the bile of dogs is very rapidly cleared from the body of rats[9]. Experiment 2, a repeat of experiment 1, was conducted to check whether possibly induced liver enzymes affect biliary excretion of tritium activity, since in the rat an increase in heptic microsomal P-448-mediated enzyme activities has been reported already at doses of 2 ng of TCDD/kg[8]. Obviously, the small dose of ^{3}H-TCDD was not sufficient for a stimulation of TCDD-metabolism in the dog. From our results it is reasonable to assume that P-448-dependent liver enzymes are involved in the biotransformation of the dioxin. Because of the very distinct effect of TCDD, the most potent out of the group of P-448 inducers, no other classical inducer was investigated. It should be considered that a faster elimination might cause the acute toxicity of TCDD to decrease. In view of data from Beatty et al.[10], who found a higher LD_{50} in male weanling rats pretreated with TCDD (but also with phenobarbital) this seems likely, because the time during which the organism is in contact with this substance certainly plays an important role. Furthermore, available data suggest that TCDD is essentially eliminated from the body only in metabolized form. Whether inducibility of TCDD-metabolism is a phenomenon unique in the dog is a question that deserves further study.

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The use of indentometry to study the effect of agents known to increase skin c-AMP content

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Summary. Local, externally applied pharmacological agents which are assumed to raise the c-AMP level, decrease the low pressure indentation value of the forehead skin of certain human volunteers.
Key words. c-AMP, skin; indentometry; pharmacological manipulation of mechanical parameter.

Recently low pressure indentometry has been used to measure 'dermal hydration'[1,2] in vivo. This method is used for measuring an aspect of the efficiency of cosmetic treatments and also as a routine diagnostic instrument in medicocosmetic consultation[3]. The measuring system, procedure and instrumentation have been described elsewhere[3]. In essence they are based on low pressure procedures. A light metal measuring rod is counterbalanced so that the net pressure of the system is less than 1 g/cm^2. A circular plate at the end of the rod, having a surface area of 0.2 cm^2, serves as the contact area with the skin. The total weight of the system (including the counterbalance) is 6 g. The measuring rod can be loaded with specially constructed weights, thereby increasing the pressure from the starting pressure to any desired value. The routine final pressure used in our laboratory for in vivo measurements on humans is 10 g/cm^2. The rod is connected to a linear variable differential transformer (LVDT), the output of which is graphically recorded. The routine paper velocity used by us is 6 cm/min. The sensitivity of the measurements is $\pm$ 0.001 cm.

For many reasons[2], the routine measurements are performed on the forehead skin. The patient lies on his/her back with eyes closed and head resting on a wooden plate to prevent recording of breathing and heartbeats. The measuring rod is adjusted so that the plate is in contact with the forehead skin, and the electronic system is zeroed (starting pressure = 1 g/cm^2). The recorder is started and the base line is recorded for about 10–15 sec. The standard weight is now suddenly applied, and the resultant indentation recorded for 6 sec. The weight is then removed and the rebound phase ('elastic recovery') of the skin is recorded for a further 6 sec.

The indentation so measured by low pressure indentometry on the forehead skin is 0.04–0.09 cm. Without treatment, the mean change in the indentation of an individual point during the day is less than $\pm$ 0.003 cm.

It was shown that indentation is usually higher in the so-called 'cosmetically dry skin' cases, and always lower in the 'cosmetically not dry skin' cases, and further, that age increases indentation[3]. We also showed that indentation under our standardized conditions is increased by intradermal hyaluronidase and decreased by water, thus indicating that indentometry reflects the state of ground substance[4].

We wish to discuss here pharmacological agents affecting indentometry. Each substance was tested on four volunteers who had 'high indentation values' (0.06–0.08 cm). Triplicate measurements were carried out at four points on each volunteer (forehead skin). Then the substance was applied to the skin (1 ml during 10 min) and the indentation was recorded at different times; at each time a triplicate measurement at the same point. Statistical evaluation by paired t-test was carried out on the individual changes of each patient.

The table shows that agents known to increase c-AMP in skin by activating adenylate cyclase, such as adenosine[5], the β-agonist isoproterenol bitartarate[6] or the β_2-agonist terbutaline sulfate, or the phosphodiesterase inhibitor papaverine[7], all cause a decrease in indentation at approximately those concentrations at which they are known or supposed to cause an increase in the c-AMP content of the skin[5–7]. This decrease in indentation represents a firmer, younger skin. The final proof that c-AMP is involved can be seen in the table, from the strong effect of 0.1% N^6,O^2,-dibutyryl c-AMP (sodium salt).

The action of the above agents is specific, since 0.3% solution of noradrenaline hydrochloride, histamine hydrochloride, serotonine hydrochloride, guanosine, or N^2,O^2,-dibutyryl c-GMP failed to influence indentation significantly. Each active agent

Effect of agents connected with the adenylate cyclase system on low pressure indentation

Agent	Concentration of active part (%)	Decrease in indentation $\times 10^{-3}$ cm 1 h	2 h	3 h	5 h	6 h	7 h	10 h
N^6,O^2,-dibutyryl c-AMP (sodium salt)	0.1	NS	2.6 ± 1.0	3.5 ± 0.8	4.5 ± 0.8	6.8 ± 1.3	8.0 ± 1.2	5.0 ± 0.8
Isoproterenol (bitartarate)	0.1	5.0 ± 0.8	7.3 ± 1.0	7.3 ± 1.7	7.3 ± 1.2	–	5.2 ± 0.8	NS
Papaverine (hydrochloride)	5.0	4.5 ± 1.0	6.3 ± 1.0	5.8 ± 1.3	4.3 ± 1.0	NS	NS	
Adenosine	0.1	4.0 ± 0.5	4.2 ± 0.8	4.2 ± 0.8	4.0 ± 1.0	NS		
Terbutaline (sulfate)	0.3	2.7 ± 1.0	6.5 ± 1.2	4.7 ± 1.5	4.5 ± 1.7	–	4.0 ± 1.3	NS

NS = not significant at $p \leq 0.05$. Agents were freshly dissolved in distilled water. A premeasured 1 ml was self-applied in successive small doses over a 10-min period to the forehead skin of the volunteers. Each figure represents the mean ± SD from the mean of 16 experimental points in four volunteers.

was also tested at one-third of the concentrations shown in the table, and at this level all were ineffective.

We also measured the elastic recovery of the skin before and after the application of all the agents mentioned in this communication (for the method see Dikstein and Hartzshtark[1]. None of these agents had any influence on elastic recovery within the time scale of these experiments.

One can only speculate on the possible role of c-AMP. In our view, it stimulates the fibroblasts to synthetize hyaluronic acid[8]. We have shown, indeed, that hyaluronidase increases indentation[9]. On the other hand, β_2 receptors have been identified in the epidermis[10].

The idea that active emollients and moisturizers could work via a pharmacological route has already been suggested by Tronnier[11] and Idson[12]. Van Dorp[13] postulated that dry skin conditions could be treated by prostaglandins and essential fatty acids externally applied to the skin. Penneys et al.[14] showed that white petrolatum interferes with the metabolism of arachidonic acid in the skin.

In this communication, however, a physical parameter (compressibility – 'firmness') of the human skin in vivo has been shown to be dependent on a biochemical intermediate *and* its pharmacological manipulation.

It is hoped that our findings will contribute to the development of cosmetic or pharmaceutical preparations aimed at hindering the effects of aging on the human skin.

Added in proof: U.S. patent 3,978,213 (31.8.1976) deals with the cosmetic use of c-AMP and agents inhibiting c-AMP degradation.

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Growth inhibitory, insecticidal and antifeedant effects of some antileukemic and cytotoxic quassinoids on two species of agricultural pests[1]

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Summary. Several quassinoids, obtained by isolation and derivatization from *Simaba multiflora* and *Soulamea soulameoides*, were evaluated for growth inhibitory and insecticidal effects against the tobacco budworm *(Heliothis virescens)* and for antifeedant effects against *H. virescens* and the fall armyworm *(Spodoptera frugiperda)*. The relative activity of the quassinoids as insect growth inhibitors generally paralleled their known relative potency as antileukemic and cytotoxic agents.

Key words. Quassinoids; *Heliothis virescens*; *Spodoptera frugiperda*; growth inhibitory effects; antifeedant effects; antileukemic activity; cytotoxic activity.

It is becoming increasingly evident that certain natural products elicit activity in a number of biological systems (e.g., antileukemic, insect antifeedant, antispomatic, insect antiecdysis, cytotoxic and brine shrimp toxic activities)[2–5]. For example, Nakanishi has pointed out that natural products with electrophilic moieties tend to be cytotoxic and insect antifeedant[6].

Such multiplicity in biological activities attributed to individual natural products has prompted us to investigate some plant products, previously isolated as anticancer agents, for their effects on pest insects. The present report describes the growth inhibitory, insecticidal and antifeedant effects of 8 quassinoids (simaroubolides) on the larvae of the economically important