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(54) Title: METHOD AND COMPOSITION FOR TREATING A PATIENT SUFFERING FROM INTERFERON-SUSCEPTIBLE DISORDER

(57) Abstract

A method for treating a mammal, in particular a human patient, suffering from interferon-susceptible disorders such as pre-cancerous or cancerous tumors or local virus infections such as Herpes simplex virus infections or other disorders such as dermatitis, e.g. seborrhea, etc., comprises local administration of interferon in a single aqueous gelled phase directly onto or close to the surroundings of an organ or site in which the disorder is located and continuing the local administration for a period of time sufficient to obtain a response to the interferon treatment. The interferon gel is prepared by mixing the gel constituents, sterilizing the resulting gel composition and aseptically mixing the gel composition with an aqueous interferon solution.

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METHOD AND COMPOSITION FOR TREATING A PATIENT SUFFERING FROM INTERFERON-SUSCEPTIBLE DISORDER

For the last 10 years, numerous publications have been published describing the clinical usefulness of human interferons in human patients against a wide variety of diseases, such as virus infections or cancers at various stages (malignant). The basis for interferon treatment of virus infections is the antiviral activity which interferon is known to have (see, e.g., William Stewart: The Interferon System, Springer Verlag, New York, 1979). It has been reported in numerous publications that interferon also has several so-called non-antiviral activities which include the stimulation of the so-called NK system, including various killer cell systems such as MLC-CML systems, cell inhibitory action on cancer cells, etc. All these findings have suggested that interferon might be useful for administration to human patients suffering from virus infections or cancers or combinations thereof.

For a long time it has been considered important to be able to clearly demonstrate that patients receiving human interferon have an increased serum level of human interferon activity, the rationale being that without any interferon activity in the blood of the patient, no effects of the administration of interferon are to be expected. Therefore, systemic treatment of human patients has been studied thoroughly by ascertaining the serum level of interferon obtained in human patients receiving interferons. Despite these numerous efforts, only relatively few positive reports have appeared that show positive effects of interferon directly on the various tumors and/or virus infections.

The present invention relates to a method for treating a mammal, in particular a human patient, suffering from interferon-susceptible disorders such as pre-cancerous or cancerous tumors or local virus infections such as Herpes simplex virus infections or other disorders such as dermatitis, e.g. seborrhea, etc., said method comprising

local administration of interferon in a single aqueous gelled phase directly onto or close to the surroundings of an organ or site in which the tumor, viral infection or the interferon-susceptible disorder is located and continuing the local administration for a period of time sufficient to obtain a response to the interferon treatment, such as regression of the tumor or elimination of the viral infection or normalization of the said surfaces.

Hence, according to the principles of the present invention, the interferon is administered topically in the proximity of a surface of the organ or site in which the interferon-susceptible disorder or condition to be treated is located. This means that in cases where the cell surface of the organ or site is physically exposed or placed so that it is immediately accessible to topically administered interferon, the interferon will normally be applied on the exterior membrane, whereas in cases where the cell surfaces (skin or mucous membranes) are not immediately accessible, the interferon may be applied topically in a region which is in fact physically accessible to the interferon and which is as close as possible to the tumor or viral infection site. At any rate, it is characteristic of the treatment according to the present invention that the interferon is brought to act on the tumor or at the viral infection site, etc., through a membrane-like limit which may be the skin or a mucous or serous membrane, or an endodermal or intradermal site dependent on the location of the interferon-susceptible disorders such as pre-cancerous or cancerous tumors or viral infections, rather than only by systemic administration to the patient.

On the basis of results obtained in accordance with the principles of the invention, it is believed that part of the failure to obtain positive results in the known art interferon treatments may partly be due to the difficulties in having the administered interferon reach the target organ. Very often, tumors or virus-infected areas are limited to certain restricted parts of the body. According to the present invention, the interferon is applied directly to the part or parts of the body where the disease is present, and a much higher interferon concentration is obtained specifically in the relevant area thus establishing a more economic utilization of the interferon. Furthermore, it is likely

that systemically administered interferon present in the blood stream is unable to pass from the blood stream to the target organ in sufficiently high quantities to elicit any direct effect. Thus, the local application of interferon directly to or close to the target organ according to the present invention will be a more efficient way of improving the condition of a patient suffering from the diseases in question.

In several cases, the interferon applied locally according to the method of the invention acts specifically and quickly, whereas systemic treatment might not work at all at the same interferon dosage. The reason for these observed improvements is believed to be the direct access of interferon to the target organ or area in question. The concentration of interferon may be 10,000 units per ml or higher in the selected area. If the same level of interferon activity were to be obtained in the same patient by means of systemic interferon administration, the patient would have to receive several billion units of interferon (such a high dosage would be harmful to the patient). There are also indications that locally applied interferon will activate the immunosystems in a much more specific manner compared with the systemic activation of the immunosystems known for patients receiving systemic interferon treatments, *vide* the following report concerning the treatment of an 18-year-old female patient.

A patient suffering from a certain disease and treated systemically with interferon in the same amount as used topically will often not respond, which may be due to the considerable dilution of the systemically applied dose as compared with the locally applied dose. On the other hand, local *injection* (not according to the invention) of interferon into the tumor or the target organ in question will often be undesirable because this incurs physical damage and uncontrolled release. It is a feature of the invention that the interferon will effectively affect the tumor or virus-infected area even in cases where the treatment is performed for a relatively short period. The lengths of these periods are in the order of weeks, which is significantly shorter than the periods normally used in or for systemic treatments (months).

Organs which may be treated by the method of the invention are typically exterior or interior organs with skin or mucous or serous membrane surfaces or other membrane-like limits which are accessible without damaging vital tissue or organs of the human body.

Examples of areas which may be treated by the method of the invention are as follows:

Exterior skin surfaces with malignancies such as tumors, virus infections or dermatitis (such as seborrhea), itching areas, etc.

Skin surfaces such as mucous or serous surfaces such as the interior cavity of the nose, the mouth cavity, the external auditory duct, uterus surfaces, anal or rectal surfaces, or rectal mucosa, surfaces on penis, the anus, urethra, etc.

Other surfaces which may be treated in accordance with the invention are surfaces adjacent to cavities containing ascitic fluids produced by tumor cells. Such surfaces may be reached by injection through tissue where any mechanical damage caused by the injection is not critical.

Examples of diseases which may be treated by the method of the invention are Herpes simplex, Herpes simplex genitalis, Herpes zoster, Herpes keratitis, Condylomata, iridocyclitis caused by a virus, pre-cancerous or cancer conditions such as dysplasia and carcinoma in situ of portio uteri or dysplasia of collum, vaginal cancers, vulva cancers, skin cancers, cell carcinomas, spinocellular carcinomas, cervical intraepithelial neaplacia of early stages in collum uteri and cervical cancers may also be treated. Finally, abnormal skin areas (itching, reddish), such as dermatitis seborrhea, etc., and possibly dandruff, are also included as disorders to be treated by the method and composition of the invention (*vide* Example 10).

The local or topical administration may be performed by applying, either directly or indirectly, a gelled interferon solution on or close to a skin surface or exterior membrane of the body or a site in which the disorder to be treated is located. The term "directly or indirectly"

is intended to indicate that the interferon gel may be applied directly to the target as such or it may be applied close to or directly onto the membrane in question by being released from any suitable deposit form which may appropriately be applied locally or topically and which will effect a suitable release of interferon which will then be available at or close to the membrane of the organ or site to be treated. In particular, the deposit is a single-phase aqueous gel containing the interferon activity. Preferably, the gel is transparent which is especially desirable when the gel is applied on exposed skin surfaces.

The administration of interferon according to the present invention is normally performed at a rate of from about 1-8 times a day to 1-3 times a week. This dosage administration should, of course, be adapted to the particular needs of the patient, the severity of the disease, etc.

The interferon administered by the method of the invention is an interferon with relevant activity in the system of the patient to whom it is administered. When the patient is a human patient, the interferon may be selected from the group consisting of human interferon α, β, or γ (HuIFN-α, HuIFN-β, or HuIFN-γ), or a combination thereof, including leucocytes and human lymphoblastoid interferons or combinations thereof, and/or proteins which show interferon activity and which are prepared by recombinant DNA techniques.

The interferon may be a crude interferon, or preferably a purified interferon, e.g. a partially purified interferon (normally designated PIF in the art), having a specific activity of about 10^6 units per mg of protein. According to a particular embodiment of the invention, the interferon is a pure interferon protein with a specific activity of at least 10^8 units per mg of protein. Such pure interferon proteins and the preparation thereof are described in Berg & Heron, Scand. J. Immunol. *11*, 1980, 489-502.

When the interferon applied is of a relatively high purity, such as a purity corresponding to about 4×10^6 International Units per mg of

protein or more, it is desirable to increase the stability of the interferon proteins by adding an immunologically acceptable protein, e.g., human albumin, in a concentration on the order of 1-2 mg of protein per ml solution used for administration with an interferon activity of $1\text{-}4\times10^6$ units per ml.

The interferon gel used according to the method of the present invention may have a concentration of interferon corresponding to about 10,000 to 1,000,000 units per ml. The administration may be performed by applying the gel locally to the areas in question.

It is known that interferon will influence the regeneration of the cytoskeletal system of cells (e.g. transformed cells). Thus, cells exposed to interferon for various lengths of time will develop a more distinct cytoskeletal system compared with non-interferon treated cells. Furthermore, transformed cells are, generally speaking, recognized as cells which have a far less organized and structured cytoskeletal system.

Several drugs are known to influence the formation of this cytoskeletal system such as isoprenacine, various salts of butyric acid, etc. (cf. Chany, C., et al.: "A role of receptors and the cytoskeleton in reverse transformation and steroidgenesis induced by interferon. In: Regulatory functions of interferons" (ed. Vilcek, J., Goesser, I., Merigan, T.C.) Ann. N.Y. Acad. Sci. *350*, 1980, 254-66). It has been reported that only when combination therapy in mice is employed, using mixtures of the said drugs and mouse interferon, will the major portion of mice survive certain tumor malignancies.

The patient undergoing the treatment according to the method of the invention should normally not be treated with any medicaments which suppress the patient's immunosystem, but it cannot be precluded that there are special cases where a treatment according to the method of the invention may be suitably combined with treatment with, e.g., cell poisons (such as Methotrexate).

When it is desired to treat bacterially or fungally contaminated/infected areas with the interferon gel, antibiotics which do not substantially inhibit the activity of interferon on the target organ may be included in the interferon gel.

The preferred antibiotics should not interfere negatively with the effect of the interferon and should at the same time retain their own activity. Suitable antibiotics are the tetracyclins, neomycin, gentamycin, polymycin B. and amfotericin B or combinations thereof.

It may be envisaged to prepare a "combination" gel which may combat both types of infections (non-viral and viral infections). Furthermore, the gel should not, by itself, support growth of microorganisms.

The interferon gel composition may also contain a medicament known to exert inhibitory influence on the replication of Herpes simplex virus Type I and II, such as phosphono formate, acycloguanosine, E-5-(2-bromovinyl)-2'-deoxyuridine (deoxyuridine) or 2'-fluoro-5-iodo-aracytosine (1-(2-fluoro-2-deoxy-β-D-arabinofuranosyl-(5)-iodocytosine).

It is also within the scope of this invention to use the interferon-containing gel on skin surfaces which appear abnormal without being atypical cells of the said area. Such areas of skin may appear as lesions. Very often the original cause for the appearance of the skin lesion is unknown (e.g. itching areas, seborrhea, dermatitis, etc). Such areas might, for example, also appear on skin surfaces of the vagina with a more or less pronounced reddish colour. Interferon-containing gel is applied to such an area twice a week for a period of three to six weeks. Depending on the specific case, variations are to be expected in this schedule (e.g. 4-8 times a day may also be envisaged). The results from such an interferon gel treatment will very often, provided that there are no bacterial infections or other non-interferon-susceptible infections, show a considerable improvement with regard to the acceleration of the normalization. For instance eczematous lesions in the skin might also be benefited by the interferon gel of the invention.

The interferon gel according to the invention may also be applied in admixture with a collagen creme. This mixture may be used as a composition for treating herpes infections or for speeding up normalization of slightly abnormal cells located in specific areas of the skin in that the cytoskeletal structure of such cells will be strengthened subsequent to the application of such a composition. The mixed composition comprising interferon gel and collagen creme may be especially advantageous as it may be envisaged that a collagen creme admixed with the interferon gel would have an appreciable normalizing effect on the skin surfaces in question.

The interferon gel should preferably be of such a nature that it is capable of substantially adhering to the said membranes or skin surfaces whereby the interferon activity may diffuse from the gel into cells of the membranes or skin surfaces. It is assumed that to obtain adhesive ("sticky") property of the gel it is necessary to use a gel containing highly charged groups (positively/negatively charged). As is generally known, the charged gels have been found to increase protein transport across biological membranes and/or to potentiate the usual action of the biologically active substance at the membrane signal level.

The gelling agent used for gelling the interferon solution should preferably be of such a nature that the gel may be subjected to freezing, thawing or sterilization (e.g. by autoclaving at 120°C), with retention of the single phase character and transparency of the gel.

Gelling agents meeting with these requirements are hydrocolloid gelling agents such as carbohydrates or carbohydrate derivatives, in particular a cationic or anionic polysaccharide, especially one containing COO^- groups, e.g. a cellulose or alginate derivative containing such groups, such as carboxymethyl cellulose (in particular as a salt). Among other gelling agents contemplated are hydroxyethyl cellulose, methylhydroxyethyl cellulose, hydroxypropyl cellulose and methyl cellulose.

Preferably, the gelling agent is of such a nature that it is physiologically acceptable. Particularly, the gelling agent should be non-toxic and non-allergenic and, furthermore, it should not substantially cause changes in the normal bacterial flora of the area. Also, it should produce no undesirable side effects. As such, CMS is particularly suitable, cf. its use as a food additive for several years. The gel may comprise about 4% or more of carboxymethyl cellulose.

It has been found that, compared to gels made with uncharged polysaccharides which are not soluble in water at all, such as modified starch, sepharose, etc., interferon gels made with charged gelling agents such as carboxymethyl cellulose (CMC) have specific advantages in that the interferon activity is released at a reduced rate. Thus, although a very high concentration of interferon is present in the CMC-interferon-gel, an aqueous environment surrounding the gel (as described in the section entitled *"Determination of Sustained Release of Interferon Activity ....."* below) will only gradually receive the interferon activity from the gel, which means that the interferon activity is only released very slowly from the gel which is believed to be advantageous because the interferon will remain active over a prolonged period compared with systems which do not have this sustained release activity.

It should be stressed that the terms interferon and interferon activity herein are used synonymously, and no special efforts have been made to distinguish between them. This is due to the current knowledge of the properties of the interferon gel system. Thus, the sustained release activity of interferon as discussed above may at least theoretically be explained as follows:

a) slow release of the interferon molecules from the interferon-containing gel yields unbound interferon molecules with a molecular weight similar to the molecular weight found for isolated purified interferon (mW-range: 16.000 - 24.000).

b) the interferon activity measured in the supernatant from the interferon gel may consist of soluble carboxymethyl cellulose bound to interferon.

The rate of release of the interferon activity may either depend on the rate of dissolution of the CMC-interferon bonds or the release of interferon molecules from the gel or, possibly, a combination of both.

Thus, a soluble carboxymethyl cellulose interferon complex could theoretically exist and exert an antiviral activity (an interferon activity). For the time being it is difficult to distinguish between these two possibilities.

An advantage of the gel system (involving highly charged gels) is that it remains in contact with the surface of the target organ and will not be repelled from the target due to its ability to attach to membranes. Hence, release of the interferon will continue at the surface of the target.

According to the invention, the rate of release of the gelled solution is so adapted that the content of the interferon activity of the solution is released in the course of about 4-48 hours (cf. Table 2). This is obtained by a suitable adjustment of the consistency of the gel composition, especially as regards the viscosity to obtain a gel with a viscosity of 500 - 100,000 cps at 100 RPM (Brookfield).

It is essential to choose a viscosity suitable to the site of application. Thus, if major amounts of body fluids are present at the target organ or are excreted by the target organ, a higher viscosity is needed. Different viscosities may be obtained either by the amount of the gelling agent or by using different molecular weights of said agent. By using higher concentrations of the gelling agents the release will be prolonged.

For most purposes thixotropic gels are advantageous. During application such gels will be easy to smear and, having been applied, the gels will nevertheless show a substantially firm consistency.

According to a preferred aspect of the present invention, the aqueous gel composition comprises a substance showing water retention capacity, such as a physiologically acceptable humectant, for instance a

polyvalent alcohol such as glycerol, propylene glycol, sorbitol, polyethylene glycol or ethylene glycol.

The humectant is added to prevent the gel from drying up when applied to exterior dry skin surfaces.

Normally, the gel should contain a buffer substance with a pH in a range acceptable for the stability of interferon and also acceptable to the cells, in particular a buffer with a pH of about 6 - 8, in particular a pH of about 7.2 - 7.5. A suitable buffer solution for use in the gel is phosphate buffered saline (Dulbecco buffer).

The interferon incorporated in the gel according to the invention may, as indicated above, be selected from the group consisting of human interferon α, β or γ (HuIFN-α, HuIFN-β, or HuIFN-γ), or a combination thereof, including human leucocyte and lymphoblastoid interferons and/or proteins which show interferon activity and which are prepared by recombinant DNA techniques.

As indicated above, the interferon may be a crude interferon, or preferably a purified interferon, e.g. a partially purified interferon (PIF) having a specific activity of about 10^6 units per mg of protein. According to a particular embodiment of the invention, the interferon is a pure interferon protein having a specific activity of at least 10^8 units per mg of protein as mentioned above.

When the interferon incorporated in the gel is of high purity, such as a purity corresponding to 4×10^6 units per mg of protein or above, it is desirable to increase the stability of the interferon proteins by adding an immunologically acceptable protein, e.g., human albumin, in a concentration of 1-2 mg of protein per ml. The amount of protein added to such interferon preparations should be in such a range that the specific activity of the final, stabilized interferon preparation will be around $1\text{-}4 \times 10^6$ units per mg protein.

The interferon-containing gel according to the invention may be prepared according to conventional principles employed to produce

gels for administration to similar surfaces. Thus, a suitable production method comprises mixing the constituents of the gel composition, sterilizing the gel composition, e.g., by autoclaving, and aseptically mixing the gel composition with an aqueous interferon solution (e.g. PIF), e.g. in a ratio of about 70% of gel composition to about 30% of interferon solution.

The concentration of interferon in the gel will normally be in the range of 5,000 - 1,000,000 International Units/ml, preferably about 100,000 - 300,000 International Units/ml.

The gel composition of the invention should be stored under conditions securing that substantially no deterioration of the interferon activity will take place during storage. For this reason, it is often convenient to pack the interferon-containing gel in single dose containers. In a preferred dispensing form the gel is contained in a collapsible tube, the outlet of which may, if necessary, be fitted with a suitable tip for convenient application.

However, the gel may also be applied to dry surfaces using an adhesive provided with a cavity in which the interferon gel is placed; thus, the gel may be applied to limited areas of dry skin surfaces without being removed by, e.g., clothes or the like.

According to another aspect of the invention, the interferon gel may be placed in the cavity of the above-mentioned adhesive immediately after the preparation. In such a single dose package the adhesive is sealed in an impermeable sterile outer package which is stored. This application form may be used directly and is especially suitable as it ensures an efficient utilization of the gel produced.

EXPERIMENTAL SECTION

EXAMPLE 1

Preparation of Interferon Gel

A gel base was prepared from sodiumcarboxymethyl cellulose (CMC) ad sol. limb. Pharm.Nord. 63 (8.6 g), glycerolum eur. (20.0 g) and PBS-buffer (171.4 g).

The CMC was added to the cold glycerol under stirring. This mixture was added under stirring to the cold PBS-buffer, and the resulting mixture was heated in a water bath until all the CMC particles had become transparent. The resulting gel was cooled under stirring to obtain a transparent, homogeneous gel. This gel was autoclaved at 121°C, after which the mixture was cooled to about 4°C. The cooling stage between the initial heating and the autoclaving may optionally be omitted.

The cooled gel base was mixed with HuIFN-α(Le)PIF diluted to 700,000 units per ml under aseptic conditions. The interferon gel obtained was packed in collapsible pointed tubes of aluminum, each tube containing 2 ml gel.

The tubes were stored in a freezer at a temperature of -18°C until use.

The viscosity was examined using a Brookfield viscosimeter Model HBT using a spindle No. RV3.

The results are shown in Table 1.

TABLE 1

RPM	Reading on 100 Scale	Factor	Viscosity CPS	Temp.°C	Time
				25	
0.5	7.5	16 M	120,000		0
10	31.2	800	24,960		60 sec.
20	40.5	400	16,200		120 sec.
50	57.5	160	9,200		180 sec.
100	73.5	80	5,880		240 sec.
100	69.0	80	5,520		300 sec.
100	65.0	80	5,200		360 sec.
50	46.5	160	7,440		380 sec.
20	31.2	400	12,480		400 sec.
10	21.8	800	17,440		420 sec.
5	15.0	1.6 M	24,000		440 sec.
2.5	10.3	3.2 M	32,960		460 sec.
1	6.1	8 M	48,800		480 sec.
0.5	4.2	16 M	67,200		500 sec.

EXAMPLE 2

A methylcellulose gel was prepared from methylcellulosum 1500 DAK (6.0 g), glycerrolum Eur. (20.0 g) and PBS-buffer (174.0 g) in the manner described in Example 1.

An interferon gel was prepared by mixing 12.5 g of the methylcellulose gel with 3.75 g of an interferon solution containing 90,000 units/ml and 1.25 g of a Neomycini solution (25 mg/ml).

EXAMPLE 3

7.5 g of a carboxymethyl cellulose gel prepared in the manner described in Example 1 from sodiumcarboxymethyl cellulose ad sol. limp. Ph. Nord. 63 (8.6 g), Glycerolum Eur. (20.0 g) and PBS-buffer (171.4 g) was mixed with 3.75 g of an interferon solution containing 90,000 units/ml and 1.25 g of sterile water to obtain an interferon gel.

EXAMPLE 4

7,5 g of the methylcellulose gel prepared in Example 2 was mixed with 3.75 g of an interferon solution containing 90,000 units/ml and 1.25 g of sterile water to obtain an interferon gel.

Determination of Interferon Activity in the Interferon Gel

200 mg of the interferon-containing gel, prepared as described in Example 1 was placed in the bottom of a test tube and 800 µliters of medium (MEM-minimal essential medium comprising 5% calf serum) was added on top of the gel. The two phases were mixed thoroughly on a Vortex for at least 30 seconds to form a suspension. It is important to secure that a finely dispersed suspension is produced. From this first dilution (1:5), the usual serial dilutions (1:10, 1:100 and 1:1000) are performed using the above medium. The above-prepared dilutions are titrated in the usual interferon titration system as described by, e.g., Berg, Scand. J. Immunol. *6*, 1977, 77-86.

Stability Tests of Interferon Gel

The stability of the interferon gel, prepared as described in Example 1, was determined by two methods:

A. An ampoule containing the interferon gel was kept at 4°C for the duration of the experiment, and the interferon gel was titrated once a week over a period of several days. The determination of the interfe-

ron content in the interferon gel was performed as described above and was found to be constant over a period of several months. A titer of 130,000 - 160,000 International Units per ml of gel was found.

B. An ampoule containing the same interferon gel batch described under A was kept at -20°C for several months. Before each interferon titration, the ampoule was thawed and kept at room temperature for 5-10 minutes while about 200 mg of a gel sample was withdrawn for titration purposes as described above. Only one phase was observed even after repeated freezing and thawing cycles. The interferon content was estimated to be between 130,000 and 170,000 International Units per g of gel. Hence, the gel was stable during the above freezing and thawing cycles. Several tubes were titrated for interferon activity at varying time intervals, and it was found that the interferon activity was stable for several (more than 9) months at -20°C. Another batch was checked at 4°C, at room temperature and at 37°C over a period of 2 weeks by taking daily samples for titrations. No loss of activity was encountered during this period (the test was still ongoing on Oct. 3, 1982).

Determination of the Sustained Release of Interferon Activity from the Interferon-containing Gel

About 0.5 ml of the interferon gel was placed in a Costar tray (about 2 cm diameter), yielding a 2 - 3 mm thick gel layer. 2 ml medium (e.g. 5% calf serum) was carefully added on top of the gel to form a two-phase system with the interferon-containing gel at the bottom and the medium on top.

150 µliter samples were withdrawn from the upper phase at various time intervals for interferon titration at the times indicated in Table 2. Each time, 150 µliter of medium was added as a replacement. A control consisting of a PIF preparation (cf. Berg & Heron, Scand. J. Immunol. *11*, 1980, 489-502) was incubated under similar conditions (no gel used). The Costar tray was sealed and placed in a humidified

chamber at 37°C for the duration of the experiments. The results stated in Table 2 clearly show that the highest level of interferon activity is obtained between 5-8 and 20 hours. Over the same period, the gel had dissolved (only one phase was seen).

TABLE 2

Release of Interferon Activity from an Interferon Gel Containing 145,000 units/ml Gel at 37°C.

Date	Time Hours	Interferon Activity Content in Supernatant Units/ml	PIF (control) Units/ml
Sept. 17	0	0	]20,000
	1	50	do.
	2	1400	do.
	3	1400	do.
	4	3600	do.
Sept. 18	22	13000	do.
	25	11000	do.
	28	11000	do.
Sept. 21	46	11000	do.
	49	13000	do.
Sept. 22	70	13000	do.
	73	11000	do.

Comments on the Results:

As appears from Table 2, the interferon activity is released gradually during the first 20 hours which is considered to be almost ideal.

It was calculated that about half the amount of interferon was recovered in the aqueous phase after the end of the "release". This calculation did not take into account the removal of units from the supernatant for titrations. This was within the expected range, when the accuracy of the interferon test system is taken into account.

EXAMPLES 5 - 11

Clinical trials

A number of clinical treatments have been executed.

In order to apply the interferon gel on the area of vagina and/or uterus it is suitable to pack the interferon-containing gel in small tubes containing 1-4 ml, preferably 2 ml of gel, under aseptic conditions. The tubes are pointed which is considered to be advantageous for administering the interferon-containing gel to the skin surface areas of the vagina and/or cervix/uterus. The interferon gel may easily be applied by squeezing the tube by hand, thus allowing the clinician properly to control the desired amount of the interferon gel used in each case (preferably ± - 2 ml of the gel). For treating exterior skin surfaces (normally dry), it is advisable to use a swab. Thus, for example, ± ml of the interferon-containing gel may be squeezed out of the tube and the gel is spread over the area in question by means of the swab. In Examples 5 - 7 the interferon gel was applied by means of a pointed tube containing 2 ml of interferon gel.

EXAMPLE 5

A female monkey (weight 2 - 3 kg) had spontaneously developed a solid malignant tumor in uterus, a cancer colli uteri (and bleeding from the uterus due to ulceration). This was verified by biopsy specimens using the usual criteria, i.e. malignant cell structures were observed in cell specimens taken several times from the uterus over a period of 5-6 months. Thus, malignant cells were clearly seen in histological samples taken from the monkey during a period of several months.

The monkey was treated as follows: 1-2 million units of PIF (cf. Berg & Heron, Scand. J. Immunol. *11*, 1980, 489-502) were applied directly onto the cervical duct of uterus 2-3 times weekly over a period of 6 weeks. No side effects such as toxic effects, or allergic effects were observed during this treatment. After the 6 weeks, bleedings from the uterus stopped.

The general health of the monkey also improved at this stage of the treatment (the 6 weeks). Several specimens from cervix uteri were taken, coded blindly, and sent to different pathologists. They were all able to verify that the specimens taken from the monkey after the 6 weeks of treatment resembled normal cells. Thus, when comparing with specimens taken from the period after the 6 weeks it was clearly documented that a regression/reversion had occurred (tumor cells had reverted/regressed to normal cells). At this stage it is tempting to suggest that the monkey has been cured as regards the tumor originally located in cervix uteri.

This finding is surprising compared with the current results reported by different researchers treating human patients suffering from tumors by means of systemic treatments (3-6 million units per day for the first 30 days followed by 2-3 weekly injections of 3 to 6 million units for a period of 5-12 months). In most of these patients, only a border line improvement has been observed, if any. It should also be noted that a spontaneous regression of the tumor of the types described above is extremely rare (less than 1 out of 100,000 cases will spontaneously regress).

EXAMPLE 6

A female monkey (weight 2 - 3 kg) was treated with an interferon gel, prepared as described in Example 1, twice a week as follows:

About ± - 1 ml of the interferon gel was applied directly on the portio vaginalis uteri. Thus, the gel covered an area of about 1 cm^2 including the cervical orificium of the uterus. This regimen was maintained over a period of 5 weeks. No allergic reactions were observed.

The monkey had a slight redness on small parts of the portio vaginalis uteri. Cells taken from this area were normal (no cancer cells were detected). It was noticed that this area changed after treatment for 3 weeks using the interferon gel in that the reddish area changed into a completely normal area. Thus, it appears that lesions on the mucous membrane of the vagina or uterus may heal and revert to normal mucous membranes subsequent to such an interferon gel treatment.

EXAMPLE 7

An 18-year-old female patient suffering from a severe attack of Herpes simplex on her abdomen and Herpes genitalis was hospitalized. Several eruptions were observed on the skin areas on her abdomen and in and around the vagina. The attack was very painful, and the general state of health of the patient was rather bad. At the beginning of this treatment, only one third of the affected areas located on the skin surfaces of the abdomen was treated with the interferon gel using a swab for the application. Thus, a thin layer of interferon gel was applied to the selected area.

After 8 hours the patient felt diminishing pains in the area which had been treated with the interferon gel. 6-10 hours after the application of the gel, the patient had also experienced a slight itching only in the areas of the skin which had been treated with the interferon gel.

The physician also observed that the lesions were beginning to heal. Another area corresponding to another third was treated with the interferon gel and the same results were experienced by the patient and clinician in contrast to the untreated skin area.

It should be noted that the pain from areas attacked by the Herpes virus was diminished subsequent to an interferon gel treatment. Thus, after five to six hours the patient reported that there was a clear difference in the pain between affected areas treated with interferon gel and affected areas not treated with interferon gel.

The following day interferon gel was applied to the remaining skin surfaces with Herpes simplex eruptions. The patient noticed that the itching phenomenon as previously described now occurred almost instantly after the interferon gel had been applied to the surface of orificium vaginae. The patient reported that the pain had decreased considerably. The interferon gel was also applied to orificium vaginae in gradual steps and wound healing was observed. After 3 days the patient was cured. The cure was surprisingly fast in comparison with the conventional treatment.

Comments:

It is well-known that Herpes simplex/genitalis patients often recover spontaneously after a herpes attack. However, two striking (and surprising) results are evident after the administration of the interferon gel to the patients:

1. A specific wound healing process was initiated at the interferon gel treated areas compared with skin areas not treated with interferon gel.

2. Apparently, the effect of the interferon gel improved as the treatment progressed in that the patient felt an itching almost instantly after the third, fourth or the fifth application of interferon gel to skin areas with unhealed Herpes simplex eruptions.

These two observations altogether appear to support a basic principle of the invention that an antiviral effect of interferon gel restricted to the area in question together with a stimulating effect of the immunosystem localized in the area causes a more rapid healing of the virus infected areas. This approach is believed to be novel and surprising. It is tempting to speculate that, apart from its well-known antiviral activity, interferon may be able to stimulate particularly NK cells locally. Thus, as a result of the above-mentioned experiments, it is considered to be advantageous to treat human patients locally with interferon-containing gels by applying the interferon on the areas in question. This type of treatment is in direct contrast to the usual systemic treatments in which the human body receives interferon systemically.

The above examples triggered pilot tests which are described below in Examples 8-11.

EXAMPLE 8

Topical Treatment of Patients Suffering from "Moderate to Severe Dysplasia" or "Carcinoma in situ" of the Cervix

Only patients showing a "stable" disease were included in the study (i.e., no spontaneous regression was allowed during at least 27 weeks prior to treatment). The disgnoses were established by Papanicolou (PAP) - smears and by biopsies of the cervix.

The patients received 0.5 ml of the interferon gel described above directly on the cervix twice weekly for six weeks and only minor clinical improvements were detected (*vide* Table 3). However, after another six weeks during which the interferon gel was administered by means of a collum pessary 6 out of 6 patients responded positively, 3 of whom recovered completely. No side effects, whatsoever, were ever observed, nor did the collum pessary cause any side effects or pain after 24 hours. No bacterial infections were detected as a result of the application of the interferon gel with or without the collum pessa-

ry (no special precautions were taken). Experiments are in progress to evaluate if longer periods may be used.

Several other gel-types (not described here) were also tested, but they all proved to be inferior compared to the gel used in this experiment. Thus, many of these gels caused bacterial infection in the patients or were difficult to administer due to lack of adhesive properties, and some did not tolerate freezing/thawing. The present interferon gel did not, in any instance, cause any allergic reactions or other side effects. Furthermore, it is easily applied by means of a swab or spatula. (It was observed that a small amount of interferon gel remained in the inner cavity of the pessary subsequent to its removal. Occasionally, the interferon content was determined to be around 3000-5000 units per ml gel. This strongly suggests the use of gels with a higher interferon activity; possibly, it should be attempted to use interferon gels with a 10-times higher interferon content - experiments are in progress.)

EXAMPLE 9

Topical Interferon Gel Treatment of Infections with Herpes Simplex Virus

Sixteen patients suffering from Herpex simplex, Herpes genitalis and Herpes zoster infections were treated by topical application of the interferon gel described in Example 1 (as the only medicament). Generally speaking, the gel was found to alleviate the symptoms by speeding up the healing processes in patients with primal as well as recurrent herpes infections (*vide* Table 4).

The interferon gel was applied 2-3 times a day on patients with perioral herpes; patients with Herpes zoster were treated once or twice a day, whereas patients with genital herpes were treated once a day only. The treatment was initiated after the "classical" symptoms (lesions) had emerged and the treatment was in most cases continued 2-3 days after the symptoms had disappeared (the lesions had healed).

As seen in Table 4, the results of the gel treatment very often caused a marked decline of the symptoms after only 1-2 applications. After 1-2 days the symptoms disappeared as far as the herpes eruptions on the lips or chin were concerned, whereas the symptoms in patients with genital herpes persisted for 3-5 days after the institution of the gel treatment. In the two patients with Herpes zoster the symptoms disappeared after 5-6 days of treatment (interferon gel applied twice daily). Characteristically, in the patients treated with interferon gel, the classical vesicles formed scabs within one or two days after the first application of the gel and healing without scarring was observed during the next few days.

Comments with regards to Example 9:

No curative treatment of herpes infections in humans has been reported (cf. reference No. 1, 3-6). Acyclovir, a drug known to interfere with viral replication, has proven to be effective, but only during the first outbreak of a herpes attack. Thus, patients suffering from recurrent herpes infections are still left without any effective treatment other than this gel.

Generally speaking, the topical application of the interferon gel as performed in the above test (Example 9) does not have a curative effect on herpes infections. Thus, it was found that recurrence of the eruptions were just as frequent before as after the treatment. However, the treatment reduced the duration of symptoms, such as pain, markedly and accelerated the healing of lesions in patients with perioral herpes and genital herpes infection, although the efficacy of the treatment was less pronounced in the latter group. This may, highly likely, be due to the fact that the gel was applied only once a day on patients with genital herpes, but 2-3 times a day in patients with Herpes simplex.

Very recently, one patient (female) suffering from a severe Herpes genitalis was hospitalized and treated with the gel 4 times a day. In contrast to the patients previously treated for herpes genitalis, she already recovered after 2-3 days, which is considered to be an unu-

sually rapid recovery. This mode of administration is now being further investigated.

EXAMPLE 10

A female patient who has suffered from "cronical seborrhea" around the nose for the last 20 years was treated (only on the right side of the reddish area, leaving about 50% of the attack untreated as a control). After 2-3 applications of the gel the itching had stopped (within 24 hours), but only in the treated area. The untreated area (control) was unchanged (reddish, itching). Further clinical investigations are being pursued in order fully to investigate the surprising effect against this type of disease.

EXAMPLE 11

A female patient who was originally included in the study discussed in Example 8 was later excluded from the study (she is not included in Table 3) due to an incorrect diagnosis, since it turned out she was suffering from a condyloma. However, the gel treatment (twice a week) turned out to be benifical in her case too. This surprising effect is now being further pursued.

TABLE 3

Histological evaluation of samples obtained from 6 patients treated with the interferon gel

Patient No.		Before treatment	After 6-8 weeks of treatment	After 23-16 weeks of treatment	Clinical Efficacy
270354	Cytoscrape	Medium/severe dysplasia	Medium dysplasia	Medium/ light dysplasia	Good
	Biopsy	Medium dysplasia	Light dysplasia	Light dysplasia	
300452	Cytoscrape	Medium dysplasia	Medium dysplasia	Light dysplasia	Excellent
	Biopsy	Medium dysplasia	Light/medium dysplasia	Normal	
100658	Cytoscrape	Carcinoma in situ	Severe dysplasia	Medium dysplasia	Excellent
	Biopsy	Severe dysplasia	Severe dysplasia	Normal (light)	
120852	Cytoscrape	Severe dysplasia	Medium dysplasia	Medium dysplasia	Good
	Biopsy	Severe dysplasia	Medium dysplasia	Light dysplasia	
281152	Cytoscrape	Medium dysplasia	Light/medium dysplasia	Light dysplasia	Good
	Biopsy	Medium dysplasia	Light dysplasia	Light dysplasia	
241250	Cytoscrape	Medium/severe dysplasia	Light dysplasia	Atypia	Excellent
	Biopsy	Severe dysplasia	Light/medium dysplasia	Normal	

TABLE 4

Topical interferon treatment of Herpes simplex virus patients

Patient No.	Localisation	Type of herpes°	Duration of disease (years)	No. of eruptions per year	Duration of symptoms without treatments (days)	Duration of symptoms with treatment (days)
1	lip/chin	HSV-1	26	3-4	10-14	4-5
2	chin	HSV-1	10	10-12	5-6	1-2
3	lip	HSV-1	6	6-8	5-6	1-2
4	lip/chin	HSV-1	20	3-4	4-6	1-2
5	lip/chin	ND	8	12	6-7	1-2
6	lip/chin	HSV-1	15	4-6	5-6	1
7	lip/chin	HSV-1	2	5-6	3-5	1-2
8	lip	ND	10	3-4	5-7	2
9	lip	ND	20	5-10	4-8	1-2
10	genitals	HSV-2	first episode	-	-	5
11	genitals	HSV-2	2-3	4-6	6-8	4-5
12	genitals	ND	5	1-2	10-14	3-5
13	genitals	ND	20	3-5	5-8	3-4
14	genitals	HSV-1	2	5-6	5	3-4
15	chest	zoster	first episode	-	-	5
16	genitals	zoster	first episode	-	-	6

° The diagnoses were established by means of identifications from cell cultures.

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Claims

1. A method for treating a mammal, in particular a human patient, suffering from interferon-susceptible disorders such as pre-cancerous or cancerous tumors or local virus infections such as Herpes simplex virus infections or other disorders such as dermatitis, e.g. seborrhea, etc., said method comprising local administration of interferon in a single aqueous gelled phase directly onto or close to the surroundings of an organ or site in which the disorder is located and continuing the local administration for a period of time sufficient to obtain a response to the interferon treatment.

2. A method according to claim 1 wherein the administration is performed at a rate of about 1-8 times a day to 1-3 times a week.

3. A method according to claim 1 or 2 wherein the administration is performed topically on the exterior membrane of the organ or site in which the disorder to be treated is located or in a region as close as possible to the tumor or virus infection site or other affected area.

4. A method according to any of claims 1 - 3 in which the interferon is selected from the group consisting of human interferon α, β, or γ (HuIFN-α, HuIFN-β, or HuIFN-γ), or a combination thereof, including human leucocyte and/or lymphoblastoid interferon, and/or proteins which show interferon activity and which are prepared by recombinant DNA techniques.

5. A method according to claim 4 in which the interferon is a crude interferon.

6. A method according to claim 4 in which the interferon is a partially purified interferon having a specific activity of about 10^6 units per mg of protein.

7. A method according to claim 4 in which the interferon is a pure interferon protein having a specific activity of at least 10^8 units per mg of protein.

8. A method according to any of the preceding claims wherein the interferon is administered by being released from a locally placed deposit form releasing the interferon.

9. A method according to claim 8 wherein the deposit is in a form suitable for topical application on the surfaces or membranes to be treated which form will release dissolved interferon.

10. A method according to claim 8 or 9 wherein the deposit is a single-phase aqueous gel containing the interferon activity.

11. A method according to claim 10 wherein the single-phase aqueous gel is transparent.

12. A method according to claim 11 wherein the gelling agent used in the single-phase transparent aqueous interferon gel is one which renders the gel capable of substantially adhering to the said membranes or surfaces whereby the interferon activity is capable of diffusing from the deposit to cell surfaces of the said membranes or surfaces.

13. A method according to any of the preceding claims in which the interferon activity is combined with an antibiotic which is water soluble and which does not substantially inhibit the interferon activity.

14. An interferon composition for application on interior or exterior surfaces such as skin surfaces (dry or wet), mucous membrane surfaces, serous membrane surfaces, etc., the interferon composition comprising a single-phase aqueous transparent interferon gel suitable for topical application on the surfaces or membranes to be treated which gel will release dissolved interferon.

15. A composition according to claim 14 wherein the gelling agent of the interferon gel is of such a nature that the composition is capable of substantially adhering to said membranes or skin surfaces whereby the interferon activity is capable of diffusing from the composition into cells of the said membranes or skin surfaces.

16. A composition according to claim 15 wherein the gelling agent is of such a nature that the gel may be subjected to freezing, thawing, sterilization (e.g. by autoclaving at 120°C), with retention of the single phase character and transparency of the gel.

17. A composition according to any of claims 14-16 wherein the gelling agent is a carbohydrate or a carbohydrate derivative.

18. A composition according to claim 17 wherein the gelling agent is a polysaccharide containing COO^- groups.

19. A composition according to claim 17 or 18 in which the gelling agent is a cellulose or alginate derivative.

20. A composition according to any of claims 17-19 in which the gelling agent is an etherified cellulose derivative, such as carboxymethyl cellulose, ethyl cellulose, or methyl cellulose.

21. A composition according to any of claims 14-20 wherein the gel constituents are of such a nature that they are physiologically acceptable, particularly non-toxic and non-allergenic.

22. A composition according to any of claims 14-21 which is so adapted that when it substantially adheres to a surface or membrane as defined in claim 1, it will release its interferon activity content at a sustained rate.

23. A composition according to claim 22 in which the release rate is so adapted that the available interferon content of the composition is transferred to the cells of the skin surface or membrane in question in the course of about 4-48 hours.

24. A composition according to any of claims 14-23 which has a viscosity in the range of 500 - 100,000 cps at 100 RPM (Brookfield).

25. A composition according to any of claims 14-24 in which the aqueous gelled phase comprises a substance having water retention capacity.

26. A composition according to claim 25 in which the substance showing water retention capacity is a physiologically acceptable polyvalent alcohol.

27. A composition according to claim 26 in which the polyvalent alcohol is a glycol or a glycol ether.

28. A composition according to claim 27 in which the polyvalent alcohol is selected from glycerol, ethylene glycol, or polyethylene glycol.

29. A composition according to any of claims 14-28 which contains a buffer substance.

30. A composition according to claim 29 in which the buffer is a buffer with a pH of from about 6 - 8.

31. A composition according to claim 30 in which the buffer has a pH of about 7.2 - 7.5.

32. A composition according to claim 31 in which the buffer is a phosphate buffered saline buffer (Dulbecco buffer).

33. A composition according to claim 32 in which the gel comprises about 4% or more of carboxymethyl cellulose.

34. A composition according to any of claims 14-33 which additionally contains an antibiotic which is water soluble and which does not substantially inhibit the activity of interferon, such as neomycin.

35. A composition according to any of claims 14-34 in which the interferon is selected from the group comprising human interferon α, β, or γ (HuIFN-α, HuIFN-β, or HuIFN-γ), or a combination thereof, including human leucocyte and/or lymphoblastoid interferon, and/or proteins which show interferon activity and which are prepared by recombinant DNA techniques.

36. A composition according to claim 35 in which the interferon is a crude interferon.

37. A composition according to claim 35 in which the interferon is a partially purified interferon having a specific activity of about 10^6 units per mg of protein.

38. A composition according to claim 35 in which the interferon is a pure interferon protein having a specific activity of at least 10^8 units per mg of protein.

39. A composition according to claim 38 wherein the interferon proteins are mixed with other suitable lymphokines such as lymphotoxines the action of which is potentiated by the said interferon.

40. A composition according to claim 35 wherein the interferon has a purity of more about $4x10^6$ International Units/mg protein and is stabilized by the incorporation of a protein such as human albumin in the gel.

41. A method for preparing an interferon composition according to any of claims 14-40 comprising incorporating an interferon according to any of claims 35-40 in a single-phase aqueous gel matrix.

42. A method according to claim 41 in which the gel matrix comprises a gelling agent according to any of claims 15-20.

43. A method according to claim 42 in which the gelling agent is carboxymethyl cellulose.

44. A method according to claim 43 in which carboxymethyl cellulose is incorporated in an amount of about 4% or more.

45. A method according to claim 41 in which the gel matrix comprises a substance according to claims 26-28 having water retention capacity.

46. A method according to claim 41 in which the gel matrix comprises a buffer according to any of claims 29-32 in the gel composition.

47. A method according to claim 41 in which the gel matrix comprises an antibiotic which is water soluble and which does not substantially inhibit the activity of interferon.

48. A method according to any of claims 1-13 wherein the interferon is applied together with a medicament influencing the formation of the cytoskeletal system.

49. A method according to claim 48, wherein the medicament is isoprenacine or a salt of butyric acid.

50. A composition according to any of claims 14-40 wherein is enclosed a medicament influencing the formation of the cytoskeletal system.

51. A composition according to claim 50 wherein the medicament is isoprenacine or a salt of butyric acid.

52. A method according to any of claims 1-13 wherein the interferon is applied together with a medicament which is known to exert an inhibitory influence on the replication of Herpes simplex virus Type I and II.

53. A method according to claim 52 wherein the medicament is phosphono formate, acycloguanosine, E-5-(2-bromovinyl)-2'-deoxyuridin (deoxyuridin) and/or 2'-fluoro-5-iodoaracytosine (1-(2-fluoro-2-deoxy-β-D-arabinofuranosyl-(5-)-iodocytosine).

54. A composition according to any of claims 14-40 wherein is enclosed a medicament which is known to exert an inhibitory influence on the replication of Herpes simplex Type I and II.

55. A composition according to claim 54 wherein the medicament is phosphono formate, acycloguanosine, E-5-(2-bromovinyl)-2'-deoxyuridin (deoxyuridin) and/or 2'-fluoro-5-iodoaracytosine (1-(2-fluoro-2-deoxy-β-D-arabinofuranosyl-(5-)-iodocytosine).

56. A method according to any of claims 1-13, 48-49 or 52-53 wherein the administration is carried out using a pointed collapsible tube, or a piece of adhesive provided with a cavity in which the interferon gel is placed.

57. A composition according to any of claims 14-40, 50-51 or 54-55 contained in a collapsible pointed tube or placed in the cavity of an adhesive provided with a cavity.

58. A method according to any of claims 1-13 comprising applying the interferon gel according to any of claims 14-40, 43-44 or 47-48 in admixture with a collagen creme.

59. A composition in which the interferon gel according to any of claims 14-40, 43-44 or 47-48 has been mixed with a collagen creme.

60. The use of the interferon composition according to any of claims 14-40, 50-51, 54-55 or 59 for the topical treatment of diseases or abnormalities in skin or mucuous or serous mambrane surfaces, such as Herpes simplex Type I and II, Herpes zoster, Herpes keratitis, Condylomata, iridocyclitis caused by a virus, pre-cancerous or cancer conditions such as dysplasia and carcinoma in situ of portio uteri or dysplasia of collum, vaginal cancers, vulva cancers, skin cancers, cell carcinomas, spinocellular carcinomas, cervical intraepithelial neaplacia of early stages in collum uteri, cervical cancers and abnormal skin areas such as dermatitis, e.g. seborrhea, or dandruff.

INTERNATIONAL SEARCH REPORT

International Application No PCT/DK82/00092

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [3]

According to International Patent Classification (IPC) or to both National Classification and IPC 3

A 61 K 45/02

II. FIELDS SEARCHED

Minimum Documentation Searched [4]

Classification System	Classification Symbols
IPC 3	A 61 K 45/02
US Cl	424:85

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [5]

SE, NO, DK, FI classes as above

III. DOCUMENTS CONSIDERED TO BE RELEVANT [14]

Category *	Citation of Document, [16] with indication, where appropriate, of the relevant passages [17]	Relevant to Claim No. [18]
X	Schweiz. Rundschau Med. (PRAXIS) Vol 68, pp 1401-05, published 1979, (FLURY F, WEGMANN T) "Klinische Erfahrungen bei der Therapie mit Interferon", see in particular p 1402, "Salbe und Gel".	14-26, 27, 35-38, 41-43
P	Int. J. Clin. Pharm. Ther. Toxicol. Vol 19, No 11, pp 498-505, published 1981, (IKIC D et al), "The clinical use of human leukocyte interferon in viral infections".	
A	J. Am. Acad. Dermatol. Vol 3, pp 585-95, published 1980, (YANCEY K B, SMITH G J Jr) "Interferon: Status in treatment of skin disease".	1-60
Y	Abstract 0476051 from MEDLINE (US National Library of Medicine accession number 81206051), Antibiotiki Vol 26(3), pp 145-9, published March 1981 (GREBENIUK V N et al)	40
A	-"-	1-60

.../...

* Special categories of cited documents: [15]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search [2]	Date of Mailing of this International Search Report [2]
1982-12-01	1982 -12- 10
International Searching Authority [1]	**Signature of Authorized Officer** [20]
Swedish Patent Office	Carl Olof Gustafsson

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. [X] OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [10]

This International search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. [X] Claim numbers * because they relate to subject matter [12] not required to be searched by this Authority, namely:

* 1-13, 48, 49, 52, 53, 56, 58, 60

Method for treatment of human body by therapy.

2. [ ] Claim numbers ....., because they relate to parts of the International application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out [13], specifically:

VI. [ ] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [11]

This International Searching Authority found multiple inventions in this international application as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International search report covers all searchable claims of the international application.

2. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the International application for which fees were paid, specifically claims:

3. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. [ ] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

[ ] The additional search fees were accompanied by applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, [16] with indication, where appropriate, of the relevant passages [17]	Relevant to Claim No [18]
A	Stomatologija Moskva, Vol. 53, pp 53-55, published 1974 (abstract in English), (DROBOTKO L N et al), "Treatment with interferon ointment of acute herpetic stomatitis in children". (Russ.)	1-60
A	US, A, 4 041 152 (CHANY C et al) 9 August 1977	14-17
A	GB, A, 2 016 015 (HAYASHIBARA K, ASHIDA S) 19 September 1979, see pp 7-8.	1-60