Dear Colleague,

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Dez. 92

Dear Doctor,

Your excellent article :

A Defective Purine Nucleotide Synthesis Pathway in Psoriatic Patients

Acta Derm Venereol.

has been selected for publication in 'Dear Colleague', an international journal consisting of letters only.
We would like to invite you to write us a letter of maximum two pages, in which you summarize the contents of your article, and possibly supply more interesting information concerning the subject of the article.
As we reproduce letters in their original state, please start your letter with the words: Dear Colleague. The letter must be written in the English language.
Include only the generic names of drugs that you cite and do not submit illustrations, references and tables (see enclosed example).
Return your letter as soon as possible. This will allow us to keep 'Dear Colleague' current.
Send your letter to:

Care & Cure Communications
P.O. Box 540
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The Netherlands

Thank you very much in advance.

Sincerely yours,

Care & Cure Communications

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Dear Colleague,

New in dermatology
vol. 2, nr. 2 1993

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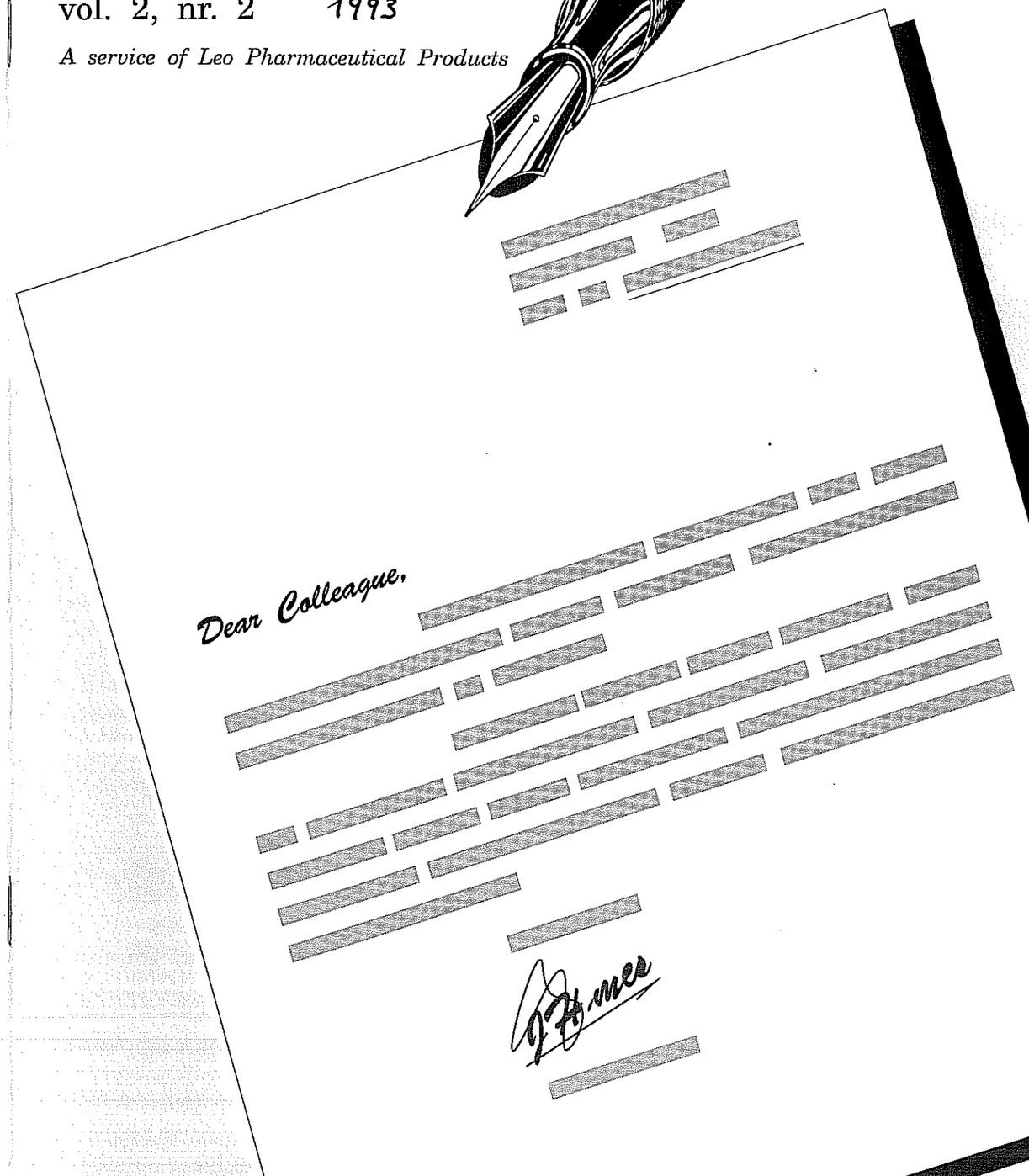

Dear Colleague,

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WORCESTER
ROYAL INFIRMARY

Dear Colleague

We all have trouble with treatment of psoriasis. After all people do not die from skin disease, and there are so many other problems in daily life that it is easy to push considerations of appearance and social life on one side. A study in America some time ago showed that 70% of patients with chronic psoriasis had an alcohol problem, and there are known to be increased risks of marital problems.
It is too easy to add to these problems by treatments wich are risky or unpleasant. Cleaning the car is a nasty job and the feel of grease is unattractive, so how can we expect patients to apply large amounts of smelly materials to their surfaces for day after day and week after week? It is no surprise that they object to the smell, the texture, the effect on bedding and clothes, let alone family, spouse, work-mates and social friends.
Unfortunately other treatments are accompanied by other problems. We all know the risks of sun-light, and the benefits of PUVA are to be considered against the long-term risks of cataract, liver damage and skin cancer. Treatments are also expensive and can be very inconvenient in terms of access and time required. No wonder they ask for pills. Here too we tend te let them down, as there is no such thing as a miracle cure. Cure is something we can not do for most inherited diseases, and the future of bio-engineering is still uncertain. The non-fatal nature of psoriasis will make sure that it is low on the list of priorities for such gene studies.
Tablets are of course available and they can be helpfull in some cases. Methotrexate in particular has stood the test of time and is very effective. It is also dangerous, as we know all too well, and marrow damage is a major limiting factor. Liver damage is alsow a risk, but can be reduced by careful screening of patients. Cyclosporin is very promising but tricky to use and it is awkward to have to do so many tests to assess safety. Patients do not like coming back too often, even if their own good is the reason for the visits. There are always delays and hanging about, and we all know that hospitals are not places of pleasure.
This brings us back to the starting point that we really have to depend on topical measures for most patients, even if they are fiddly and messy. We therefore have to be concerned with cosmetic accept-ability, or patients just will not use these agents in the long term. And we cannot blame them. Many things just do not work, or if they do, it is only for a short time. Steroids are a good example. In the first few weeks, benefit is so great that there is decreased tolerance of visible lesions when they return, wich they inevitably will. The skin is also thinned and damaged, so there may be ugly addi-tions to the problems of appearance. Infection plays a part, as do reactions to many components such as preservatives, so we often end up with a worse state than before treatment.
Tars have largely had their day. Dithranols, in short application, have had a new lease of life, but are very tricky for fair-skinned patients and cause staining of clothes and bedding. They can also produce a spectacular colour of hair and face if used on the scalp. Are there other possibilities? Many have been tried and most of these fall by wayside. A recent addition to the list shows signs of being more enduring. It is related to vitamin D3 which is known to influence the maturation of fibroblasts and keratinocytes as well as influencing the immune system. Orally the chances of toxicity are too high

Dear Colleague,

for use, as hypercalcaemia and renal damage can be expected from animal studies. Luckily a topical form is now available-calcipotriol, and it is this which we have used in several dozen patients in the last year. Other centres have longer term use and we are getting more familiar with its strengths and weaknesses. These can be quickly summarised. On the good side are the light texture, the lack of smell, colour and staining, and hence the ease of use, which other people can not detect. There will not be any damage to clothes, and the patient does not smell like an off-duty mechanic. On the other side are the tendency to produce soreness and local irritation, and features like the hyper-retinism one sees with oral etretinate. Usually this passes off with a short rest period, but I usually recommend that fair-skinned people should only apply it once a day and then not so lavishly that it spreads on to the surrounding skin. Another problem-production of peri-oral dermatitis means that it cannot be used on the scalp or face. This may well be due to the ointment base rather than to the calcipotriol itself, and a cream is being prepared wich will extend its use. Then we can also treat flexures and scratched areas.

Most patients have chronic localised plaques mainly on the extensor aspect of the limbs, and these areas respond well to this ointment. It may take 4-6 weeks, but it is worth the wait. Apart from faces, this still leaves the difficult cases of nail dystrophy, hand and foot involvement, and perineal disease. We still have further progress to make, and it is possible that there will be further vitamin analogues to come, as with the new generation of Neo-Tigason. There is no reason to be smug and to stop looking, but at least we now have another weapon in our armoury.
Perhaps skin diseases do matter....

Yours sincerely

Dr P C H Newbold DM FRCP
Consultant Dermatologist
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SPEZIALKLINIK NEUKIRCHEN

PRIVATKLINIK ZUR BEHANDLUNG ALLERGISCHER
UND DEGENERATIVER ERKRANKUNGEN

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Dear Colleague

In the white population, there is worldwide an about three per cent incidence of psoriasis vulgaris. This disease is a multifactorial condition. A genetic component has been demonstrated in 50 to 65 per cent of the patients and the disorder may be triggered by various somatic factors. We are especially interested in the pathogenesis and therapy of psoriasis.

More than 30 years have passed since the biochemist Schweckendick in 1959 discovered by successful treatment of his own psoriatic lesions the fumaric acid therapy. Since then some investigators found with high dosages of fumaric acid in 5 out of 6 patients an anti-psoriatic activity accompanied by pathological kidney parameters. To find a plausible explanation for the effect reported after treatment with fumaric acid we investigated the related purine nucleotide levels in the blood cells of psoriatic patients (20) and healthy controls (13).

The concentrations of the purine nucleotides cAMP, ADP and ATP in the sera of the psoriatic patients were normal, which is contrary to the whole blood-nucleotide levels. Mean blood ATP level in psoriatic patients was 187 µM vs 309 µM in controls, mean ADP level 212 µM vs 292 µM and mean ADP plus ATP concentrations 399 µM vs 600 µM. The change in the described nucleotide concentrations manifests entirely in the cell. The ATP/(ADP+ATP) ratio remains unchanged and makes clear that ATPase/synthetase and PGK (3-phosphoglycerate kinase) are not involved in alterations of the nucleotide levels.

As expected, the ADP plus ATP concentrations during the 4 weeks of oral fumaric acid treatment remained unchanged. ATP values increase significantly while ADP levels decrease according to the increasing fumaric acid dimethylester concentrations. A slow rise to a dosage of 120 to 240 mg fumaric acid dimethyl-ester results in clearing of the patients skin after 4 weeks therapy. There is a clear-cut correlation between raise in ATP concentration and clearing of the skin. No changes in the urine and blood parameters were noticed.

It is suggested, that a generalized defect in the purine nucleotide metabolism is responsible for the changed nucleotide concentration in the patients. ATP and GTP were used in RNA and DNA synthesis, cAMP and cGMP control protein-biosynthesis activity. cAMP levels in psoriatic skin were reported significantly lower than in normal skin, while on the other hand cGMP levels in psoriatic epidermis were higher than in the normal skin. The measured cellular concentrations of ADP, ATP, cAMP and cGMP make the suggestion most probable and imply the measurements of the remaining purine nucleotide levels.

It has been shown, that in adult human epidermis low levels of cAMP stimulated proliferation, whereas high levels inhibited growth. On the other hand, it has been postulated that an increase in the steady state level of cGMP may be associated with an enhanced rate of cellular proliferation. The nucleotide concentrations in our patients favor a high rate of cellular proliferation, via acceleration of the protein-biosynthesis activity. Fumaric acid accelerates Krebs cycle, respiratory chain as well as ATPsynthetase and then elevates ATP- and consequently cAMP-levels. Another important result of elevated fumaric acid is its end-product inhibition which slows down purine nucleotide synthesis, especially of cGMP. It should be remembered, fumaric acid dimethylester alone can cross membranes and only its hydrolysis in mitochondria makes it a substrate for the Krebs cycle.

The genetic defect leading in psoriatic manifestations may be localized at the level of adenylosuccinate formation. Polyamines play no role, as originally suggested in analogy to cancer patients.

Many triggering factors are acting via adenylate cyclase, including psychogenic stress and associated elevated norepinephrine levels. These factors are not only triggering the disease, but also further weakening immune response with development of secundary infections. Adenosine may counteract and relaxation therapy (± psychotherapeutic attendance) restore the abnormal distribution of the α- and ß-receptors, the associated low concentrations of membrane bound adenylate-cyclases and of cAMP.

Yours sincerely

Reinhold Kiehl

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