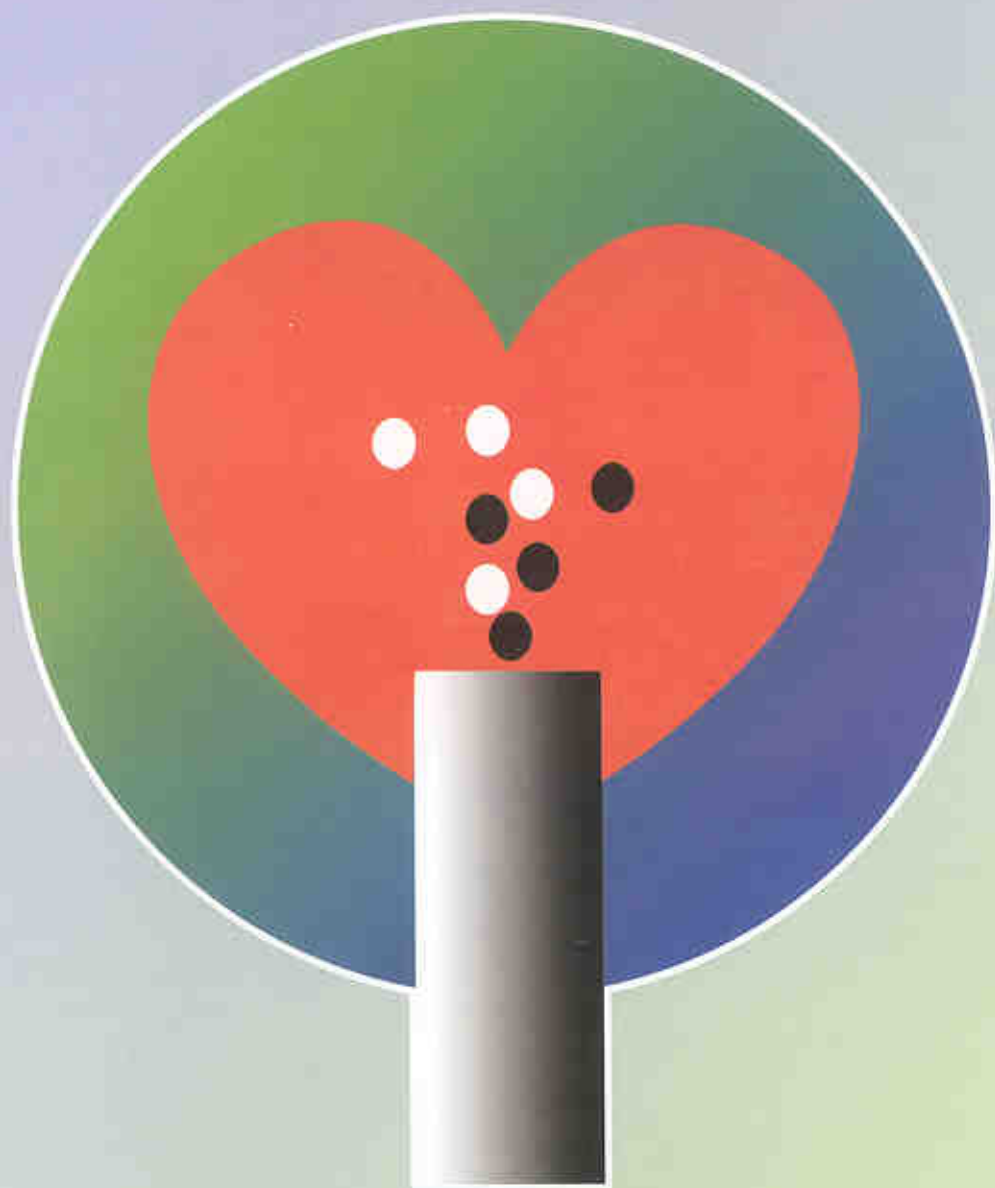


TABEX

For clean lungs

For a healthy heart



sopharma

TABEX

**FOR
CLEAN LUNGS**

**FOR
A HEALTHY HEART
S O P H A R M A**



sopharma

**SOFIA
2000**

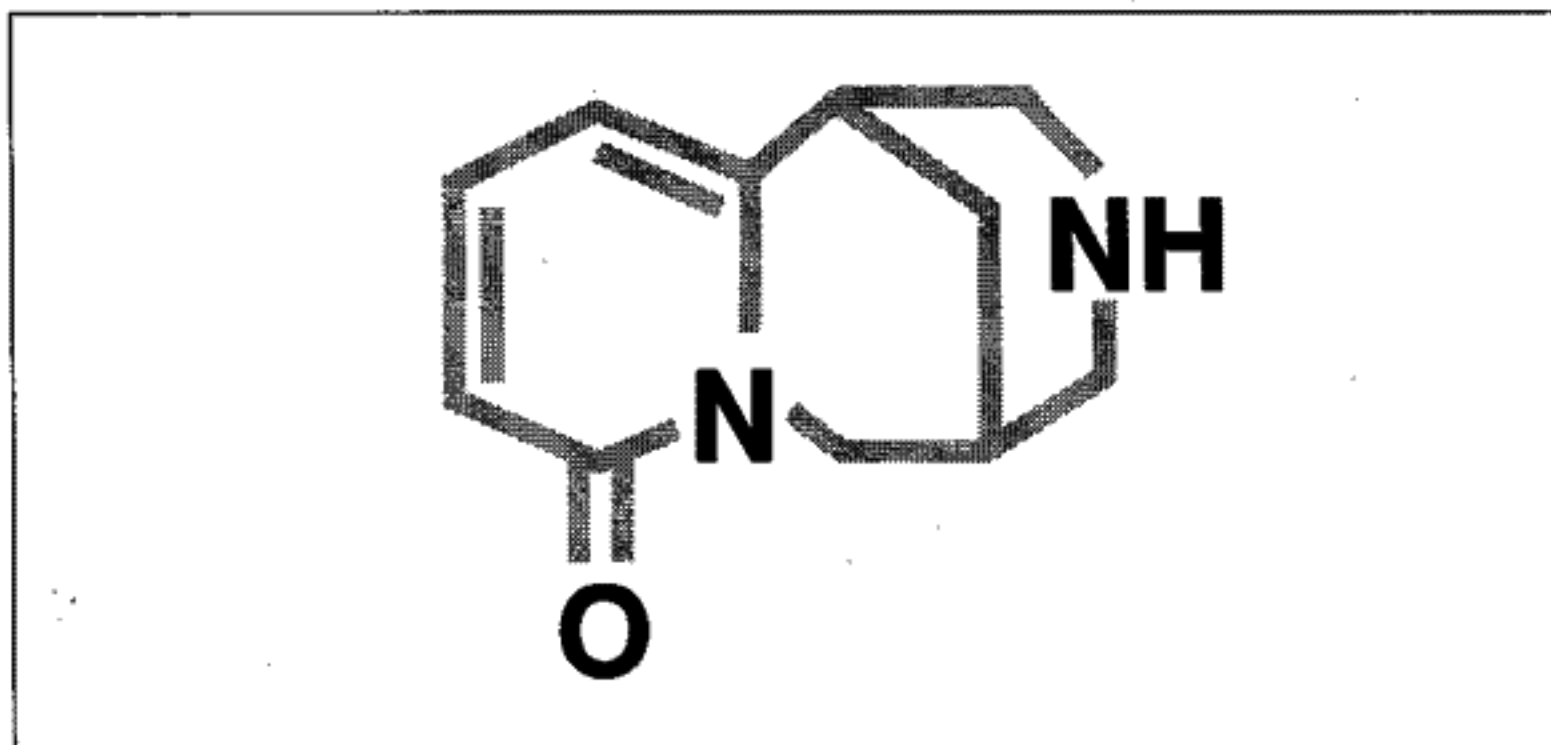
TABEX

filmtablets

Tabex is an original Bulgarian drug of vegetal origin for the treatment of nicotine. It is developed on the basis of the alkaloid cytisine contained in the plant *Cytisus laborinum* L., also called golden rain, widespread in the southern areas of Central Europe and Italy. All parts of the plant contain alkaloid cytisine, the greatest amount (up to 3%) being found in the seeds.

Fig. 1

Structural
formula of
cytisine (1R-
cis)-
1,2,3,4,5,6-
Hexahydro-
1,5-metano-
8h-pyrido
[1,2a][1,5]
diazocin-8-on



Chemical characteristics and content of Tabex

Each tablet contains 0.0015 g cytisine

Empirical formula of cytisine: $C_{11}H_{14}ON_2$

Ensuing from the molecular orbital calculations after Kier (1969), it is evident that the molecular configurations of nicotine and acetylcholine have a quaternary nitrogen atom which is with a negative charge and located at 4.85 ± 0.1 Å, considered to be responsible for the nicotine-like activity. In cytisine the nitrogen atom in ring C appears at 4.8-9 Å from the oxygen atom of the pyridine group and is also negatively charged.

The prolonged clinical and toxicological studies in many countries all over the world have proved the enormous harm of smoking on all organs and systems of the human organism. The danger of cardiovascular incidents (myocardial infarction, stenocardia, peripheral vascular diseases), diseases of the respiratory system (lung cancer, tracheobronchitis, etc.), diseases of the digestive system (gastritis, inflammation of the oral mucosa, etc.), as well as psychic and physiological dependence of addictive type is mostly emphasized.

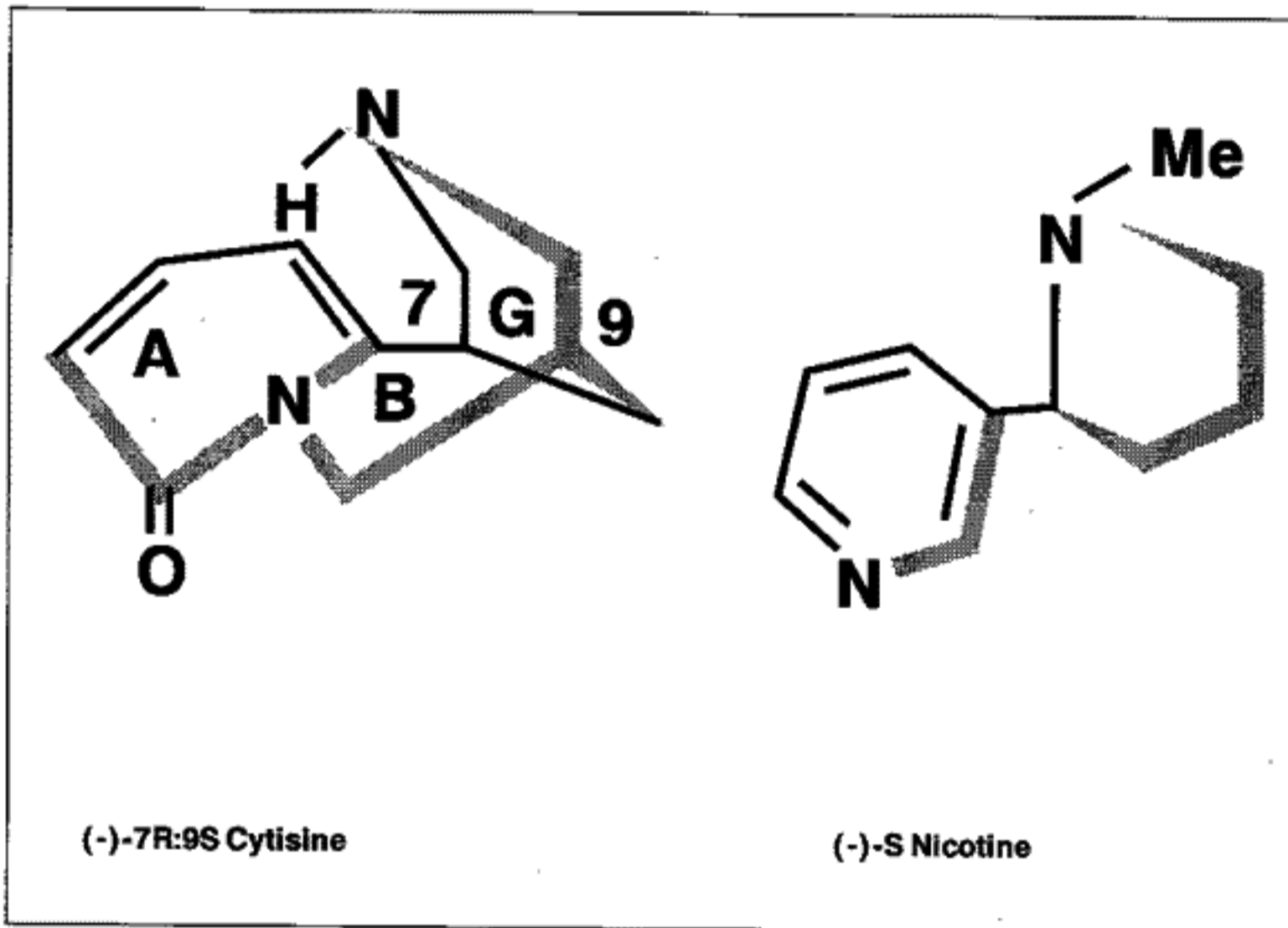


Fig. 2

Stereoisomeric formulae of cytisine and nicotine (after Barlow, R.B. and McLeod, L.J.)

The treatment of nicotine addiction is a complex process in which drug therapy occupies an important part. The Sopharma company produces the drug Tabex, developed on the basis of the alkaloid cytisine, which has an action similar to that of nicotine.

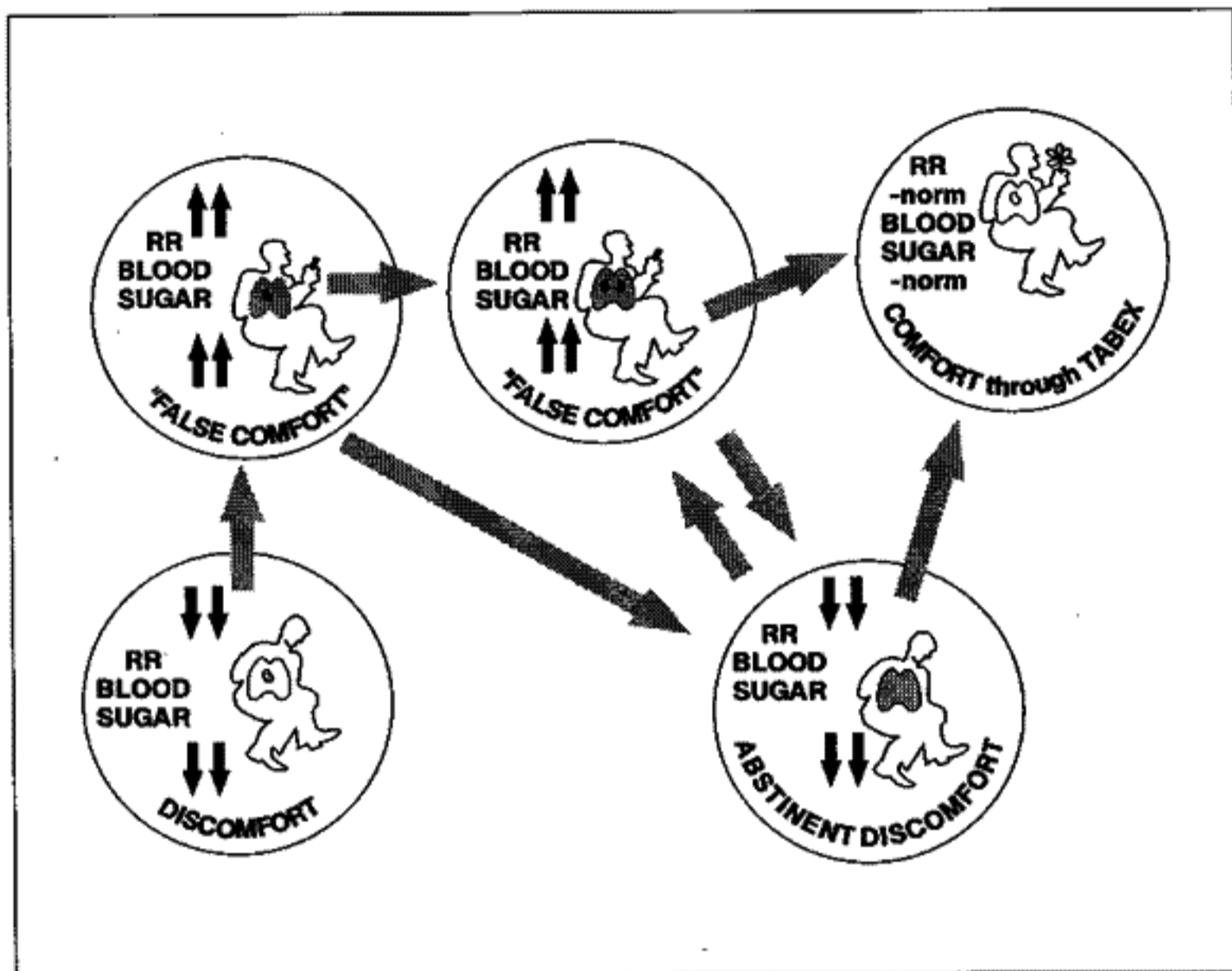
PHARMACODYNAMICS OF CYTISINE

Cytisine is an agonist of the cholinoreceptors in the vegetative ganglia and belongs to the group of the gangliostimulating drugs. It excites the nicotine-sensitive cholinoreceptors of the postsynaptic membranes in the vegetative ganglia, chromaffin cells in the medullar part of the suprarenal gland and sinocarotid reflexogenic zone, which results in excitation of the respiratory centre, predominantly through the reflexes, stimulation of adrenaline release by the medullar part of the suprarenal glands and a rise in the blood pressure. After its absorption in the gastrointestinal tract, cytisine plays the part of a nicotine-substitute substance which decreases the period of interaction between nicotine and the corresponding receptors. This in turn leads to a gradual decrease and interruption of the smokers' psychic and physical nicotine dependence.

Many researchers confirm in different pharmacological experiments the similarity between the pharmacological properties of cytisine and nicotine, as described by Dale & Laidlaw (1912) and confirmed also by the conclusions of Zachowsky (1938), Anichkov (1937), Dobrev and Paskov (1953), Daleva (1963), etc., in whose opinion cytisine is more potent as a gangliostimulating than as a ganglioblocking agent.

Fig. 3

Mechanism of action of cytisine
Creation of the vicious circle of tabacisme and the way to exit from it by means of TABEX



This similarity between the peripheral effects of cytisine and nicotine is more quantitative than qualitative. Comparable effects of both drugs have been obtained in experiments on cats and rats (studies on the blood pressure), or on guinea-pig ileum and rat diaphragm, the doses of cytisine being 1/4 to 2/3 from the nicotine dose.

As regards the effects on the central nervous system, cytisine has a weaker effect on the respiration of anesthetized rabbits, compared to the effects on the peripheral nervous system.

PHYSIOLOGICAL MECHANISMS OF THE ORIGIN OF NICOTINE DEPENDENCE AND ITS OVERCOMING

Paun D. and Franze J. have studied and analysed the physiological prerequisites for the harmful habit of smoking. After inhalation of a cigarette by a person with low blood pressure and possibly also with low blood sugar content, for about 20 minutes nicotine increases the blood pressure and the blood sugar level. In persons with normal blood pressure and blood sugar values, the nicotine in the blood leads to hormonal and vegetative changes in the organism, while the discontinuation of

smoking leads to a decrease in the blood pressure and blood sugar values. That is why, nicotine abstinence is clinically manifested with exhaustion, tiredness, poor concentration and irritability (abstinence manifestations), which provokes a strong craving for nicotine. The abstinence syndrome can be controlled by restoring the normal blood pressure and blood sugar values by means of analeptics, tranquilizers and mostly by means of specific drugs, such as cytisine, lobeline, etc. These specific drugs „replace“ nicotine by acting on the same functional receptor constellations.

TOXICITY OF CYTISINE

Tabex was experimentally studied for its toxicological action on different kinds of experimental animals. The acute LD₅₀ toxicity, the subchronic (30 days) and the chronic (80-180 days) toxicity were determined. The acute toxicity was determined on line H albino mice (intravenously, subcutaneously and orally); rats (intraperitoneally, subcutaneously and orally); dogs (subcutaneously and orally).

Mice		
Intravenously	♂	2.3 (1.3-3.6)
	♀	3.1 (1.8-5.2)
Subcutaneously	♂	13 (11-15.3)
Orally	♀	13 (8.5-19.9)
		29 (22-37)
Rats		
Intraperitoneally		9 (8.9-10.3)
Subcutaneously		11 (7.7-15.6)
Orally		38 (17-83.6)
Dogs		
LD ₀		4 mg/kg
LD ₀		25 mg/kg

Table 1

Acute LD₅₀ toxicity in mice, rats and dogs with different modes of administration

The mice and the rats were divided in groups of six animals and the dogs in groups of 2 animals for each dose used. The behaviour of the animals and the lethality were observed daily for 7 days after the drug was applied. All the results obtained were statistically processed according to Litchfield-Wilcoxon's method. During the experiments the animals received standard food and water *ad libitum* (Angelova, O.).

During the observation the following toxic symptoms were found: accelerated respiration, clonic and tonic convulsions, motility disturbances in the hind legs, lower muscle tonus. The absorption index in rats was 4.2. In dogs, injected subcutaneously with 4 mg/kg, the changes occurred one hour after the treatment. The animals began vomiting, clonic and tonic convulsions of body and limbs muscles appeared. The movement was slow and phlegmatic. When stimulated by force, they became aggressive. On the following day the animals restored their normal behaviour. No lethality was noted. After oral administration of doses of 15-25 mg/kg, the dogs showed no external symptoms of toxicity.

The results of the acute toxicity studies showed that cytisine was much less toxic than intravenously applied nicotine, but it was more toxic after intraperitoneal and oral administration.

Table 2

Comparison between acute toxicity of cytisine and nicotine

		<i>Mode of administration</i>			
		i.v.	i.p.	p.o.	
<i>Nicotine</i>	LD ₅₀ μmoles/kg	1.92	59.0	1.425	
		1.75-2.12	53.665.0	1.370-1.486	
	LD ₅₀ mg/kg	0.3	9.5	230	
		(6)	(7)	(9)	
	<i>Time of death</i>		32.0±0.8	2.42±0.1	2.86±0.1
			sec (28)	min (38)	min (45)
<i>Equipotential molar ration</i>		1	1	1	
<i>Cytisine</i>	LD ₅₀ μmoles/kg	9.10	49.5	535	
		7.9-10.5	46.6-57.5	411-696	
	LD ₅₀ mg/kg	1.73	9.4	101	
		(6)	(6)	(7)	
	<i>Time of death</i>		37.2±3.1	5.32±0.4	12.7±0.6
			sec (36)	min (28)	min (46)
<i>Equipotential molar ration</i>		4.75	0.84	0.37	

SUBACUTE TOXICITY

The experiments for subacute toxicity were carried out on line H albino mice and Wistar rats of both sexes equally, treated orally with aqueous solution of Tabex with the following terms and doses: mice - for 45 days with a dose of 3.3 mg/kg and rats - for 30 days with a dose of 7.6 mg/kg.

The chronic toxicity was studied on Wistar rats and on dogs treated orally with aqueous solution for the rats and substance in the feed - for dogs, at the following terms and doses:

Rats - for 90 days with doses: 1.36, 0.45, 0.90 mg/kg;

Rats - for 180 days with doses: 0.45, 0.90 mg/kg;

Dogs - for 180 days with doses: 0.45 mg/kg.

The control groups of animals were treated with equivalent amounts of water. All the animals received standard feed and water ad libitum. The behaviour and lethality of the animals were observed daily. The following clinical-laboratory and pathoanatomical examinations were carried out:

Hematological:

Hb, RBC, WBC, platelets, leukocyte formula, prothrombin index

Biochemical:

serum bilirubin, blood sugar, blood urea

Urine:

albumin and sediment

Pathoanatomical:

examination of internal organs

The data obtained were statistically processed according to Student-Fisher's method.

No changes in the behaviour of the experimental animals were observed during the experiment carried out. No changes were likewise noted in the clinical-laboratory indices studied. The pathoanatomical examinations showed a different degree of dystrophic changes in the liver of the mice treated with 3.3 mg/kg and in the dogs treated with 0.45 mg/kg.

The following enzyme indices were examined: transaminases - SGOT and SGPT, and alkaline phosphatase in chronic experiment on white Wistar rats and dogs treated orally with the following doses and terms:

Rats - for 90 days with a dose of 1.35 mg/kg;

Rats - for 180 days with doses of 0.45 and 0.90 mg/kg;

Dogs - for 180 days with a dose of 0.45 mg/kg.

A statistically significant increase of SGOT was found in the group treated with 1.35 mg/kg for 90 days. The SGOT level was twice higher than that of the control group. The results obtained showed hyperenzymemia of SGOT and coincided with the data of Veress and Rengei about the influence of nicotine on the level of this enzyme.

On the basis of the toxicological studies we can make the following conclusions:

1. According to Hodge and Sterner's classification for oral administration to rats, Tabex belongs to the group of strongly toxic drugs with a good absorption index.

2. When given orally to rats for 30 and 90 days, Tabex shows no toxic changes in the hemopoiesis and internal organs of the experimental animals.

3. When applied orally to mice for 45 days and to rats and dogs for 180 days, Tabex does not cause any toxic changes in the hemopoiesis and in the internal organs, except different degrees of dystrophic changes in the liver.

THERAPEUTIC RANGE AND TOLERANCE

The therapeutic range of cytisine is much greater than that of nicotine.

The daily therapeutic saturating doses of Tabex is 1.5 to 9 mg. The pharmacodynamic results obtained by Barlow et al. show that when applied at much higher concentrations in comparison with those of nicotine, Cytisine causes parasympathetic block of N-cholinergic receptors. Thus, for instance, the upper cervical ganglion of cat is blocked with 1.17 ± 0.07 against 100 nmol for nicotine.

Tabex is very well tolerated, it does not provoke anorexia, nausea and vomiting in therapeutic doses. When applied according to appropriate schedule, it enables smokers to give up smoking gradually, without developing abstinence symptoms.

CLINICAL STUDIES

Tabex was clinically tested on a large number of patients. Stoyanov S. and Yanachkova M. studied 70 volunteers with a long experience in smoking and found that 57% stopped smoking, in 31.4% the result was partial: reduction of the cigarettes smoked from 20-30 to 3-4 a day. The results were negative in about 11% of the patients, which is due to the premature abandoning of the therapeutic course: before the 3rd day of treatment - a period of time necessary to saturate the organism with cytisine. In a second group of 17 smokers with serious psychic diseases (schizophrenia, epilepsy and reactive psychosis), the administration of Tabex together with neuroleptics, antidepressants and insulin led 5 patients to stop smoking and induced significant decrease - in 7. Tabex does not interact unfavourably with the drugs received by the mentioned groups of patients.

Vlaev S. et al. consider the possibility to control the depressive symptoms in 5 patients with psychogenic and periodic depression, parallel with the treatment of the pathologically fixed wish to smoke. Tabex was applied in gradually increasing doses, the maximum daily dose being 15 mg (5 tablets 3 times daily). The author has observed a rapid reduction of the depressive symptoms, the improvement of the patients with reactive depression being obtained at the end of the first week, in the patients with periodic depression - by the end of the second week. The improvement is particularly good with respect to the patients' activity, followed by the mood and finally by the depressive mental symptoms. As a side effect, the slight internal tension and a slight decrease of blood pressure are pointed out. The antidepressive action of the drug is explained with the increase of the catecholamine level, especially that of adrenaline, which is reduced in depressive patients. The adrenostimulating effect of Tabex has been well known for a long time, but its antidepressive activity is reported by Antonov L. and V. Velkov in an experiment on laboratory rats (by overcoming Persolt's test of immobility).

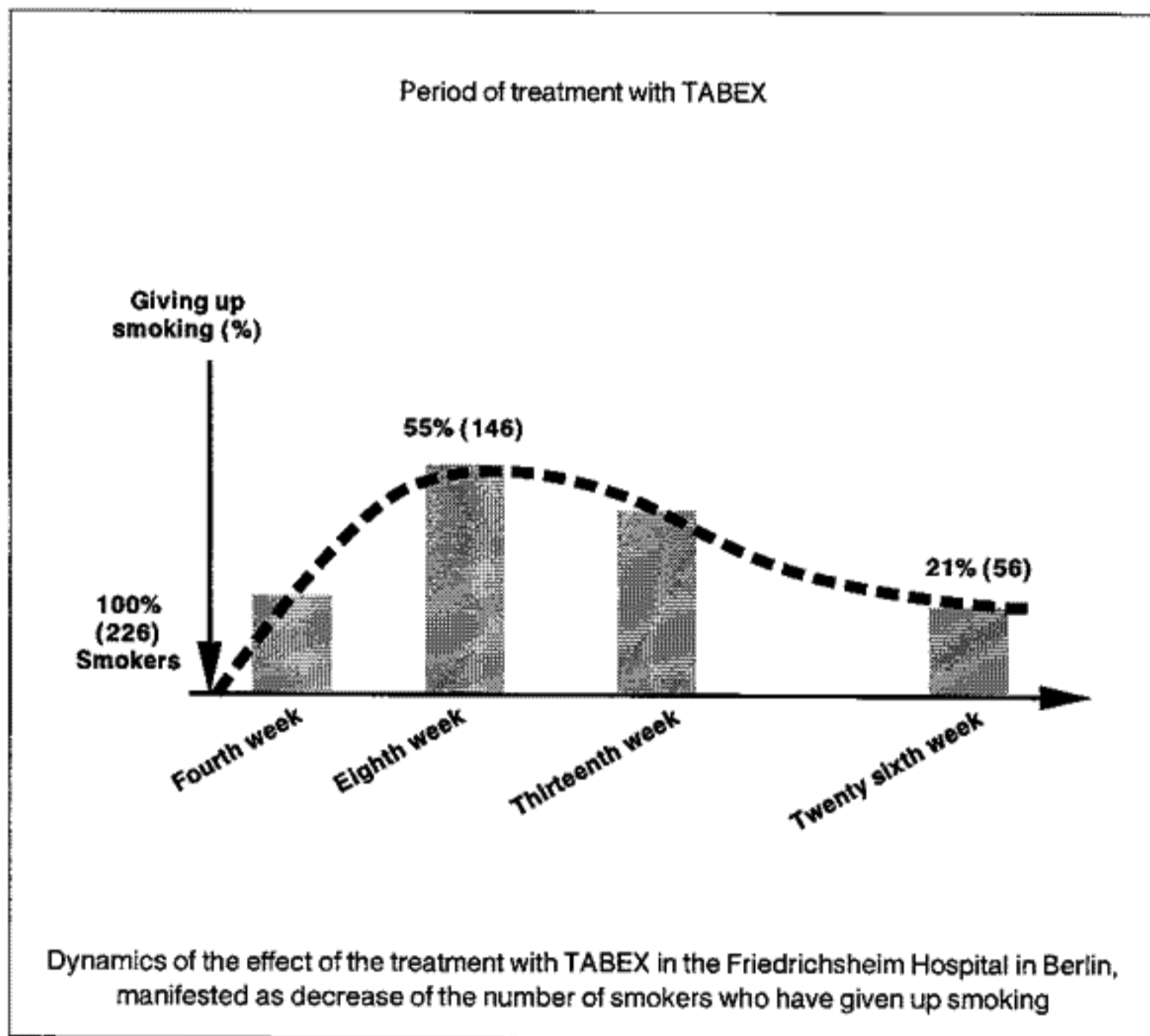


Fig. 4
Clinical testing of Tabex in smokers without concomitant bronchitis

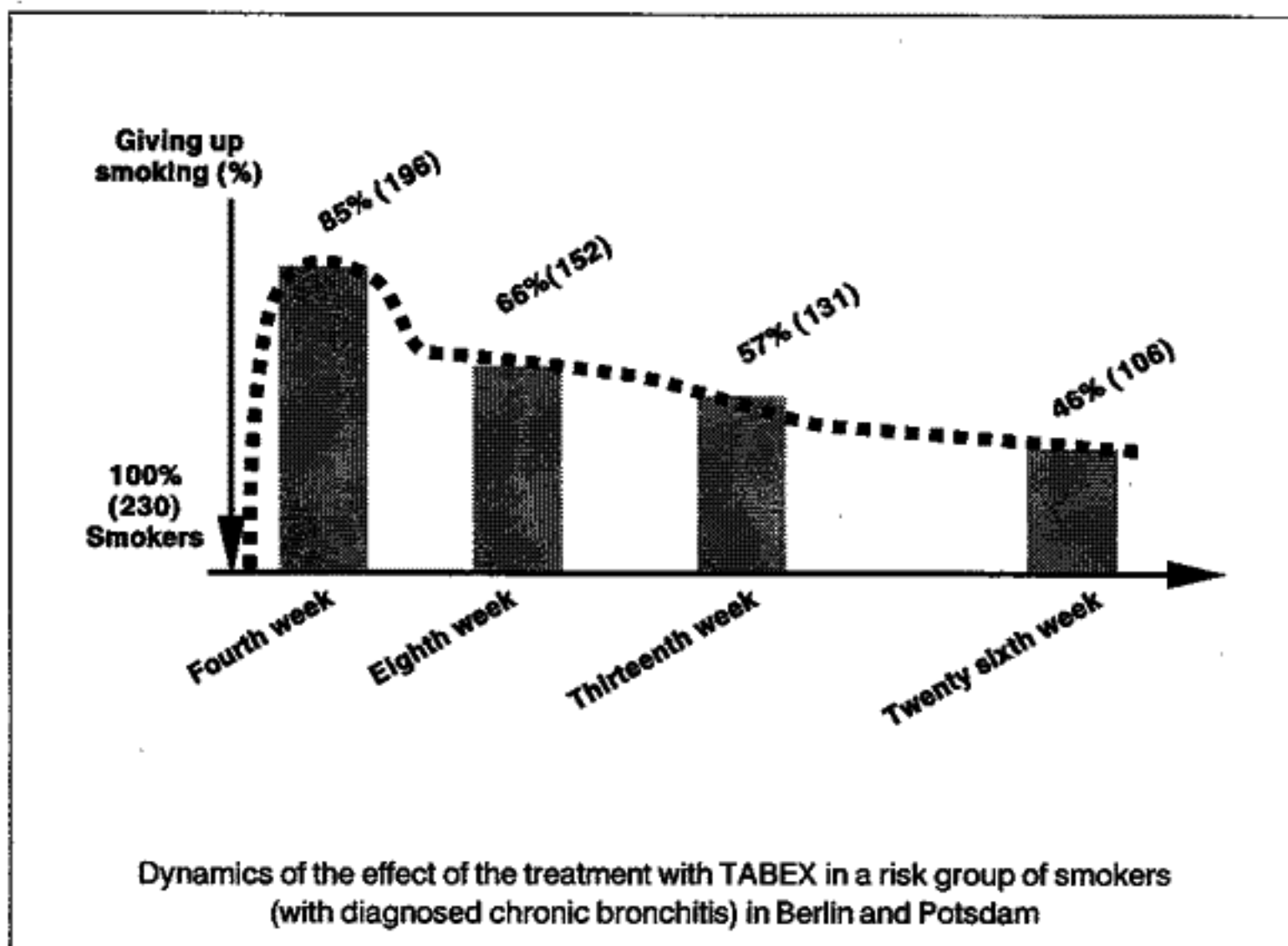
The antidepressant action is confirmed by the exacerbation of the schizophrenic psychosis in two patients who have received Tabex in a state of remission. The effect resembles the picture of the application of the antidepressant psychoforin to schizophrenic patients. These data are confirmed by Stoyanov and Yanachkova in psychic patients. These authors pointed out that the simple form of depression is appropriate for Tabex treatment with very careful increase of the daily doses.

Paun D. and Franze J. from the Friedrichsheim Hospital in Berlin studied the therapeutic effectiveness of Tabex in 266 smokers, by comparing it to the effect obtained in 239 patients treated with placebo. The therapeutic results were followed on the 4th, 8th, 13th and 26th week of Tabex treatment. The patients with a serious intention to give up smoking have priority. On the 8th week, 55% of the patients treated with Tabex gave up smoking, this percentage decreasing to 26% at the end of the 26th week. However, the recidivists in the main group reduced twice the number of cigarettes smoked. The authors emphasize the statistically significant very good effect in the group treated with Tabex, compared to the group treated with placebo, and conclude that the drug may be successfully used when the patient has a serious intention to give up smoking, especially when the concomitant psychotherapeutic means cannot obtain such an effect.

The authors have also treated with Tabex 366 smokers with concomitant bronchitis and 239 patients treated with placebo. After completing the full treatment course (maximum duration 4 weeks), 55% of the patients gave up smoking, while in the group with placebo there was an effect in only 34%. Out of 230 smokers with chronic bronchitis (Berlin and Potsdam), treated with Tabex, 85% gave up smoking by the end of the 4th week, after 8 weeks - 66% and after 23 week - 46%. Almost all patients who had given up smoking manifested subjective improvement of the bronchitic symptoms.

Fig. 5

Clinical testing of Tabex in smokers with chronic bronchitis



Schmidt F. conducted volume testing of 14 preparations on 1975 smokers by means of a double-blind placebo-controlled experiment. Tabex was given to 181 patients. The results obtained show that patients treated with Tabex have had optimum improvement. 103 patients (57%) gave up smoking, after 3 months this percentage decreased to 38%. Tabex is followed by the drugs niperli (54% and 48% respectively), atabaco (54% and 29% respectively), citotal (50% and 36% respectively), unilobin, potassium chloride, potassium granulate, potassium citrate, nicobrevin, targophagin,

etc. The volunteers received by mail instructions concerning the mode of treatment, thus avoiding the influence of the extrapharmacological factors, hence the results registered by the patients themselves in inquiry forms are maximally reliable.

On the basis of the multicentre clinical-pharmacological studies, we can make the following general conclusions concerning the therapeutic effectiveness of Tabex:

1.

The drug was tested on 1045 volunteers and compared to 400 patients treated with placebo and 1500 patients treated with other anti-smoking drugs.

The results obtained show that 55 to 76% of the patients treated with Tabex gave up smoking. These generalized percentages from different studies are statistically significant and are higher than those of the other preparations compared.

2.

Tabex showed a good effect on the chronic pulmonary diseases accompanying prolonged smoking, as well as on patients with psychic diseases of a depressive nature.

3.

No serious side effects have been noticed by observing the cited contraindications: severe hypertension and atherosclerosis.

4.

An improvement of the general state of the patients was observed, due to the discontinuation of the chronic intoxication with nicotine.

5.

An active approach is necessary in patients who have failed during the first course by repeating the treatment course at intervals of 4-5 months.

INDICATIONS

Tabex is a drug of choice for treatment of chronic nicotine dependence. It is particularly appropriate for treatment of risk groups of smokers with health problems on the part of the cardiovascular and respiratory systems, as well as smokers professionally subjected to tension and stress that predispose to seek a „false comfort“ by nicotine or other drugs causing dependence.

CONTRAINDICATIONS

Advanced atherosclerosis, some forms of schizophrenia, pheochromocytoma, conditions connected with severe impairment of the cardiovascular system and malignant hypertension.

DOSAGE

Tabex is administered orally in a dose of 1 tablet every 2 hours (6 tablets daily) for 3 days at corresponding reduction of the number of smoked cigarettes.

The treatment proceeds according to the following scheme:

- from the 4th to 12th day - 1 tablet every 2,5 hours

(5 tablets daily);

- from the 13th to 16th day - 1 tablet every 3 hours

(4 tablets daily);

- from the 21st to 25th day - 1-2 tablets daily.

Complete discontinuation of smoking must occur by the 5th day of treatment.

OVERDOSAGE

As antidotes at overdosage of the preparation Tabex one may use tranquilizers (anticonvulsive effect) and antihypertensive drugs (decrease of the blood pressure).

SIDE EFFECTS

The high doses may provoke nausea, vomiting, dizziness, tachycardia and muscle weakness. These effects pass quickly after the dose is decreased.

DRUG INTERACTIONS

The analeptic effect of cytosine decreases during combined therapy with antituberculosis drugs (PASA, streptomycin, etc.).

WARNING

The drug should be administered carefully to patients with exacerbated peptic ulcer.

After completing the treatment course, the patients should refrain from smoking even one cigarette, in order to obtain a lasting effect.

SUPPLIED

Filmtablets of 1.5 mg in packages of 100.

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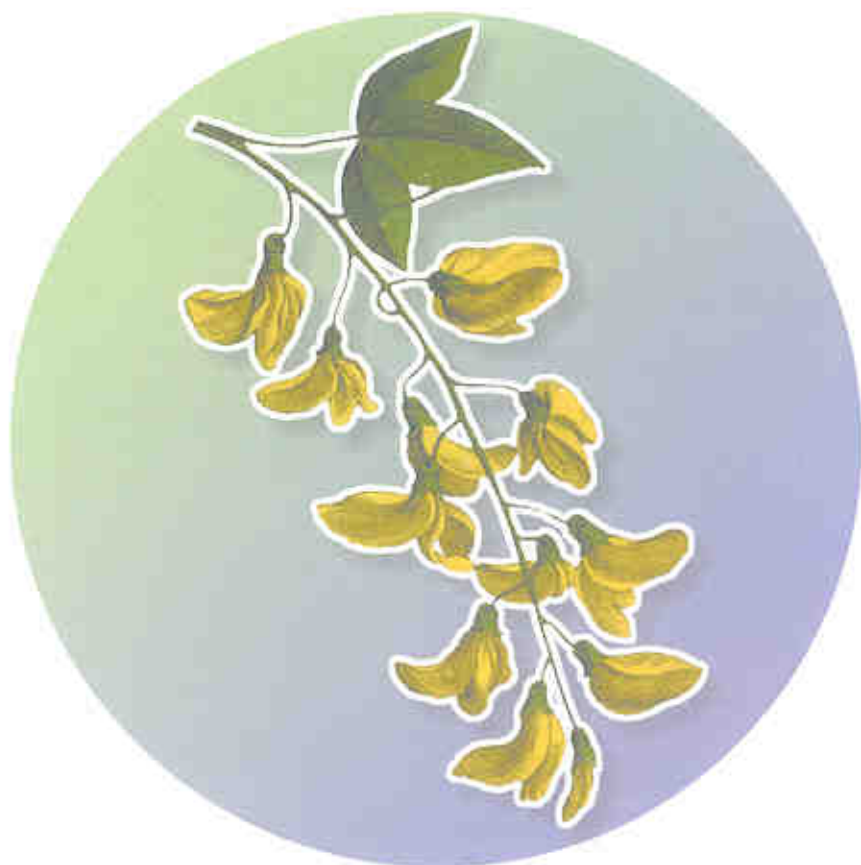
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