcohol: 1 glacial acetic acid) for 24 hours. Feulgen squash technique is applied for cytological investigation according to Darlington and LaCour (1976). The mitotic and stage indices and the different cytological observations are determined from at least 20 root tips from each treatment.

RESULTS

Mitotic abnormalities induced by Novalgin

Novalgin induced a wide range of mitotic abnormalities involving all stages of mitosis in the meristematic region of *Allium cepa* roots. However, its main effect is exerted on both metaphase and anaphase stages.

Chromosome stickiness is one of the abnormalities that appeared in roots treated with high concentrations (Fig. 1). C-metaphase is the most common type of metaphase abnormality as seen in Fig. 2. This abnormality is mainly due to the effect of the drug on spindle fibre formation. Other metaphase abnormalities are noticed with lower frequencies such as star metaphase where the chromosomes orientate themselves into a star shape (Fig. 3).

Among the abnormalities induced by Novalgin at anaphase is c-anaphase (Fig. 4). After prolonged treatment and recovery c-anaphase is restituted to form a polyploid cell (Figs. 5 & 6). Fig. 7 shows disturbances that did occur at the anaphase stage. The most prominent abnormality in both anaphase and telophase is the formation of chromosome and chromatin bridges as seen in Figs. 8 & 9. Lagging chromosomes are also noticed during anaphase stages (Fig. 10). Other abnormalities at anaphase are also seen, such as tri- and multipolar where the chromosome set is distributed to give more than two poles (Fig. 11). This phenomenon is due to the splitting of the spindle apparatus in more than two directions. Consequently, more than two chromosome groups are formed. Each chromosomal group is surrounded by nuclear membrane. Thus multi-nucleated cells are formed (Fig. 12).

One of the most conspicuous types of abnormalities is chromosome breakage, which is noticed

in roots treated for different periods of time and at different concentrations specially low concentrations. The chromosome breaks are seen at different stages of mitosis. However, they are quite clear at metaphase and anaphase stages. The number of breaks vary from one single break at metaphase to more as seen in Figs. 13, 14, 15 & 16. The breaks have sometimes appeared as gaps at both metaphase and anaphase chromosomes. The number of these gaps restricted to the same chromosome vary from one to five. Most of these breaks lead to the formation of acentric fragments which appear lagging at the equatorial plane (Figs. 17 & 18). At telophase, they become surrounded with a nuclear membrane forming micronuclei, as seen in Fig. 19.

The frequencies of the different types of abnormalities varied according to the concentration and period of treatment. Tables 1 to 5 show the percentage of total abnormal phases after treatment with different concentrations and periods of time. In general, the total abnormalities of both metaphase and anaphase increase with the increase of concentration for each period of treatment.

Effect of Novalgin on frequencies of mitotic stages

Seven concentrations of Novalgin were used ranging from 2.81×10^{-4} M to 1.50×10^{-4} M in roots treated for 4 hours. The concentration 2.81×10^{-4} M proved to be the sublethal above which the *Allium cepa* roots died. More diluted concentrations were used ranging from 1.50 to 0.001×10^{-4} M in roots treated for a longer duration, i.e. for 8, 24, 48 and 72 hours. The details of the concentrations are shown in Tables 1-5.

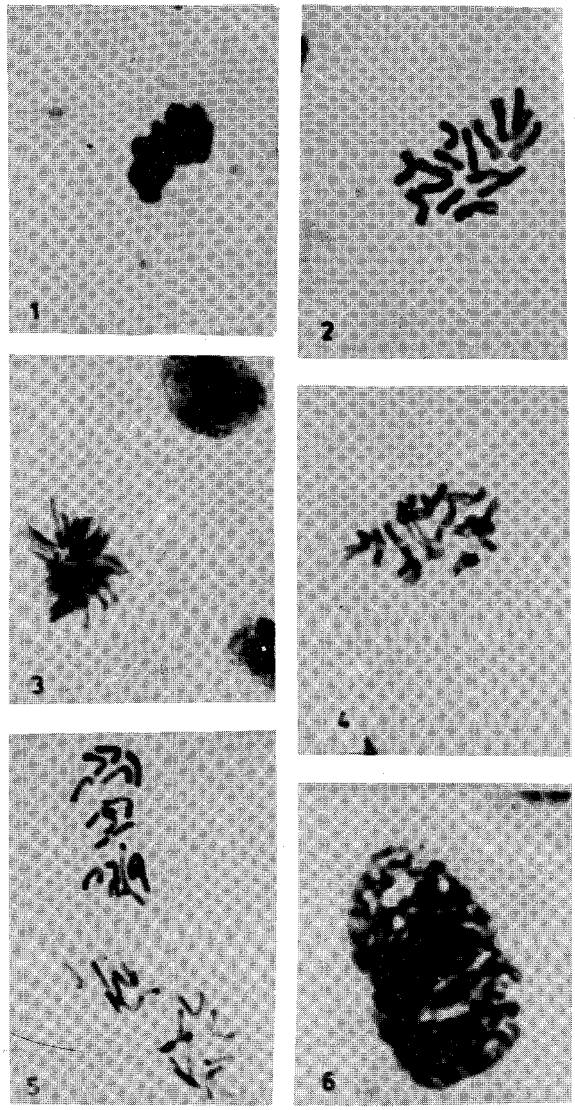
In all the treatments the prophase frequency fluctuated slightly at lower concentrations, then declined in roots treated with higher concentrations. It is noticed that there is an inverse correlation between the frequency of prophase and metaphase. The frequency of anaphase and telophase fluctuates slightly compared with the control values. Figs. 20, 21, 22, 23 & 24 show the relationship between frequencies of different stages and MI in roots treated with various concentrations for 4, 8, 24, 48 and 72 hours.

Effect of Novalgin on the mitotic index (MI)

Novalgin shows its effect on the mitotic activity in all the treatments. Fig. 25 shows clearly that a drop in the mitotic index is observed in all the roots treated with different concentrations and duration of treatment when compared with the control. In 4 hours treatment a minimum value of 2.62% at the highest concentration is obtained compared with the control value of 7.09%. The lowest mitotic index value is 1.00% reached after treating the roots with the concentration 1.5×10^{-4} M for 24 hours. In general, the mitotic activity is more affected after treating the roots for a longer duration.

MI after 8 hours treatment and fixed for 4, 24 & 48 hours

In roots treated for 8 hours and fixed for 4 hours, the MI values of the lowest three concentrations exceed the control value, while the highest concentrations show a depression in MI compared with the control value. It reached a maximum value of 9.70 at the concentration 0.02×10^{-4} M and a minimum value of 0.33 at the highest concentration 1.50×10^{-4} M (Fig. 26). After 24 and 48 hours recovery, the MI at all concentrations exceeds the control value except at the highest concentrations, where there is a slight decrease. In general, the MI at all concentrations after 4, 24 and 48 hours recovery is higher than that of the corresponding concentrations after 8 hours treatment without an intervening recovery period.



Figures 1-6. Mitotic abnormalities induced by Novalgin:

1. Chromosome stickiness after treatment with 2.81×10^{-4} M for 25 h. 2. C-metaphase after treatment with 0.19×10^{-4} M for 4 h. 3. Star metaphase after treatment with 2.06×10^{-4} M for 24 h. 4. C-anaphase after treatment with 2.06×10^{-4} M for 48 h.
5. Polyploid cell (tetraploid) at metaphase after treatment with 0.01×10^{-4} M for 24 h.
6. Polyploid cell at prophase after treatment with 2.06×10^{-4} M for 48 h.

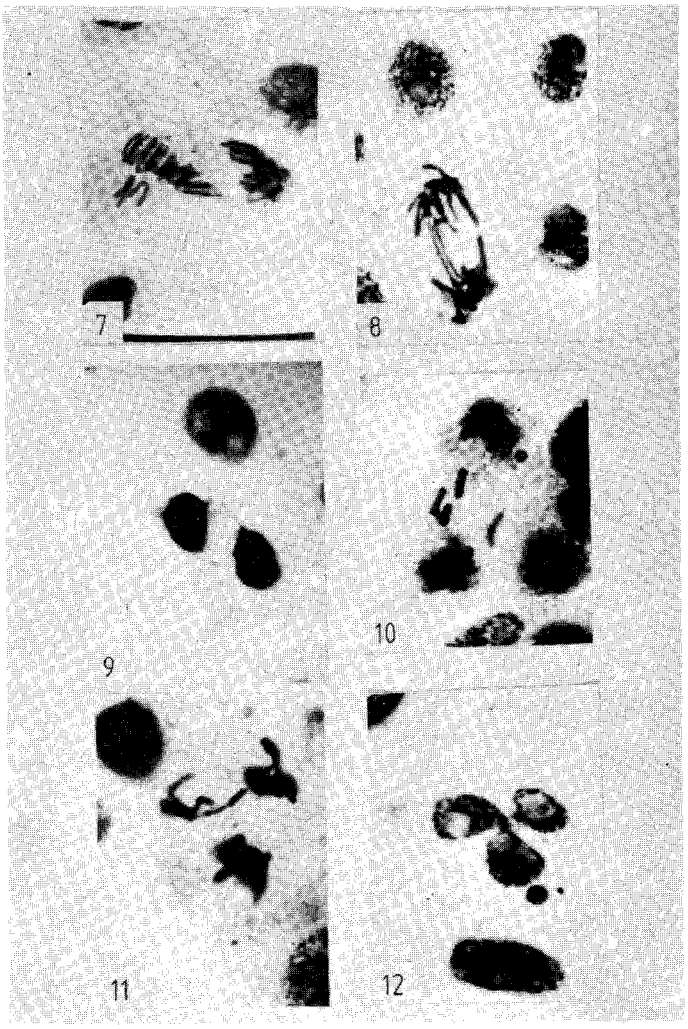


Figure 7. Disturbed anaphase induced by Novalgin after treatment with $0.002x10^{-4}$ M for 48 h.

Figures 8 & 9: Chromosome bridges induced by Novalgin

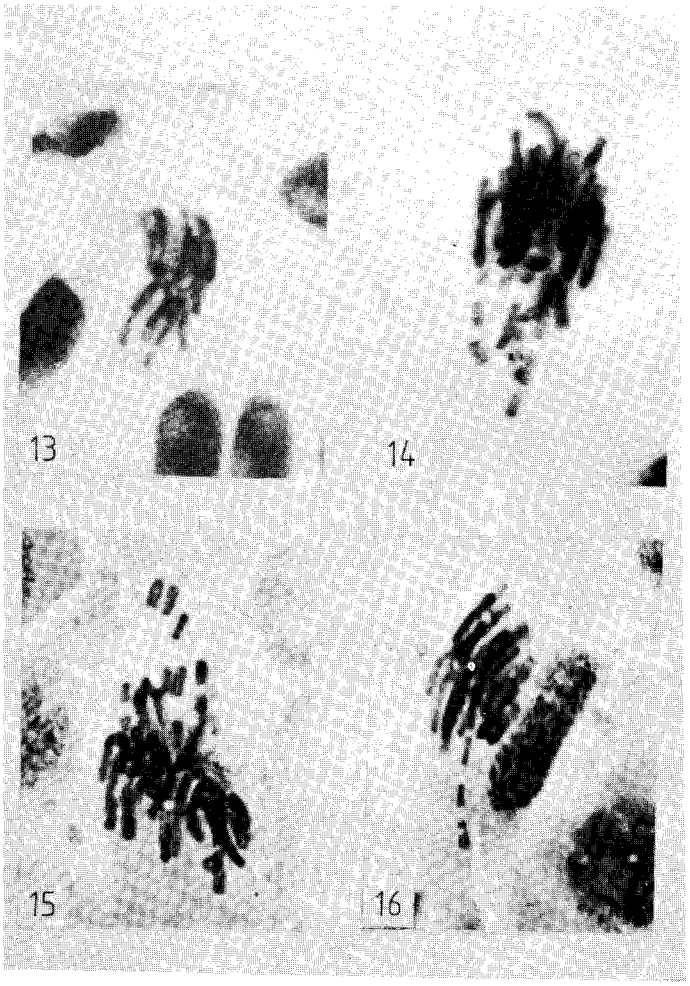
8. After treatment with $2.06x10^{-4}$ M for 4 h. 9. After treatment with $0.19x10^{-4}$ M for 8 h.

Figure 10. Lagging chromosomes at anaphase and telophase induced by Novalgin after treatment with $2.06x10^{-4}$ M for 8 h.

Figures 11 & 12: Tripolar and multinucleate cells induced by Novalgin

11. Tripolar with chromatin bridges after treatment with $2.6x10^{-4}$ M for 4 h.

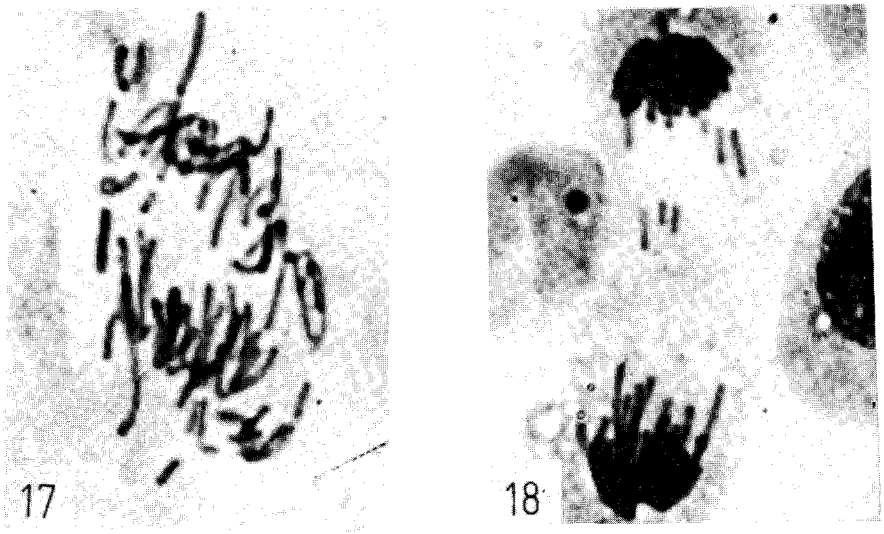
12. Multinucleate cell after treatment with $2.81x10^{-4}$ M



Figures 13-16. Chromosome breakage induced by Novalgin at metaphase stage, the number of breaks varying from one to 8

13. After treatment with $0.01x10^{-4}$ M for 24 h. 14. After treatment with $0.01x10^{-4}$ M for 24 h.

15. After treatment with $0.01x10^{-4}$ M for 48 h. 16. After treatment with $0.01x10^{-4}$ M for 8 h.



Figures 17 & 18. Anaphase with chromosome breaks and lagging acentric fragments induced by Novalgin after treatment with 0.01×10^{-4} M for 24 h.

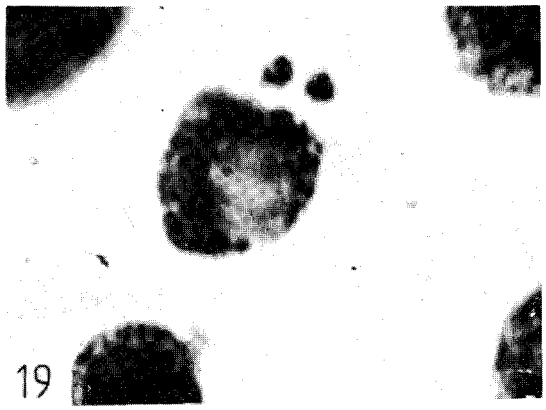


Figure 19. Interphase with micronuclei after treatment with 2.8×10^{-4} M for 4 h.

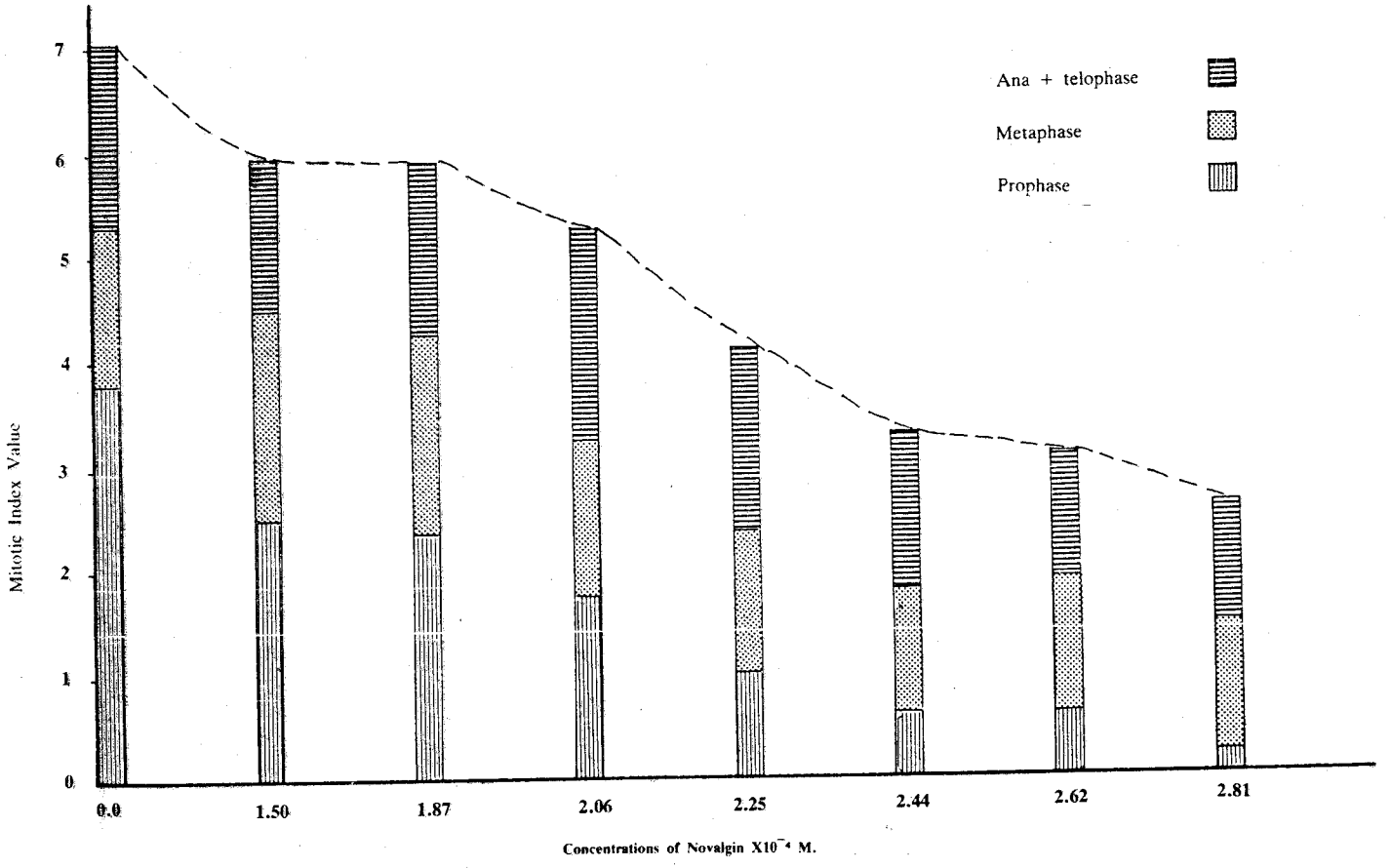


Fig (20) Frequencies of mitotic phases and mitotic indices after treating root tips of *Allium cepa* with different cocentrations of Novalgin for 4 hours.

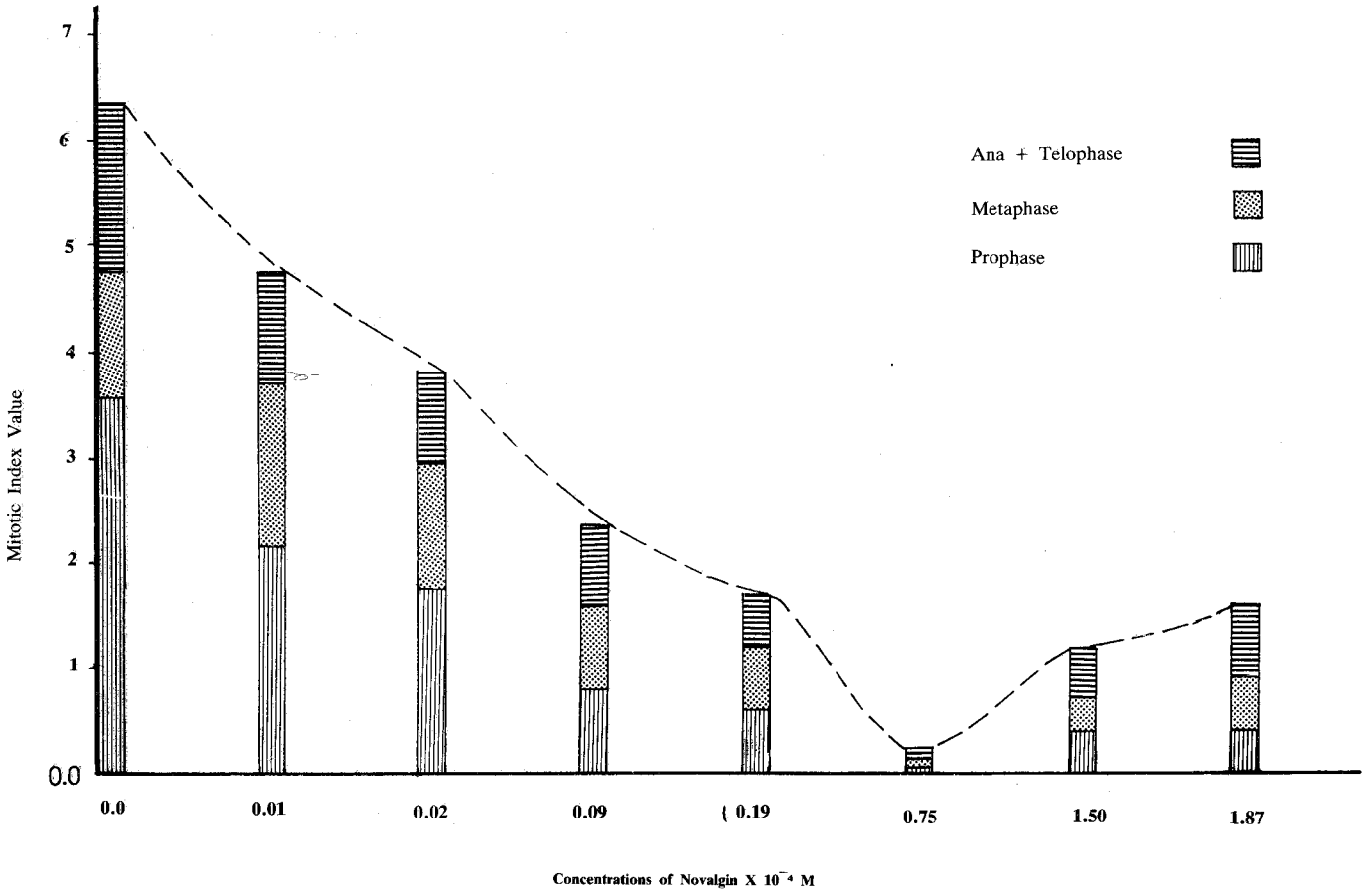


Fig. (21) Frequencies of mitotic phases and mitotic indices after treating root tips of *Allium cepa* with various concentrations of Novalgin for 8 hours.

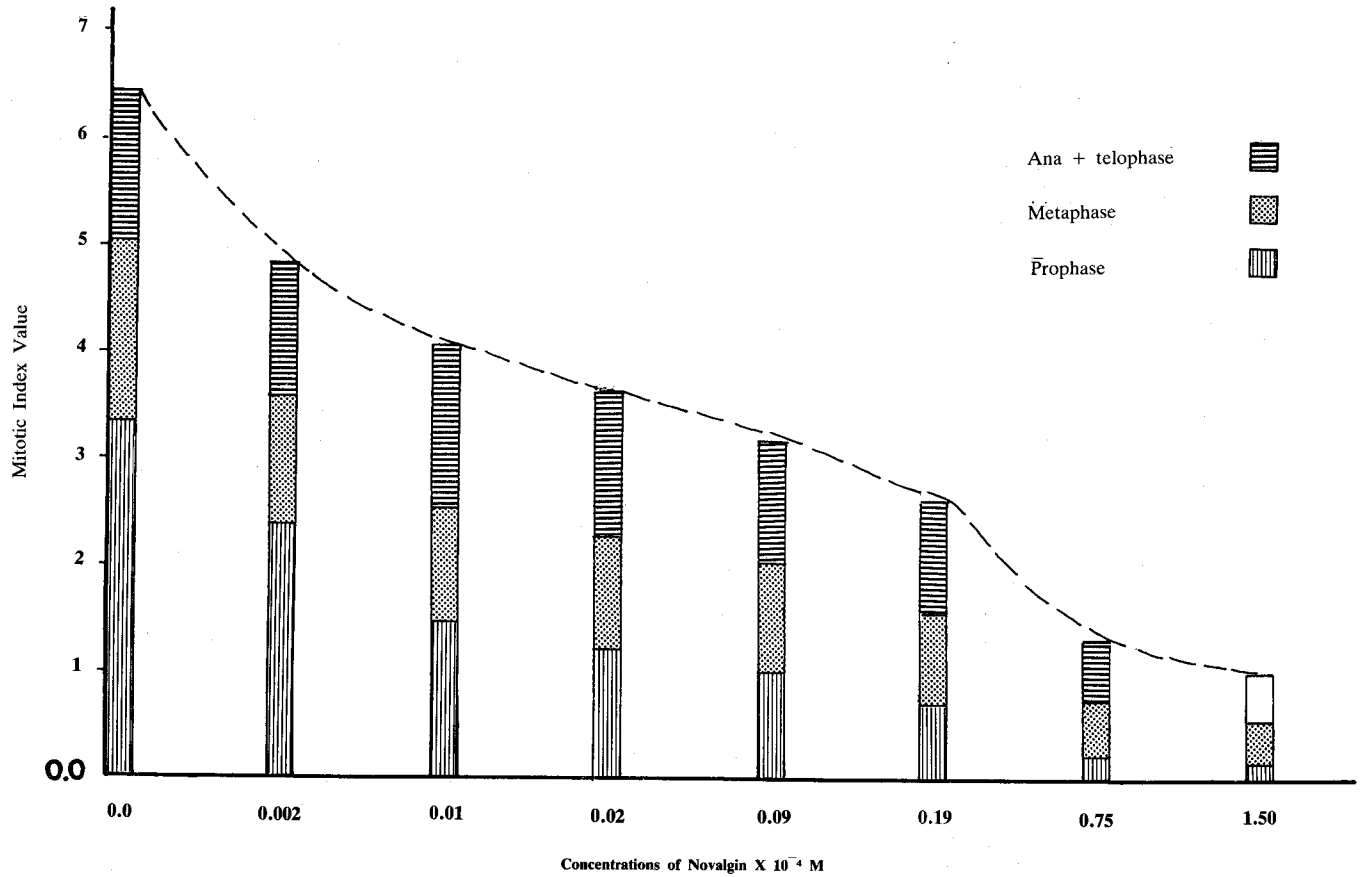


Fig (22) Frequencies of mitotic phases and mitotic indices after treating root tips of *Allium cepa* with different concentrations of Novalgin for 24 hours.

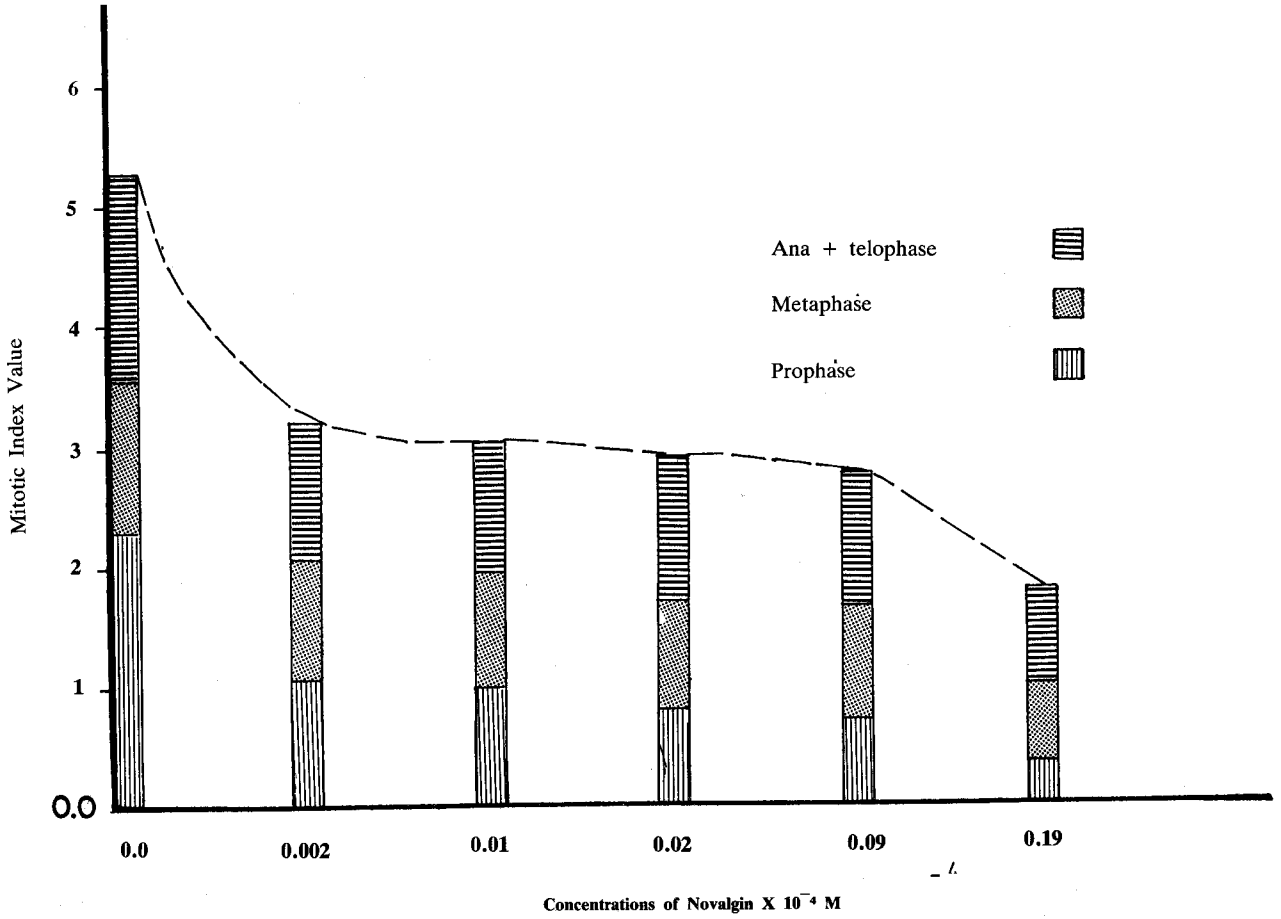


Fig. (23) Frequencies of mitotic phases and mitotic indices after treating root tips of *Allium cepa* with different concentrations of Novalgin for 48 hours.

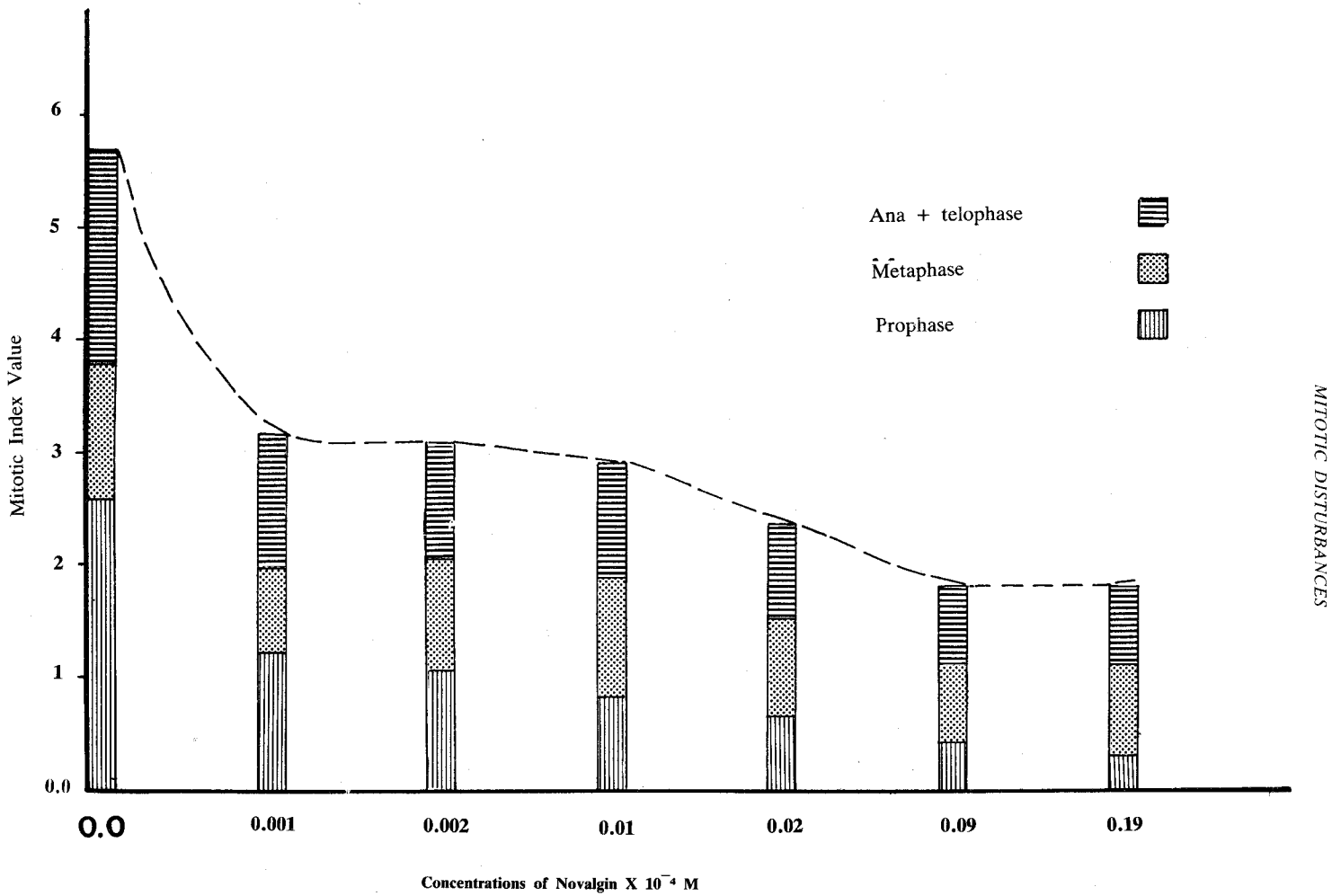


Fig. (24) Frequencies of mitotic phases and mitotic indices after treating root tips of *Allium cepa* with different concentrations of Novalgin for 72 hours.

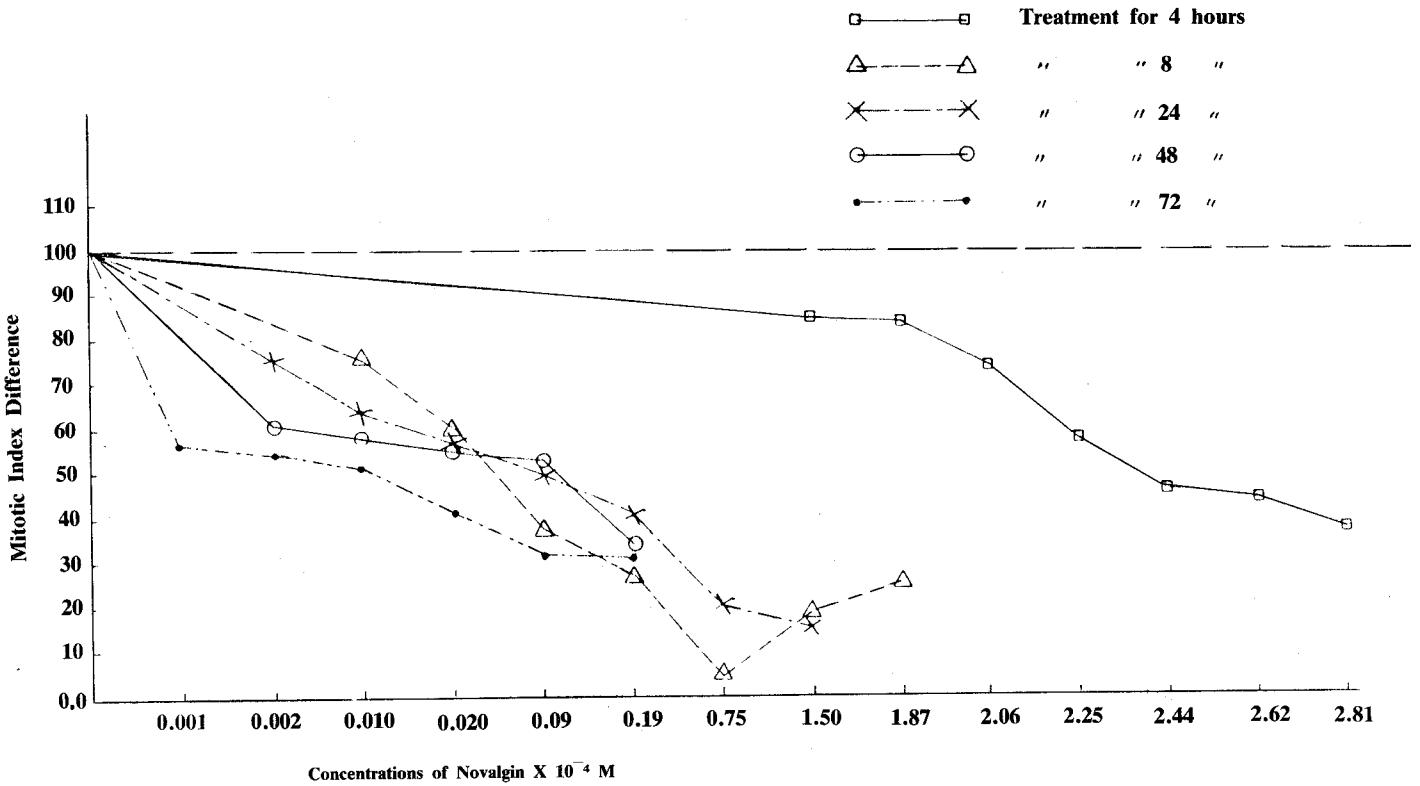


Fig. (25) Mitotic indices after treating root tips of *Allium cepa* with different concentrations of Novalgin for 4, 8, 24, 48 and 72 hours.

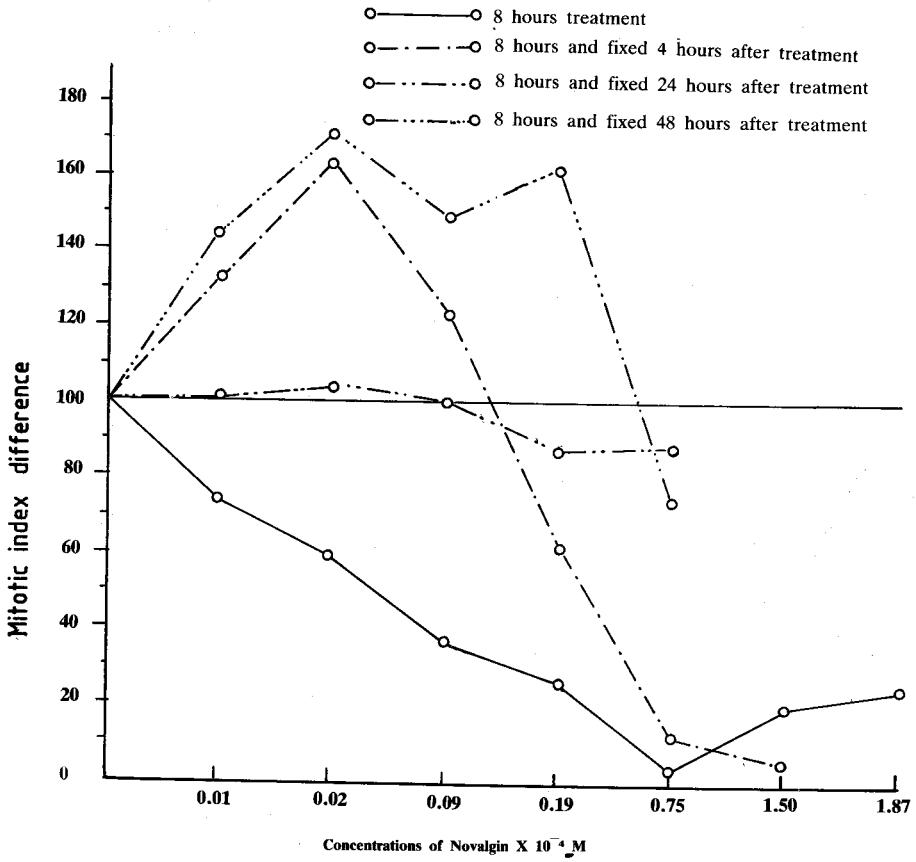


Fig. (26) Mitotic index difference after treating *Allium cepa* root tips with different concentrations of Novalgin for 8 hours and fixed for 4, 24 and 48 hours later.

Table 1

Total mitotic abnormalities and the percentage of abnormality for each stage and Mitotic index in roots treated with Novalgin for 4 hours.

Concentration X 10^{-4} M	Total No.	Total Mitosis	Total abn.		Prophase		Metaphase		Ana + Telo Anaphase		MI
			No.	%	No.	%	No.	%	No.	%	
2.81	12263	330	256	77.5	9	36.0	148	94.27	99	66.89	2.62
2.62	11674	377	209	55.43	11	15.49	140	89.74	58	38.67	3.13
2.44	11302	383	204	53.26	7	10.14	120	85.71	77	44.25	3.28
2.25	11720	498	179	35.94	10	7.87	104	63.41	65	31.4	4.08
2.06	11955	664	134	20.18	13	5.94	63	33.16	58	22.75	5.26
1.87	11700	733	103	14.05	16	5.5	56	23.73	31	15.05	5.90
1.50	11665	738	70	9.48	15	4.87	34	13.88	21	11.35	5.95
Control	11160	852	—	—	—	—	—	—	—	—	7.09

Table 2

Total mitotic abnormalities and percentages of abnormalities for each stage and Mitotic index in roots treated with Novalgin for 8 hours.

Concentration X 10^{-4} M	Total cells examined	Total cells mitosis	Total mit. abn.		Prophase		Metaphase		Ana +Telo		MI
			No.	%	No.	%	No.	%	No.	%	
1.87	13284	211	125	59.24	7	13.21	69	100	49	55.06	1.59
1.50	12608	150	64	42.66	7	13.73	39	95.12	18	31.03	1.19
0.75	11100	28	12	42.85	1	12.50	8	80.0	3	30.0	0.25
0.19	11476	198	57	28.78	3	4.62	39	57.35	15	23.08	1.73
0.09	11205	265	65	24.52	—	—	45	48.39	20	25.0	2.37
0.02	11294	431	32	7.42	—	—	27	19.85	5	5.10	3.82
0.01	10807	516	17	3.32	—	—	13	7.78	4	3.45	4.77
Control	10307	657	—	—	—	—	—	—	—	—	6.37

Table 3

Total mitotic abnormalities, percentages of abnormalities for each stage and mitotic index in roots treated with Novalgin for 24 hours.

Concentration X 10^{-4} M	Total cells examined	Total Mitosis	Total mit. abn.		Prophase		Metaphase		Ana +Telo		MI
			No.	%	No.	%	No.	%	No.	%	
1.50	9472	95	62	65.26	9	56.25	37	100.0	16	38.10	1.00
0.75	99.67	128	63	49.21	4	18.18	41	82.0	18	32.14	1.28
0.19	12679	328	79	24.08	8	9.20	42	39.25	29	21.64	2.59
0.09	12557	395	80	20.25	8	6.4	42	33.33	30	20.83	3.15
0.02	12801	458	63	13.75	5	3.25	32	23.70	26	15.38	3.58
0.01	12580	507	60	11.83	3	1.62	29	22.31	28	14.58	4.03
0.002	12741	613	19	3.09	3	1.01	7	4.52	9	5.63	4.81
Control	12734	814	—	—	—	—	—	—	—	—	6.39

Table 4

Total mitotic abnormalities, percentages of abnormalities for each stage and mitotic index in roots treated with Novalgin for 48 hours.

Concentration X 10^{-4} M	Total cells examined	Total Mitosis	Total mit. abn.		Prophase		Metaphase		Ana +Telo		MI
			No.	%	No.	%	No.	%	No.	%	
0.19	12293	222	120	54.05	15	35.71	76	90.48	29	30.21	1.81
0.09	13205	366	140	38.25	27	28.42	88	69.84	25	17.24	2.77
0.02	11358	330	98	29.69	12	13.33	62	59.62	24	17.65	2.91
0.01	12365	378	69	18.25	5	4.0	50	42.74	14	10.29	3.06
0.002	12189	388	44	11.34	2	1.52	32	27.35	10	7.19	3.18
Control	12288	648	—	—	—	—	—	—	—	—	5.27

Table 5

Total mitotic abnormalities, percentages of abnormalities for each stage and mitotic index in roots treated with Novalgin for 72 hours.

Concentration X 10^{-4} M	Total cells examined	Total Mitosis	Total mit. abn.		Prophase		Metaphase		Ana + Telo		MI
			No.	%	No.	%	No.	%	No.	%	
0.19	13604	242	132	54.54	12	28.57	96	87.27	24	26.67	1.78
0.09	13932	250	117	46.8	14	23.33	78	82.11	25	26.32	1.79
0.02	11470	268	90	33.58	16	21.05	56	58.33	18	18.75	2.34
0.01	12668	369	75	20.32	11	10.38	53	40.15	11	8.40	2.91
0.002	12368	382	64	16.75	8	6.06	46	37.70	10	7.81	3.09
0.001	12643	401	40	9.97	4	2.65	24	24.24	12	7.95	3.17
Control	12320	700	—	—	—	—	—	—	—	—	5.68

Cytological observation on the types of mitotic abnormalities induced by Novalgin for 8 hours treatment and recovery for 4, 24 and 48 hours

Mitotic abnormalities which were noticed in roots treated with Novalgin still appear after recovery in water for 4, 24 and 48 hours but with lower frequencies. The most characteristic abnormality observed at metaphase stage is C-metaphase. Chromosome fragments resulting from chromosome breakage are observed at this stage. Chromosome or chromatid bridges are still the most conspicuous types of abnormalities at anaphase. Such bridges were also seen at telophase stage. C-anaphase was frequently noticed which leads after restitution to the production of polyploid cells. Chromosome fragments resulting from chromosome breakage are also observed at anaphase and telophase stages. In addition, a tripolar anaphase is also observed at this stage.

DISCUSSION

The results obtained in the present study showed that Novalgin induced a number of mitotic abnormalities covering all the mitotic stages. C-metaphase appeared frequently in all the treated roots with variable frequencies. This indicated that Novalgin exerts its effect on the spindle fibres. However, its effect is partial, since there is no complete inhibition of the formation of spindle fibres. These results are in accordance with previous observations obtained after treating the cells with various drugs, e.g. antibiotic mycin (Nagl 1970), morphine sulphate and cannab' 'Kabarity *et al* 1974, 1976), and different tranquillizers (El-Bayoumi *et al* 1979, 1980).

The chromosome stickiness appearing after Novalgin treatment could be attributed to the high depolymerization of DNA (Darlington and La Cour 1945). Such depolymerization makes the surfaces of the chromosomes sticky. Chromosome stickiness has been observed in many types

of tissues after treatment with various chemicals and drugs (Soderman 1972, Mitra 1970). Sometimes, the stickiness may be specific at various points involving one or more chromosomes. This may lead to cross linkage between non-homologous chromosomes. Such stickiness is generally explained on the basis of breakage of the chromosomes at certain points and reunion. This type of stickiness was also observed in the present study.

The star metaphase appearing in the present study is explained on the basis that the chemical interferes in the free movement of chromosomes and thus they could aggregate together and be directed towards the centre.

One of the abnormalities induced by Novalgin was its ability to cause chromosome breakage. These breaks sometimes appeared to be localized at different positions in the same chromosome in both metaphase and anaphase forming gaps or appeared as separate acentric fragments. The presence of breaks in both metaphase and anaphase indicate that most of the breaks occured after DNA synthesis. Previous reports showed that there is a relationship between DNA synthesis and chromosome breakage (Evans 1969, Sturlied 1971). However, these results indicated that chromosomal aberrations were induced during all stages of the mitotic cycle. This differs from the results obtained in the present investigation, where a large number of breaks are observed during both metaphase and anaphase. The appearance of fragments at metaphase and anaphase and also micronuclei immediately after the treatment suggests that the breakage must occur in the post synthetic period of DNA either at late G_2 or at prophase.

Chromosome or chromatid bridges were observed at anaphase as a result of Novalgin treatment. The appearance of these bridges could be due either to the chromosome stickiness or to breakage and reunion at certain points. This is reasonable since Novalgin showed its ability to cause chromosome stickiness and chromosome breaks. In this respect, these results are similar to those obtained by Koerting-Kieffer and Mickey 1969, Gudkova *et al* 1970 and El-Bayoumi *et al* 1980.

One of the major effects of Novalgin on root tips of *Allium cepa* is shown on their influence on the rate of cell division. A drop in motitic index was noticed in all treated roots with various concentrations and for different periods of time compared to the control. Such a drop in mitotic indices indicates that Novalgin interferes with the normal sequence of cell division, thus preventing or reducing the number of cells entering the prophase stage at interphase. One of the reasons for reduction in mitotic activity could be due to inhibition of DNA synthesis, as indicated by Schneiderman *et al* (1971). Similar results were observed after treatment with ethyleneimine (Orvo 1969) and the drug Chlorimipramine (Mitwoch and Wilkie 1971). Reduction in cell division activity could also be due to changes in the relative durations of the mitotic stages in the mitotic cycle. Vant Hoff (1968) explained the drop of MI due to an increase in duration of the G_2 period rather than inhibition of DNA synthesis. Various chemicals are reported by other authors, which show the same effect such as the antibiotic mitomycin (Reich *et al* 1961). The recovery test showed that the effect of Novalgin is temporary and appears immediately after the treatment. The cells show a quick recovery after 12 or 24 hours following treatment.

Novalgin is widely used clinically. However, it is taken in an uncontrolled way. This may interfere with the genetic machinery. These results show the ability of Novalgin to induce a wide variety of mitotic abnormalities which could be an indication of dangerous cytological effects of Novalgin if extrapolation to human beings is possible.

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استحداث التغيرات في الانقسام غير المباشر
نتيجة تأثير العقار نوفالجين في القمم النامية لنبات البصل

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عوملت القمم النامية لنبات البصل بسبعة تركيزات من عقار النوفالجين تتراوح بين ٢,٨١×١٠$^{-٤}$ مول و ١,٥×١٠$^{-٤}$ مول لمدة ٤ ، ٨ ، ٢٤ ، ٧٢ ساعة .

وقد لوحظ ان معدل مراحل الانقسام غير المباشر اختلفت تبعا لتركيز العقار ومدة المعاملة ، وبصورة عامة فإن معدل الانقسام انخفض مع زيادة تركيز العقار .

وقد أحدث عقار النوفالجين العديد من الشذوذ فى الانقسام غير المباشر وتعتمد نسبة كل نوع من الشذوذ ـ الطور الاستوائى الكولشسينى ، لزوجة الكروموسومات ، الطور الانفصالى الكولشسينى ، ثلاثية الاقطاب ، الجسور الكروموسومية ، تخلف الكروموسومات فى الطور الانفاصلى ، والانوية الصغيرة ومتعددة الانوية فى الطور البينى .

ومن أهم تأثير عقار النوفالجين هو قدرته على احداث الكسور الكروموسومية والتى لوحظت عند معاملة الجذور بتراكيز مختلفة وفترة معاملة مختلفة وخاصة عند المعاملة بالتراكيز المخففة . وتختلف عدد الكسور من كسر واحد الى عدة كسور فى المرحلة الاستوائية وكذلك فى اعداد القطع الكروموسومية اللاسنترومرية .

وقد اجريت تجربة للتعرف على المدة اللازمة للاستشفاء من تأثير العقار ، فعوملت الجذور لمدة ٨ ساعات ثم نقلت الى الماء المقطر وتركت لمدد ٤ ، ٢٤ ، ٤٨ ساعة ثم قطعت الجذور وثبتت وفحصت . لوحظ ان الخلايا بدأت تسترجع قدرتها الطبيعية وتشفى من تأثير العقار بعد تركها فى الماء لمدة ٤٨ ساعة بالرغم من وجود عدد محدود به شذوذ فى مراحل الانقسام المختلفة .