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(54) Title: METHODS AND COMPOSITIONS FOR AMELIORATION OF SKIN WRINKLES

(57) Abstract

There are disclosed compositions for the amelioration of wrinkles of the skin, an methods for their use. The compositions comprise, as active substance, elastin, at least some of which has a molecular weight of less than 10,000. The compositions may further comprise an agent for reducing corneocyte cohesion of the lower levels of the hyperkeratotic stratum of the skin, such agent being typically an alpha-hydroxy acid. The methods of use of the compositions of the invention may comprise topical application or subcutaneous injection.

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METHODS AND COMPOSITIONS FOR AMELIORATION OF SKIN WRINKLES

TECHNICAL FIELD

This invention relates to a method and composition for the amelioration of wrinkles in wrinkled skin.

BACKGROUND OF THE INVENTION

It has long been desirable to slow, halt or reverse the effects of natural and photo-aging and exposure to wind and sunlight on the physiology and in particular the appearance of the skin. Of particular concern has been the wrinkling of the skin which occurs with age and which it is believed is accelerated by exposure to harsh conditions.

While many pharmaceutical or cosmetic compositions for application to the skin for improving its condition are known, there remains a need for an effective and widely applicable treatment for ameliorating skin wrinkles and in particular the condition known as 'crows-feet' associated with skin wrinkling adjacent the eye.

Known treatments for skin wrinkling or sagging are those involving cosmetic surgery. However, these are both costly and traumatic to the patient. Accordingly, there is a need for an improved pharmaceutical or cosmetic composition providing effective treatment for alleviating skin wrinkles.

It has now unexpectedly been found that the use of partially degraded and solubilised elastin of relatively low molecular weight in compositions for application to the skin is particularly effective in treating aging skin, and reduces wrinkles and the aged appearance of skin, including for example the skin condition known as crows-feet.

It has also been found that the use of an agent for reducing corneocyte cohesion of the lower levels of the hyperkeratotic stratum of the skin, with a composition comprising elastin, provides additional advantages for the treatment of aged or wrinkled skin.

OBJECTS OF THE INVENTION

Accordingly, it is an object of this invention to provide a method and composition for the amelioration of wrinkles in wrinkled skin.

DETAILED DESCRIPTION OF THE INVENTION

Elastin is a fibrous protein which is found in the connective tissue and arterial walls of higher organisms, such as mammals. It is present in larger amounts, for example, in the bovine neck ligament. The bovine neck ligament is solubilised to polypeptides containing desmosine and isodesmosine by certain proteolytic enzymes, notably crystalline elastase.

In the description and claims, "elastin" is defined, unless the contrary indication appears, as native fibrous elastin or a polypeptide derived therefrom or a mixture of different polypeptides derived therefrom or a mixture of any of the foregoing.

It has been found unexpectedly that there are substantial advantages in the amelioration of skin wrinkling by providing and using a composition (and in particular a pharmaceutical or cosmetic composition) which includes elastin having a reduced molecular weight.

Thus, in this invention a composition is provided wherein at least some of the elastin has a molecular weight of less than 10000. It has been found that by providing such elastin of a reduced molecular weight the elastin more rapidly and efficiently rejuvenates (it is assumed at this stage this occurs by penetration) the skin layers so as to maximise the effects of elastin in the compositions.

Because of the reduced molecular weight and size of at least some of the elastin within such compositions such advantages are obtained. Thus, by application of such compositions it has been found that improvements can be achieved in the treatment of aging, wrinkles and under-eye skin problems associated with skin aging.

Additional advantages have further been found when a composition comprising elastin is used with an agent for reducing corneocyte cohesion of the lower levels of the hyperkeratotic stratum. In this way, rejuvenation of

the skin by the elastin is further facilitated. The agent may be applied prior to, at the same time as, and/or after the application of elastin.

According to a first embodiment of the invention there is provided a method for the treatment of wrinkled skin in a human in need of such treatment, comprising administering to the wrinkled skin a wrinkle ameliorating effective amount of a composition comprising elastin, as hereinbefore defined, together with at least one acceptable carrier, diluent or adjuvant, wherein at least some of said elastin has a molecular weight of less than 10000.

According to a second embodiment of the invention there is provided a method for the treatment of wrinkled skin in a human in need of such treatment, comprising administering to the wrinkled skin a wrinkle ameliorating effective amount of a composition comprising:

elastin, as hereinbefore defined, wherein at least some of said elastin has a molecular weight of less than 10000 and

an agent for reducing corneocyte cohesion of the lower levels of the hyperkeratotic stratum.

Typically the composition used in the method of the second embodiment also includes at least one carrier, diluent or adjuvant.

The methods of the first and second embodiments may include topical and/or subcutaneous treatment of wrinkled skin.

Generally, in the invention according to the first or second embodiments, each administration comprises the steps of:

(a) topically applying the composition to said wrinkled skin and/or subcutaneously injecting the composition;

(b) allowing the composition to be absorbed into the skin or to dry, and

(c) optionally repeating steps (a) and (b) one or more times.

Generally, in the method according to the first or second embodiments, the composition is applied from once weekly to between once daily and ten times daily, most usually between once daily and three times daily.

In the method according to the first or second embodiments, the composition may be applied for any period of time desired to achieve the required degree

of amelioration of wrinkles. The application may be for as short as one day. Usually, the application will be for at least one week, and more usually for at least four weeks. The application may continue, however, for longer times, for example for three months, one year, five years, ten years or a lifetime.

In the method according to the first or second embodiments, the composition is usually applied to the face, neck, ears, hands or other skin areas; more particularly to the forehead, eyelid or the under or side eye area.

According to a third embodiment of the invention there is provided a composition for administration to the skin for ameliorating wrinkles, comprising elastin, as hereinbefore defined, together with at least one acceptable carrier, diluent or adjuvant, wherein at least some of said elastin has a molecular weight of less than 10000.

According to a fourth embodiment of the invention there is provided a composition for administration to the skin for ameliorating wrinkles, comprising:

elastin, as hereinbefore defined, wherein at least some of said elastin has a molecular weight of less than 10000 and

an agent for reducing corneocyte cohesion of the lower levels of the hyperkeratotic stratum.

Typically the composition of the fourth embodiment also includes at least one carrier, diluent or adjuvant.

In the first to fourth embodiments, from about 1% by weight of the elastin to substantially all of the elastin has a molecular weight less than 10000; more typically, from about 10% by weight of the elastin to about 80% by weight of the elastin has a molecular weight less than 10000; even more typically about 30% to about 75% by weight of the elastin has a molecular weight less than 10000.

Typically, from about 15% by weight of the elastin to about 30% by weight of the elastin has a molecular weight between 10000 and 30000; from about 10% by weight of the elastin to about 30% by weight of the elastin has a molecular weight between 30000 and 45000; from about 3% by weight of the elastin to about 10% by weight of the elastin has a molecular weight between 45000 and 60000; and from about 2% by weight of the elastin to

about 10% by weight of the elastin has a molecular weight between 60000 and 150000. Alternatively, from about 5% by weight of the elastin to about 95% by weight of the elastin has a molecular weight of less than 30000.

Generally, in the first to fourth embodiments the composition is a cream, ointment, paste, solution, emulsion, lotion, milk, jelly, gel, stick, roll-on or smooth-on, wherein the elastin comprises up to about 90%, more typically 10%, by weight or volume of the composition, even more typically from about 0.1% to about 4% by weight, for example 3.5% by weight.

In a further form of the invention there is provided a method for the amelioration of wrinkles of the skin by applying to the wrinkled skin a composition of the third embodiment before, together with and/or after a composition of the fourth embodiment.

Generally, in the first to fourth embodiments the composition will be a pharmaceutical composition, wherein the at least one carrier, diluent or adjuvant will be pharmaceutically acceptable for topical skin administration or for subcutaneous skin administration; or a cosmetic composition, wherein the at least one carrier, diluent or adjuvant will be cosmetically acceptable for topical skin administration.

Illustrative of pharmaceutically or cosmetically acceptable carriers or diluents are demineralized or distilled water; saline solution; vegetable based oils such as peanut oil, safflower oil, olive oil, cottonseed oil, maize oil, sesame oil, arachis oil or coconut oil; silicone oils, including polysiloxanes, such as methyl polysiloxane, phenyl polysiloxane and methylphenyl polysiloxane; volatile silicones; mineral oils such as liquid paraffin, soft paraffin or squalane; cellulose derivatives such as methyl cellulose, ethyl cellulose, carboxymethylcellulose, sodium carboxymethylcellulose or hydroxypropylmethylcellulose; lower alkanols, for example ethanol or iso-propanol; lower aralkanols; lower polyalkylene glycols or lower alkylene glycols, for example polyethylene glycol, polypropylene glycol. ethylene glycol, propylene glycol, 1,3-butylene glycol or glycerin; fatty acid esters such as isopropyl palmitate, isopropyl myristate or ethyl oleate; polyvinylpyrridone; agar; carrageenan; gum tragacanth or gum acacia, and petroleum jelly. Typically, the carrier or carriers will form from 10% to 99.9% by weight of the composition.

Adjuvants typically include emollients,emulsifiers, thickening agents, preservatives, bacteriocides and buffering agents.

Emollients suitable for inclusion in a composition of the invention include fatty esters such as isopropyl myristate, cetyl acetate, diisopropyl adipate or C_{12} - C_{15} alcohol benzoates; fatty alcohols such as lauryl alcohol, myristyl alcohol, cetyl alcohol, stearyl alcohol or cetostearyl alcohol; mineral and vegetable oils such as aloe vera and jojoba oil; lecithin; Vitamin E; lanolin; sorbitol and glycerin. Typically, the emollient or emollients will form from 10% to 99.9% by weight of the composition.

Suitable thickening agents include sodium stearate, calcium stearate, magnesium stearate, calcium palmitate and magnesium palmitate, dextran, , dextrins, starch and starch products, gelatin, cellulose derivatives as exemplified above, collagen, water soluble polymers such as carboxyvinyl polymer, polyvinyl alcohol or polyvinyl acetate, pectin, xanthan gums, , bentonite, hyaluronic acid, fumed silica and the like. Typically, the thickening agent or agents will form from 0.1% to 20% by weight of the composition.

Typical preservatives include ascorbic acid and its salts, erythorbic acid and its salts, ethyl and iso-propyl p-hydroxybenzoates, benzalkonium chloride, benzyl alcohol, phenylethanol and glydant chlorobutanol. Typically, the preservative or preservatives will form from 0.1% to 12% by weight of the composition.

Suitable buffering agents are salts of boric, acetic, phosphoric, citric, malic, succinic acids and the like, for example sodium citrate, sodium bicarbonate, sodium acetate and sodium phosphate. Additionally or alternatively, the free acids may be used, together with an alkali such as sodium hydroxide, sodium carbonate, sodium bicarbonate, potassium hydroxide, potassium carbonate or potassium bicarbonate. Typically, the buffering agent or agents will form from 0.1% to 20% by weight of the composition.

Emulsifiers may also be included in a composition of the invention. Illustrative nonionic emulsifiers include fatty acids such as oleic acid, stearic acid and palmitic acid; esters of lactic acid, tartari acid, ascorbic acid or citric acid; polyalkylene glycol esters such as polyoxyethylene glycol monostearates, polyoxyethylene glycol monolaurates; polyoxyethylene glycol distearates or polyoxyethylene glycol dilaurates; polyalkylene glycol ether derivatives of

aliphatic or cycloaliphatic alcohols such as polyoxyethylene nonylphenol ether, polyoxyethylene cetyl ether or polyoxyethylene stearyl ether; hexitan esters, for example sorbitan monolaurate, sorbitan monooleate, sorbitan distearate, sorbitan tristearate, sorbitan dilaurate or sorbitan trilaurate; fatty esters such as glyceryl monostearate, ethylene glycol monostearate, propylene glycol monostearate or butylene glycol monostearate; sorbitol and ethoxylated sorbitol esters of fatty acids such as polyoxyethylene sorbitan monostearate, polyoxyethylene sorbitan monolaurate, polyoxyethylene sorbitan monooleate, polyoxyethylene sorbitan distearate, polyoxyethylene sorbitan dilaurate, polyoxyethylene sorbitan dioleate, polyoxyethylene sorbitan tristearate, polyoxyethylene sorbitan trilaurate or polyoxyethylene sorbitan trioleate; long-chain alcohols such as lauryl, myristyl, stearyl, oleyl, cetyl or cetostearyl alcohol; polysaccharides such as starch and starch derivative, cellulose derivatives as exemplified above, agar, tragacanth, acacia and alginic acid; and steroidal derivatives such as lanolin alcohols or ethoxylated lanolin alcohols, and beeswax. Illustrative ionic surfactants include triethanolamine and amine soaps such as triethanolamine stearate; anionic soaps such as calcium or magnesium salts of stearic acid or palmitic acid; fatty alcohol sulphates, for example sodium lauryl sulphate; alkyl or aralkyl sulphonates such as sodium sulphosuccinates or sodium dodecylbenzenesulphonate; quaternary ammonium salts containing at least one long-chain alkyl group as N-substituent, for example stearyl trimethylammonium chloride, and phosphate esters of polyalkylene glycols. Typically, the emulsifier or emulsifiers will form from 0.1% to 99% by weight of the composition.

The compositions of the invention may further include a sunscreen. Suitable sunscreens include opacifiers such as titanium dioxide or zinc oxide;p-aminobenzoic acid, isobutyl p-aminobenzoate, glyceryl p-aminobenzoate, or N-substituted derivatives of p-aminobenzoic acid such as isoamyl p-dimethyl-aminobenzoate, pentyl p-dimethylaminobenzoate, octyl p-dimethylamino-benzoate or ethyl 4-[bis(2-hydroxypropyl)amino]benzoate; 2-hydroxy-1,4-naphthoquinone; octocrylene; octyl p-methoxycinnamate or 2-ethoxyethyl p-methoxycinnamate; salicylate esters such as octyl salicylate, homomenthyl salicylate or 2-[bis(2-hydroxyethyl)-amino]ethyl salicylate; oxybenzone and methyl anthranilate. Typically, the sunscreen or sunscreens will form from 0.1% to 10% by weight of the composition.

The compositions of the invention may further include an agent for reducing corneocyte cohesion of the lower levels of the hyperkeratotic stratum.

Suitable such agents are the alpha-hydroxy acids, such as lactic acid, malic acid, citric acid, citramalic acid, tartaric acid, mucic acid, glycolic acid, hydroxyglutaric acid, hydroxybutyric acid, hydroxyvaleric acid, acetonic acid, ascorbic acid, erythorbic acid, glucuronic acid, gluconic acid or gluconolactone. Typically, the moisturiser or moisturisers will form from 0.1% to 50% by weight of the composition.

Suitable bacteriocides include hexachlorophene, dichlorophenol, and halogenated anilides such as trichlorocarbanilide, trichlorosalicylanilide, tribromosalicylanilide, or tetrachlorosalicylanilide. Typically, the bacteriocide will form from 0.05% to 0.5% by weight of the composition.

Additionally, it will be understood that the compositions of the invention may include suitable colouring agents and/or perfumes well known in the art. Typical examples of suitable perfuming agents are provided in S. Arctander, "Perfume and Flavor Chemicals", Montclair, New Jersey, 1969.

It will be appreciated that the examples referred to above are illustrative only and other suitable carriers, diluents, excipients and adjuvants known to the art may be employed without departing from the spirit of the invention.

BRIEF DESCRIPTION OF THE DRAWINGS

Figures 1 to 9 present bar graphs representing the results of a field trial of a composition of the invention among one of the groups of subjects of the field trial.

Figures 10 to 15 present bar graphs representing the results of a field trial of a composition of the invention among another of the groups of subjects of the field trial.

BEST MODE AND OTHER MODES FOR CARRYING OUT THE INVENTION

The elastin suitable for this invention may be prepared by the controlled hydrolysis of defatted, shredded bovine neck ligament which has been made free of other proteins, etc. by boiling with dilute alkali. Removal of fats may be conveniently achieved by successive soaking in solvents such as acetone, butanol or ethanol. The shredded ligament is repeatedly soaked in an

aqueous salt solution to remove soluble protein. Suitably the aqueous salt solution may be a solution of sodium chloride of concentration from 0.1M to 0.5M. After washing the tissue to remove the salt, it may be treated with an aqueous alkali to remove proteins, etc. other than elastin. Suitable alkalies are aqueous solutions of sodium hydroxide or potassium hydroxide in concentrations from 0.05M to 1M. The treatment is suitably accompanied by boiling for a period of from 10 minutes to several hours. It will be appreciated that the conditions of treatment necessary to remove proteins other than elastin will vary depending of the character of the bovine neck ligament used. Such conditions will be well known or readily determinable by those skilled in the relevant art.

The elastin as prepared is solubilized by controlled hydrolysis. Suitable for the controlled hydrolysis of the native elastin are proteolytic enzymes such as elastase or pepsin; preferred is crystalline elastase, and most preferred is highly purified crystalline elastase. Pancreatic elastase may be prepared by the method described by Lewis et al. (J. Biol. Chem. 222 705 (1956)). Other proteases that could be used are papain, bromelain, subtilisin or ficin.

The hydrolysis with crystalline elastase is carried out at pre-determined pH, ionic strength, time and temperature in order to ensure that desmosine and isodesmosine cross linking amino acids are attached in the elastin polypeptides. Suitable conditions when crystalline elastase is used are:

pH:	8.5 to 9.3
ionic strength:	0.05 to 1M
time:	15 minutes to 2 hours
temperature	20°C to 40°C

The duration and temperature of the controlled hydrolysis affects the molecular weight composition of the elastin produced. Longer hydrolysis times and/or higher temperatures result in lower molecular weights, and in particular lower minimum molecular weights. By adjusting the conditions, which will vary depending on the source of the fibrous elastin used, any desired minimum molecular weight can be achieved. The molecular weight distribution of the elastin may conveniently be measured by gel diffusion chromatography. By sampling a hydrolysis reaction mixture periodically and analysing the molecular weight distribution by this technique, the reaction may be terminated at any desired stage and reaction conditions to achieve a desired minimum molecular weight may thus be determined.

After controlled hydrolysis of the elastin, the proteolytic enzyme is destroyed by acid hydrolysis and the elastin is filtered, concentrated and, if necessary, lyophilized.

Other proteolytic enzymes may be used at higher temperatures than the working temperature range of elastase. For example, papain remains active up to 70°C at least.

The compositions of the invention may be prepared by mixing, blending, homogenising, emulsifying or combining the elastin with the selected carriers, adjuvants and other ingredients. Preferably, the compositions are prepared by homogeneous blending. If necessary the compositions may be heated to bring about homogenisation.

A typical cream or ointment composition of the invention has the composition:

0.1 - 10% (w/w) elastin, preferably 0.1 - 4%
40 - 90% (w/w) demineralized or distilled water, preferably 50 - 80%;
1 - 10% (w/w) polyoxyethylene based non-ionic surfactants, preferably 2 - 6%;
0.1 - 2% (w/w) thickening agents, preferably 0.1 - 1%;
0 - 10% (w/w) alpha-hydroxy acids, preferably 5 - 8%;
0.1 - 1% (w/w) parabens, preferably 0.1 - 0.5%;
5 - 20% (w/w) vegetable oil, preferably 10 - 15%;
0 - 10% (w/w) mineral oil, preferably 1 - 6%;
0 - 10% (w/w) stearic acid, preferably 0 - 5%;
0 - 10% (w/w) glycerin, preferably 0 - 6%;
0 - 5% (w/w) octyl methoxycinnamate, preferably 1 - 3%.

A typical jelly or gel composition of the invention has the composition:

0.1 - 10% (w/w) elastin, preferably 0.1 - 4%;
40 - 90% (w/w) demineralized or distilled water, preferably 60 - 80%
0 - 5% (w/w) polyoxyethylene based non-ionic surfactants, preferably 0 - 1%;
0.1 - 2% (w/w) thickening agents, preferably 0.1 - 1%;
0.1 - 1% (w/w) parabens, preferably 0.1 - 0.5%;
0 - 10% (w/w) alpha-hydroxy acids, preferably 0 - 2%;
0 - 20% (w/w) vegetable oil, preferably 0 - 5% ;
0 - 10% (w/w) mineral oil, preferably 0 - 5%;

0 - 10% stearic acid, preferably 0 - 5%;
0 - 10% glycerin, preferably 0 - 6%;
0 - 25% 1,3-butylene glycol, preferably 5 - 15%.

A typical solution or lotion composition of the invention has the composition:
0.1 - 10% (w/w) elastin, preferably 0.1 - 4%;
40 - 95% (w/w) demineralized or distilled water, preferably 60 - 90%
0 - 5% (w/w) polyoxyethylene based non-ionic surfactants, preferably 0 - 1%;
0 - 1% (w/w) thickening agents, preferably 0 - 0.5%;
0.1 - 1% (w/w) parabens, preferably 0.1 - 0.5%;
0 - 30% (w/w) glycerin, preferably 0 - 20%;
0 - 25% (w/w) 1,3-butylene glycol, preferably 5 - 15%.

A typical subcutaneously injectable solution composition of the invention has the composition:
0.1 - 10% (w/w) elastin, preferably 0.1 - 4%;
90- 99.9% (w/w) saline solution, preferably 96 -99.9%

A typical milk composition of the invention has the composition:
0.1 - 10% (w/w) elastin, preferably 0.1 - 4%;
40 - 95% (w/w) demineralized or distilled water, preferably 60 - 90%
0 - 5% (w/w) polyoxyethylene based non-ionic surfactants, preferably 0 - 2%;
1 - 25% (w/w) emulsifiers, preferably 5 - 15%;
3 - 15% (w/w) vegetable oil, preferably 3 - 8%;
0 - 1% (w/w) thickening agents, preferably 0 - 0.5%;
0.1 - 1% (w/w) parabens, preferably 0.1 - 0.5%;
0 - 30% (w/w) glycerin, preferably 0 - 20%;
0 - 25% (w/w) 1,3-butylene glycol, preferably 5 - 15%.

A typical stick composition of the invention has the composition:
0.1 - 10% (w/w) elastin, preferably 0.1 - 4%;
30 - 80% (w/w) volatile silcone oil, preferably 50 - 75%
5 - 20% (w/w) non-ionic surfactants, preferably 10 -15%;
2 - 8% (w/w) thickening agents, preferably 3 - 6%;
0.1 - 1% (w/w) parabens, preferably 0.1 - 0.5%;
10 - 40% (w/w) long-chaim fatty alcohol, preferably 20 -35%;

A typical roll-on composition of the invention has the composition:

0.1 - 10% (w/w) elastin, preferably 0.1 - 4%;
30 - 95% (w/w) demineralized or distilled water, preferably 40 -70%
20 - 60% (w/w) ethanol, preferably 30 - 50%;
1 -10% (w/w) non-ionic surfactants, preferably 2 - 8%;
0 - 1% (w/w) thickening agents, preferably 0 - 0.5%;
0.1 - 1% (w/w) parabens, preferably 0.1 - 0.5%;
0 - 10% (w/w) polyvinypyrrolidone, preferably 1 - 4%.

A typical smooth-on composition of the invention has the composition:

0.1 - 10% (w/w) elastin, preferably 0.1 - 4%;
40 - 70% (w/w) volatile silcone oil, preferably 45 - 60%
10 -35% (w/w) non-ionic surfactants, preferably 15 -25%;
1 - 4% (w/w) thickening agents, preferably 1.5 - 3%;
0.1 - 1% (w/w) parabens, preferably 0.1 - 0.5%;
5 - 25% (w/w) long-chaim fatty alcohol, preferably 10 - 20%;
5 - 25% (w/w) waxes, preferably 10 -20%.

For treatment of wrinkles of the neck or the facial area other than the eyes, a composition of the third embodiment containing from about 1% (w/w) elastin to about 4% (w/w) elastin is usually applied together with a composition of the fourth embodiment twice daily for from 21 to at least 28 days. For persons over 45 years or in greater need of anti-wrinkle treatment, a composition of the third embodiment containing about 4% (w/w) elastin may be used together with a composition of the fourth embodiment. Typically, the composition of the third embodiment will be applied immediately after the composition of the fourth embodiment.

For more rapid results, two or three drops of a gel according to the third embodiment, containing about 3.5% (w/w) elastin, may be applied after cleansing and toning the skin, followed by a cream according to the fourth embodiment or a cream according to the third embodiment.

For treatment of the skin in the eye area, a cream or gel according to the third embodiment is usually applied twice daily for from 21 to at least 28 days.

For subcutaneous treament of the skin, a saline solution according to the third embodiment by be subcutaneously injected by hypodermic or by high pressure air injection.

EXAMPLES

EXAMPLE 1 - FIELD TRIALS

The field trials utilised a cream according to the invention and containing 3% (w/w) of elastin, and a placebo of the same compositional base as the elastin-containing cream but not containing elastin.

Such parameters as container appearance, consistency, colour and smell were matched for the placebo and the elastin-containing cream to allow for double blind application. The containers were labelled with an identifier number and the eye to be treated.

Subjects selected for the trials were members of three groups, designated Groups 1 to 3. They were groups of middle class Caucasian males and females, born in the country of their present residence and having lived in metropolitan areas for most of their life; currently living in a similar locality; aged 27 - 50 yrs; normally distributed for age; healthy and having indoor employment with regular outdoors recreation. Only subjects who had had no previous use of wrinkle treatment products were included in the study.

To normalise for diet, living conditions, environment, socio-economic and logistic factors, husband/wife groups were chosen as a matter of preference.

A split face control technique was chosen by which placebo was used on one side of the face and elastin-containing cream on the other. Assignment of treatments was randomised in a double blind statistical design by which neither the investigators nor the subjects knew the identity of the treatment or placebo.

All subjects were screened for suitability against survey criteria. Each subject was examined by an independent specialist dermatologist at the conclusion of the study.

Twice daily (morning and prior to retiring in the evening) double blind application for four weeks of all treatments to the under and side eye areas were requested, in accordance with general instructions supplied.

Prior to the study and weekly for four weeks thereafter, silicone casts were applied to the treated areas. These casts were aligned and mounted on a card for general examination and topographical measurement.

Controlled triple light angle still photographs were taken prior to treatment and at the end of the study in a specially prepared photographic studio and using a previously established protocol. The photographs were designed to show the subjects in a natural, uniformly lit condition. At the end of the study research was conducted on alternate lighting angles and conditions to highlight wrinkle development.

The silicone casts of both under-eye and side-eye "crows-feet" areas of the left and right eyes were measured as closely spaced transects at 8,000 points for precise surface shape at a resolution of approximately 1:12,000 with a field of view of 72 square millimetres and an accuracy of 1.0 micrometre.

After mathematical surface fitting, two levels of surface filtration using Fourier Transform Techniques were used to compute three indices of surface roughness (R), namely, the Relative Mean Square (R RMS), Centre Line Average (R CLA) and Peak To Valley Height (R P-V). Roughness is the standard technical term used to mathematically describe the micro-undulation of a surface and has been universally used by industry for a long time throughout the world.

Validation of the accuracy of measurements of wrinkle imprints on silicone casts was conducted by three independent techniques, namely:

(a) Active optical triangulation,
(b) Confocal Microscopy using laser light, and
(c) Profilometry using a stylus based instrument.

Accurately produced, engineered test pieces were measured by optical microscopy and active optical triangulation to confirm the accuracy of the technique in being able to measure width and depth at micrometre levels. Standard roughness test pieces were used to confirm the ability of the measurement technique and the calculations to produce accurate and precise roughness data. Some of the casts were independently measured using profilometry and image analysis.

All product tubes were weighed at the completion of the study to estimate

any dose response effects.

The statistical analysis of the study was based on a Longitudinal Panel Study Method as discussed by Moser and Kalton in "Survey Methods in Social Investigation", with internal subject controls by use of the split face model.

During the trial, subject attrition was minor: a few subjects did not proceed beyond the first week due to eye sensitivity. All remaining subjects found both the issued creams to be pleasant to use and without any side effects provided they were applied away from the immediate vicinity of the eye, in accordance with the instructions supplied with the products. The dermatological examinations found no evidence of lasting irritation or sensitisation.

The physical measurement of wrinkles, regular attendance by the survey staff and the monitoring of cream consumption was designed to compensate for attitudinal conditioning.

The Surface shape measurement yielded three sets of Surface Roughness measurements at two levels of filtering or sensitivity to yield information on the effects of the treatments on coarse and fine wrinkles. These data were combined with the measured subject data and subject profile data.

The four, weekly measurements on the side of the face using the placebo (Casts 2 to 5) and the one measurement before commencing treatment (Cast 1) were considered to be the baseline of the subject's skin condition without the action of the elastin-containing cream. Each of the Cast 2 to 5 measurements were then subtracted from the Cast I and expressed as a percentage weekly variation due to placebo or natural skin changes without the action of elastin. Similar subtractions and percentage calculations were made for the side of the face using the elastin-containing cream. Each of the values of the percentage change for elastin treatment over pre-treatment (for the elastin-containing cream) were subtracted from their corresponding weekly measurements for the percentage change for placebo from pre-treatment and expressed as the percentage change over the placebo. An average percentage change over placebo (the average of results for Weeks 1 to 4) and a percentage change over placebo by the end of the trial (the percentage difference of the pre-treatment Cast 1 and the cast after the treatment period) were calculated. The wrinkle measurement results for the

percentage change over placebo by the end of the trial were then tabulated and plotted.

Computer surface topographical plots were made of the first cast for each subject.

The results reported below show the effects of the elastin-containing treatment cream over and above the effects of the placebo or, the 'Percentage Change over placebo by end of trial' wrinkle measurement results.

There has been no published report on the status of skin wrinkles or the effect on them of products containing elastin. For this reason, no existing population descriptors or variances of facial under eye skin measurement are known by which comparison can be made.

The results from the photographs were affected by skin oils and small changes in angle of the head and printing tones and thus could not supply the detail comparable to the surface profile measurement technique, the results of which are summarised below.

Results: Modification of Skin Roughness or Wrinkles

GROUP 1

Calculations were made of the difference in skin roughness measurements of the side of the face using the elastin-containing cream subtracted from the side using the placebo for the 75 Group 1 subjects. The results are summarised in Table 1.

Table 1

Group 1 results

Number and percent of subjects where elastin treatment gave greater smoothness than placebo/no treatment

	RMS (coarse)	RMS (fine)	CLA (coarse)	CLA (fine)	P-V (coarse)	P-V (fine)
FEMALE total = 45	34 76%	29 64%	31 69%	26 58%	31 69%	28 62%
MALE total = 30	20 67%	22 73%	20 67%	24 80%	21 70%	24 80%
TOTAL = 75	54 72%	51 68%	51 68%	50 67%	55 73%	52 69%

Figures 1 and 2 present bar graphs representing the percentage change in the skin roughness of the elastin-treated area over the placebo-treated area for the female subjects using the Centre Line Average index of roughness. Bars extending below the zero line indicate an improvement in surface roughness. Figures 3 and 4 present similar graphs for the same subjects, using the Peak-to-Valley height index of surface roughness, and Figures 5 and 6 present the corresponding results using the Relative Mean Square index.

Figures 7 to 9 present the corresponding bar plots for the male subjects.

Of the 45 females, improvement in coarse under-eye skin condition (e.g. coarse wrinkles and expression lines) was measured, using the relative mean square method, for 76% of the subjects whilst 64% had improvements in their fine skin condition e.g. fine lines, pores and fine wrinkles. The range of both coarse and fine line improvement was between a few percent to over 80% with most of the improved females showing 15 to 30% net reductions on an individual basis.

Of the 30 males, improvement in coarse under-eye skin condition was measured for 67% of the subjects whilst 73% had improvements in their fine skin condition . The range of both coarse and fine line improvement was between a few percent to over 80% with most of the improved males showing 20 to 50% nett reductions on an individual basis.

Over all of the 75 Group 1 subjects, 72% had net improvements in their coarse wrinkles and 68% in their fine wrinkles after four weeks of treatment.

The above reduced results have been statistically tested (t-test and F-test by analysis of variance) and shown to be very significantly (confidence level 99.9%) a different group of results to the non-reduced. In other words, it can be concluded that the decreases are real and not subtle variations which may have occurred just by chance. No data was excluded from the analysis.

Various other changes were seen in the rest of this group but a measurable effect in more than half of the subjects is highly significant considering this was a normal cross-section of the population with no prior selection of subjects most likely to be assisted. In this sense this study differs from a hospital related clinical study.

The results are clear and discriminate well even small changes in the skin surface.

GROUP 2

The results for subject group 2 are summarised in Tables 2 to 4. In these tables, the percentage difference of averages (AVG%) values are the difference of averages of measurements for each eye over the test period. That is, all of the results other than the pre-treatment value are averaged and the average for the elastin-containing cream treatment is subtracted from the placebo treatment area result.

Table 2

Group 2 results

Percent of subjects where elastin treatment gave greater smoothness than placebo/no treatment

Coarse wrinkles- Centre Line Average roughness

	FEMALES					MALES			
GROUP	No.	AVG %	4 wks %	8 wks %		No.	AVG %	4 wks %	8 wks %
All subjects	13	42	66	50		13	62	62	66
25-36 yrs	8	50	75	50		8	75	75	75
37-50 yrs	4	25	50	25		5	67	67	50

Table 3

Group 2 results

Percent of subjects where elastin treatment gave greater smoothness than placebo/no treatment

Fine wrinkles- Centre Line Average roughness

	FEMALES					MALES			
GROUP	No.	AVG %	4 wks %	8 wks %		No.	AVG %	4 wks %	8 wks %
All subjects	13	54	54	58		13	54	69	58
25-36 yrs	8	63	38	63		8	88	88	62
37-50 yrs	4	50	75	66		5	0	40	50

Table 4

Group 2 results

Percent of subjects where elastin treatment gave greater smoothness than placebo/no treatment

Overall results- Centre Line Average roughness

	COARSE				FINE		
GROUP	No.	AVG %	4 wks %	8 wks %	AVG %	4 wks %	8 wks %
All subjects	26	52	64	58	54	62	58
25-36 yrs	16	62	75	62	75	62	62
37-50 yrs	9	50	44	75	22	55	57
Range of values*							
Maximum smoothing		43	36	43	32	15	30
Minimum smoothing		21	7	12	0.5	4	2.3
Max. roughening		18	17	33	42	44	18
Min. roughening		21	7	0.2	5	1.2	8.3

* These are actual % decreased roughness (smoothing) or % increased roughness (roughening) of the eye with elastin-containing cream compared to the other eye with placebo treatment

Over all subjects, 66% of females and 62% of males showed net smoothing of the skin over the placebo for coarse wrinkles. However when broken down by ages, within the 25 to 36 year old group, this increased to a level of 75% of both females and males who showed net smoothing after 4 weeks of treatment.

For fine wrinkles, over all females, 54% showed net smoothing at 4 weeks whilst males were more affected at 69%. Within the younger age group of females, 38% showed improved smoothing (possibly reflecting their better skin condition) but within the older group, 75% showed improvement. In contrast, 88% of younger men showed smoothing whilst within the older men, only 40% showed improvement in fine wrinkles, possibly indicating a higher degree of irreversible skin damage.

At 4 weeks, net coarse wrinkle smoothing was achieved in 64% of all subjects and in 75% of the 25 to 36 year age group.

Similarly, 62% of both all and the younger age group subjects achieved fine wrinkle smoothing but without the further higher percentage of younger subjects being improved.

In the older subjects, 44% had smoothed coarse wrinkles and 55% had smoothed fine wrinkles. The range of actual individual smoothing of the active treatment over the placebo at 4 weeks ranged from 7 to 36% for the coarse wrinkles and from 4 to 15% for the fine wrinkles. That is, for any one subject there was up to 36% smoothing of coarse wrinkles over and above the effects of the placebo.

Subject to statistical tests of significance, the Group 2 results suggest that, within the ranges quoted above, the active product does have a net effect in further smoothing both male and female skin over and above the effect of the moisturising components.

GROUP 3

A total of 26 subjects were surveyed.

The results for the subjects of group 3 are summarised in Table 5. Figures 10 to 15 provide bar graph plots of the results for the male and female subjects using each of the three indexes of surface roughness.

Table 5

Group 3 results

Number and percent of subjects where elastin treatment gave greater smoothness than placebo/no treatment

	RMS (coarse)	RMS (fine)	CLA (coarse)	CLA (fine)	P-V (coarse)	P-V (fine)
FEMALE total = 16	13 81%	8 50%	14 88%	10 63%	14 88%	6 38%
MALE total = 10	5 50%	6 60%	5 50%	5 50%	5 50%	5 50%
TOTAL = 26	18 69%	14 54%	19 73%	15 58%	19 73%	11 42%

Of the 16 females improvement in coarse under-eye skin condition using the relative mean square method, was found for 81% of the subjects whilst 50% had improvements in their fine skin condition. The range of both coarse and fine line improvement was between a few percent to 50% with most of the improved females showing 10 to 30% net reductions on an individual basis.

Of the 10 males, improvement in coarse under-eye skin condition was measured for 50% of the subjects, whilst 60% had improvements in their fine skin condition . The range of both coarse and fine line improvement was between a few percent to 40% with most of the improved males showing 5 to 25% net reductions on an individual basis.

Over all of the 26 Group 3 subjects, 69% had net improvements in their coarse wrinkles (RMS) and 54% in their fine wrinkles after four weeks of treatment.

Various other changes were seen in the rest of this group but a measurable effect in more than half of the subjects is highly significant considering this was a normal cross-section of the population with no prior selection of subjects most likely to be assisted.

In summary, the results for all groups showed a majority of both males and females gained a net improvement in their skin wrinkling when using the

elastin-containing cream for four weeks. The range of improvements vary according to group, sex and age but, individually can range from a few percent (not readily visually perceived) to over 80% (easily perceived).

EXAMPLE 2 - PREPARATION OF ELASTIN

Bovine neck ligament from inspected meat is scraped free of superficial fat, connective tissue and shredded. The shredded tissue is soaked in 0.15 M NaCl at 5°C with several changes to remove soluble protein. The tissue is further soaked in deionized water at 5°C until free of NaCl. The tissue is brought to a boil (100°C) in 10 volumes of deionized water and NaOH is added to a final concentration of .1 M and the tissue boiled 120 minutes. After cooling the tissue is washed with deionized water until neutral and partially dried at 60°C. The tissue is stirred in 4 volumes ethyl alcohol and air dried.

The elastin as prepared is solubilised by controlled hydrolysis with crystalline elastase at a pH of 9, in a 0.1M bicarbonate buffer, and temperature of 37°C until the elastin is solubilised. The pH is lowered to 5.9 and the preparation boiled (100°C) 2 hours to entirely destroy elastase and to further hydrolyse the elastin. After cooling, sodium benzoate is added so that 0.05% (w/w) is the final concentration. The temperature is lowered to 5°C and the elastin is filtered, concentrated if necessary, and lyophilised.

Analysis of the product by gel diffusion chromatography gives the following approximate molecular weight distribution:

Below 10000:	approximately	50% by weight
10000 - 30000		20% by weight
30000 - 45000		15% by weight
45000 - 60000		5% by weight
60000 - 150000		5% by weight.

The elastin is granular to powdery in appearance and has a light tan colour. It has a nitrogen content of 16.2% to 16.3% and contains about 1% sodium chloride (w/w) and about 0.05% sodium benzoate (w/w)).

EXAMPLE 3 - Composition for a cream

Elastin	2
Non-ionic surfactants	9

Oils	23
Thickeners	0.5
Glycols	8
Parabens	0.4
Sunscreen	3
Deionised Water	q.s. 100

EXAMPLE 4 - Composition for a cream including alpha-hydroxy acid

Elastin	0.1
Non-ionic surfactants	14
Oils	5
Thickeners	0.7
Glycols	2
Parabens	0.4
Sunscreen	3
Malic acid	5
Deionised Water	q.s. 100

EXAMPLE 5 - Composition for a gel

Elastin	3.5
Non-ionic surfactants	0.1
Thickeners	1
Glycols	18
Parabens	0.1
Deionised Water	q.s. 100

EXAMPLE 6 - Composition for a subcutaneous injection

Elastin	3.5
Saline solution	q.s. 100

EXAMPLE 7 - Composition for a gel

Elastin	3.5
alpha-hydroxy acid	2
Water	q.s. 100

CLAIMS

1. A composition for administration to the skin for ameliorating wrinkles, comprising elastin, as hereinbefore defined, together with at least one acceptable carrier, diluent or adjuvant, wherein at least some of said elastin has a molecular weight of less than 10000.

2. A composition for administration to the skin for ameliorating wrinkles comprising:

elastin, as hereinbefore defined, wherein at least some of said elastin has a molecular weight of less than 10000 and

an agent for reducing corneocyte cohesion of the lower levels of the hyperkeratotic stratum.

3. A composition according to claim 2, further comprising at least one carrier, diluent or adjuvant.

4. A composition according to claim 1, wherein from about 1% by weight of said elastin to substantially all of said elastin has a molecular weight less than 10000.

5. A composition according to claim 2, wherein from about 1% by weight of said elastin to substantially all of said elastin has a molecular weight less than 10000.

6. A composition according to claim 1, wherein:

from about 30% by weight of said elastin to about 70% by weight of said elastin has a molecular weight less than 10000;

from about 15% by weight of said elastin to about 30% by weight of said elastin has a molecular weight between 10000 and 30000;

from about 10% by weight of said elastin to about 20% by weight of said elastin has a molecular weight between 30000 and 45000;

from about 3% by weight of said elastin to about 10% by weight of said elastin has a molecular weight between 45000 and 60000; and

from about 2% by weight of said elastin to about 10% by weight of said elastin has a molecular weight between 60000 and 150000.

7. A composition according to claim 2, wherein:
from about 30% by weight of said elastin to about 70% by weight of said elastin has a molecular weight less than 10000;
from about 15% by weight of said elastin to about 30% by weight of said elastin has a molecular weight between 10000 and 30000;
from about 10% by weight of said elastin to about 20% by weight of said elastin has a molecular weight between 30000 and 45000;
from about 3% by weight of said elastin to about 10% by weight of said elastin has a molecular weight between 45000 and 60000; and
from about 2% by weight of said elastin to about 10% by weight of said elastin has a molecular weight between 60000 and 150000.

8. A composition according to claim 1 wherein the elastin comprises from about 0.1% to about 10% by weight of the composition.

9. A composition according to claim 2 wherein the elastin comprises from about 0.1% to about 10% by weight of the composition.

10. A composition according to claim 8 wherein the elastin comprises from about 0.1% to about 4% by weight of the composition.

11. A composition according to claim 9 wherein the elastin comprises from about 0.1% to about 4% by weight of the composition.

12. A composition according to claim 2, wherein the agent for reducing corneocyte cohesion of the lower levels of the hyperkeratotic stratum is selected from the group consisting of lactic acid, malic acid, citric acid, citramalic acid, tartaric acid, mucic acid, glycolic acid, hydroxyglutaric acid, hydroxybutyric acid, hydroxyvaleric acid, acetonic acid, ascorbic acid, erythorbic acid, glucuronic acid, gluconic acid and gluconolactone.

13. A composition according to claim 1, further comprising a sunscreen.

14. A composition according to claim 2, further comprising a sunscreen.

15. A method for the treatment of wrinkled skin in a human in need of such treatment, comprising administering to the wrinkled skin a wrinkle ameliorating effective amount of a composition comprising elastin, as hereinbefore defined, together with at least one acceptable carrier, diluent or adjuvant, wherein at least some of said elastin has a molecular weight of less

than 10000.

16. A method for the treatment of wrinkled skin in a human in need of such treatment, comprising administering to the wrinkled skin a wrinkle ameliorating effective amount of a composition comprising:

elastin, as hereinbefore defined, wherein at least some of said elastin has a molecular weight of less than 10000 and

an agent for reducing corneocyte cohesion of the lower levels of the hyperkeratotic stratum.

17. A method according to claim 15 or 16, wherein from about 5% by weight of the elastin to about 95% of the elastin has a molecular weight of less than 30000.

18. A method according to claim 16, wherein the composition further comprises at least one carrier, diluent or adjuvant.

19. A method according to claim 15 or 16, wherein the administering comprises :

(i) topically applying the composition to the wrinkled skin and/or subcutaneously injecting the composition;

(ii) allowing the composition to be absorbed into the skin or to dry; and

(iii) optionally repeating steps (i) and (ii) one or more times.

20. A method for the treatment of wrinkled skin in a human in need of such treatment, comprising administering to the wrinkled skin a wrinkle ameliorating effective amount of a composition according to claim 1 and a wrinkle ameliorating effective amount of a composition according to claim 2.

21. A method according to claim 20, wherein the administering comprises:

(i) administering to the wrinkled skin a wrinkle reducing effective amount of a composition according to claim 1 together with a wrinkle reducing effective amount of a composition according to claim 2;

(ii) allowing said compositions to be absorbed into the skin or to dry; and

(iii) optionally repeating steps (i) and (ii) one or more times;

wherein the administration is by topical application and/or by subcutaneous injection.

22. A method according to claim 20, wherein the administering comprises:

(i) topically applying to said wrinkled skin a composition according to claim 2

(ii) allowing the composition to be absorbed into the skin or to dry;

(iii) topically applying to the wrinkled skin a composition according to claim 1;

(iv) allowing the composition to be absorbed into the skin or to dry; and

(v) optionally repeating steps (i) to (iv).

23. A method for the treatment of wrinkled skin in a human in need of such treatment, comprising administering to the wrinkled skin a wrinkle ameliorating effective amount of a composition according to any one of claims 3 to 14.

24. A method according to claim 15 or 16 wherein the administering is from once daily to between once weekly and ten times daily.

25. A method according to claim 24 wherein the administering is between once daily and three times daily.

26. A method according to claim 25, wherein the administering is twice daily

27. A method according to claim 25, wherein the administering is twice daily for at least four weeks.

28. A method according to claim 15 or 16 wherein the administering is to the face, neck or hands.

29. A method according to claim 28 wherein the administering is to the eyelid or the under or side eye area.

30. A composition according to claim 1 or 3, wherein the at least one carrier, diluent or adjuvant are cosmetically acceptible.

31. A method according to claim 15 or 16, wherein the composition is a cosmetic composition and wherein the at least one carrier, diluent or adjuvant are cosmetically acceptible.

32. A method according to claim 15 or 16, wherein the composition is a

pharmaceutical composition and wherein the at least one carrier, diluent or adjuvant are pharmaceutically acceptible.

Figure 1 - Group 1

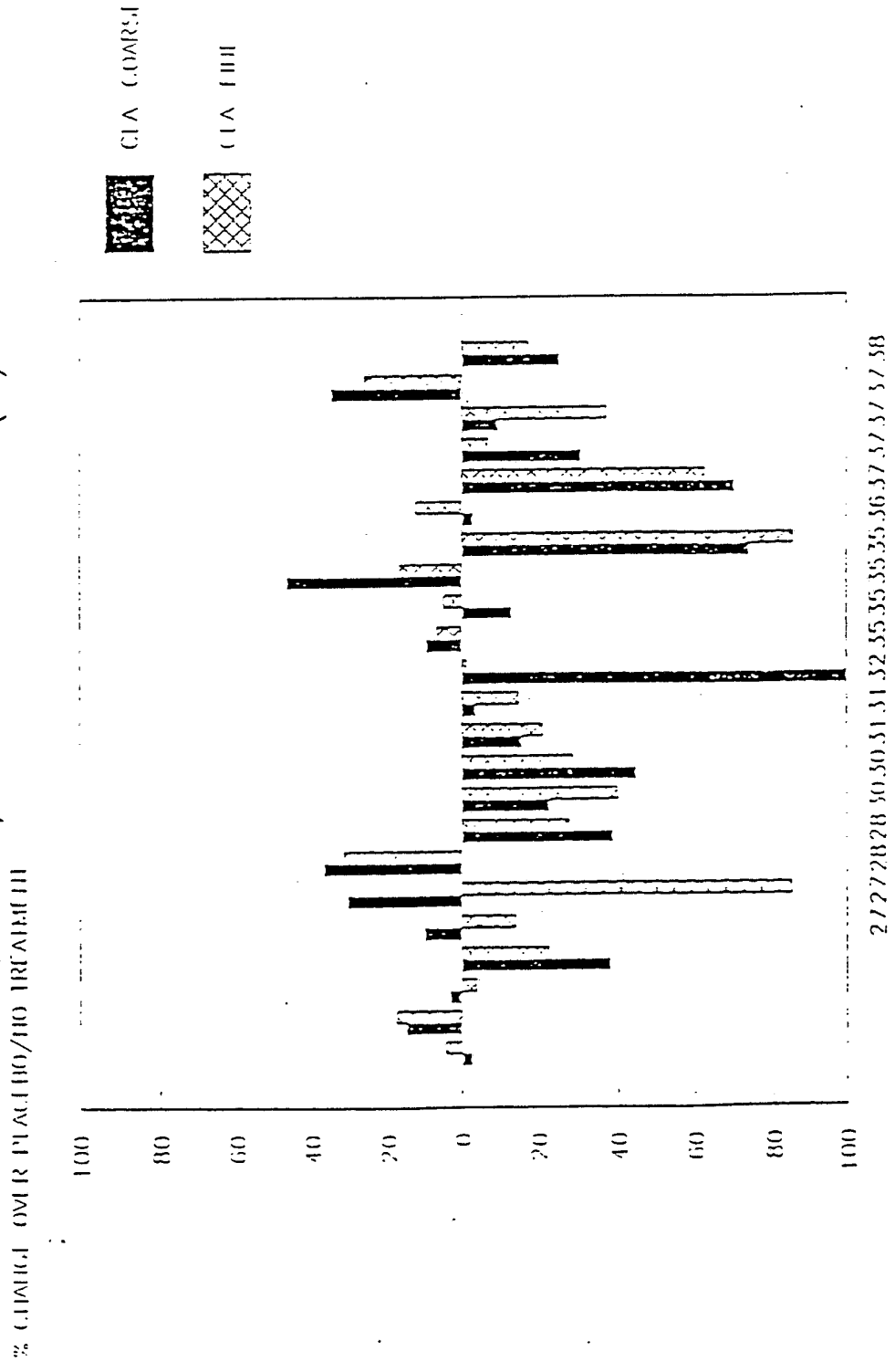


Figure 2 - Group 1

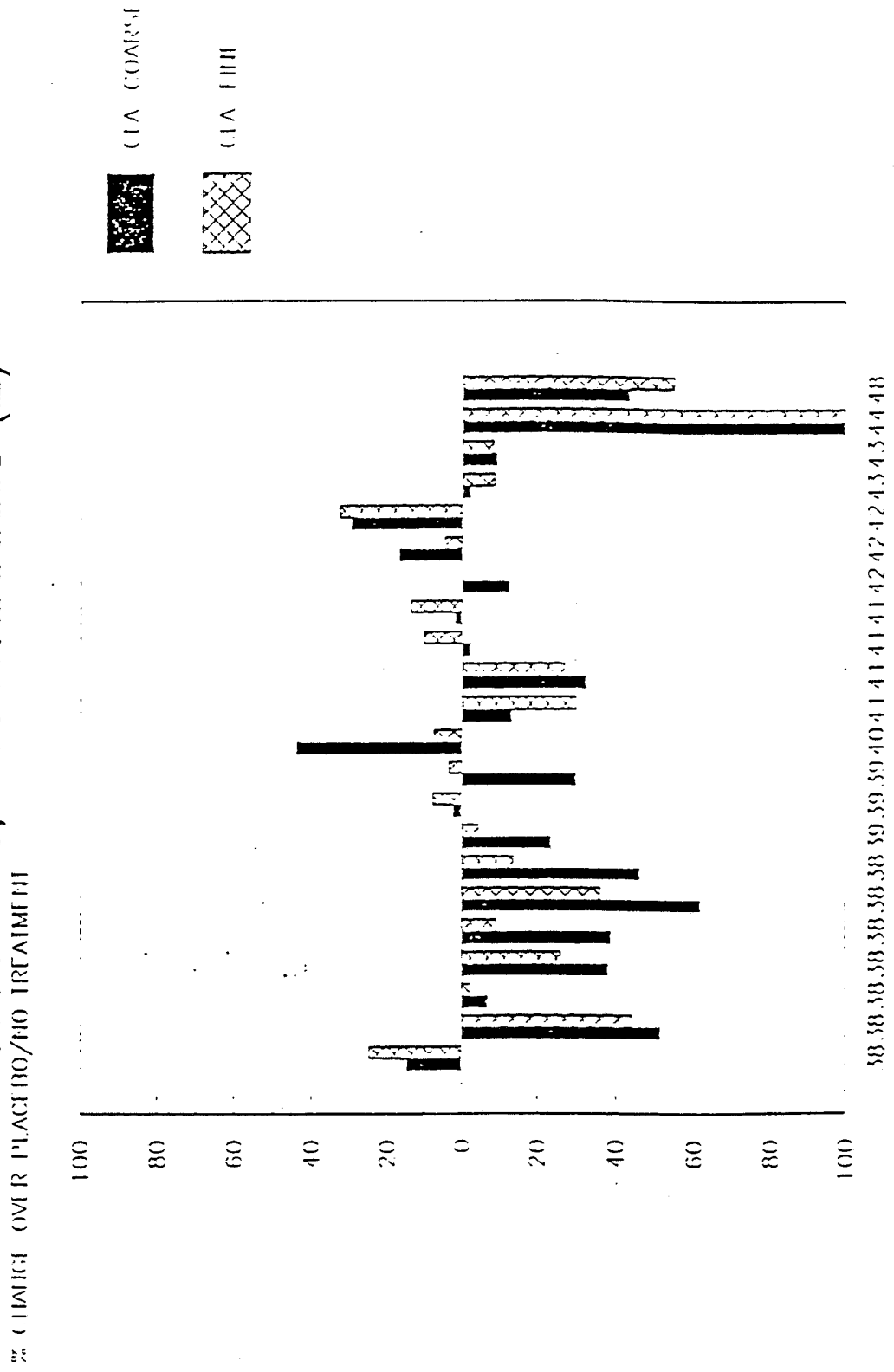


Figure 3 - Group 1

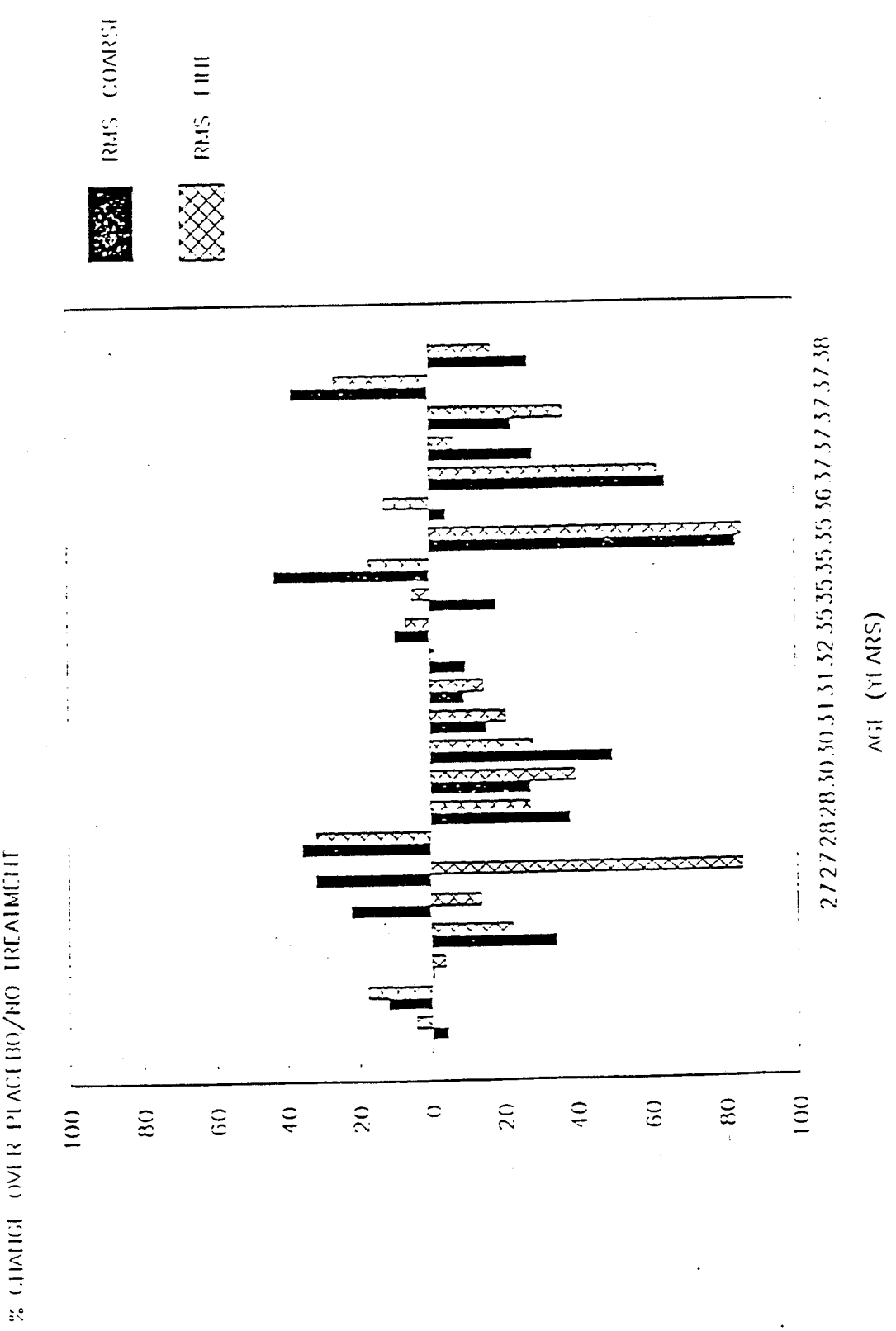


Figure 4 - Group 1

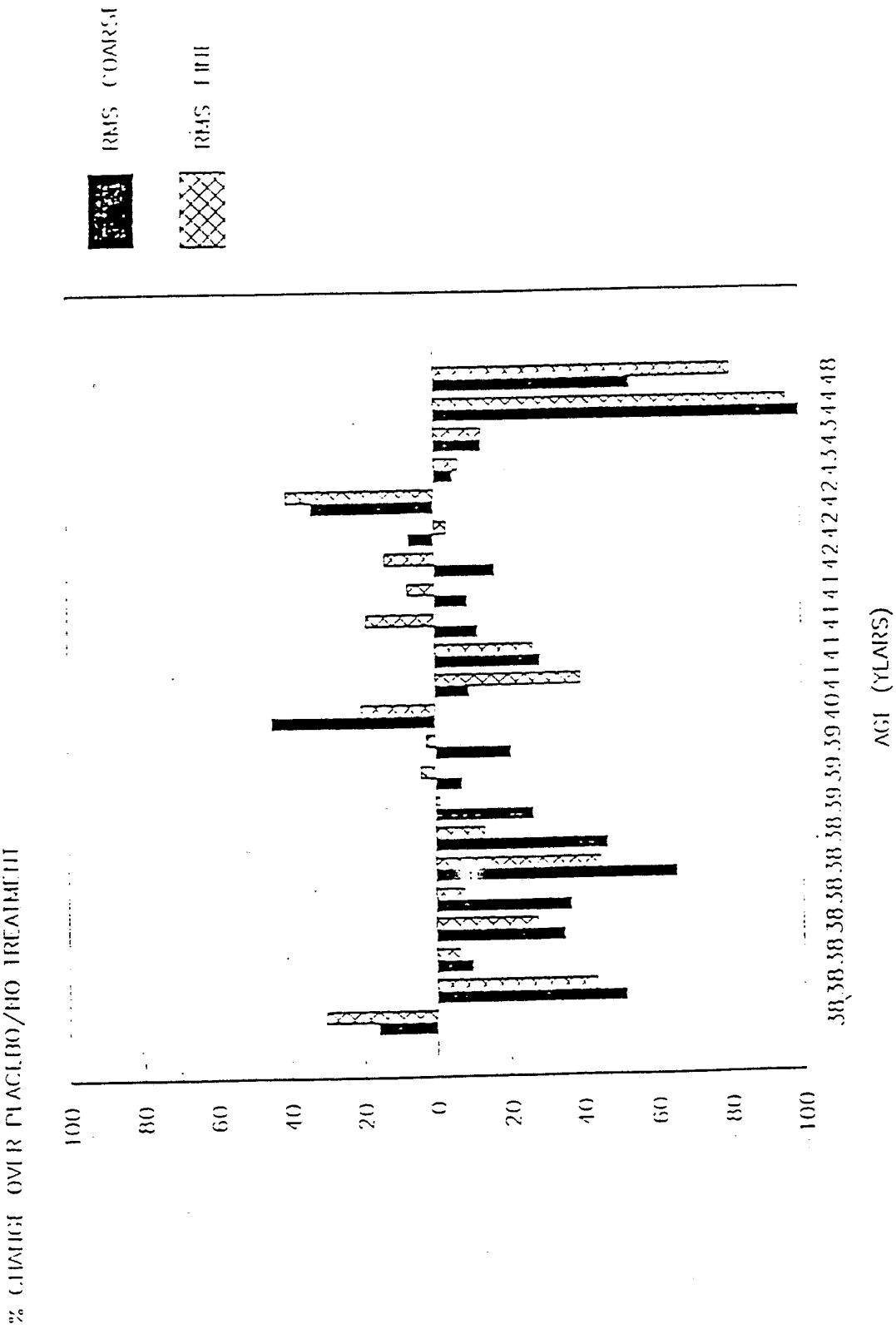


Figure 5 - Group 1

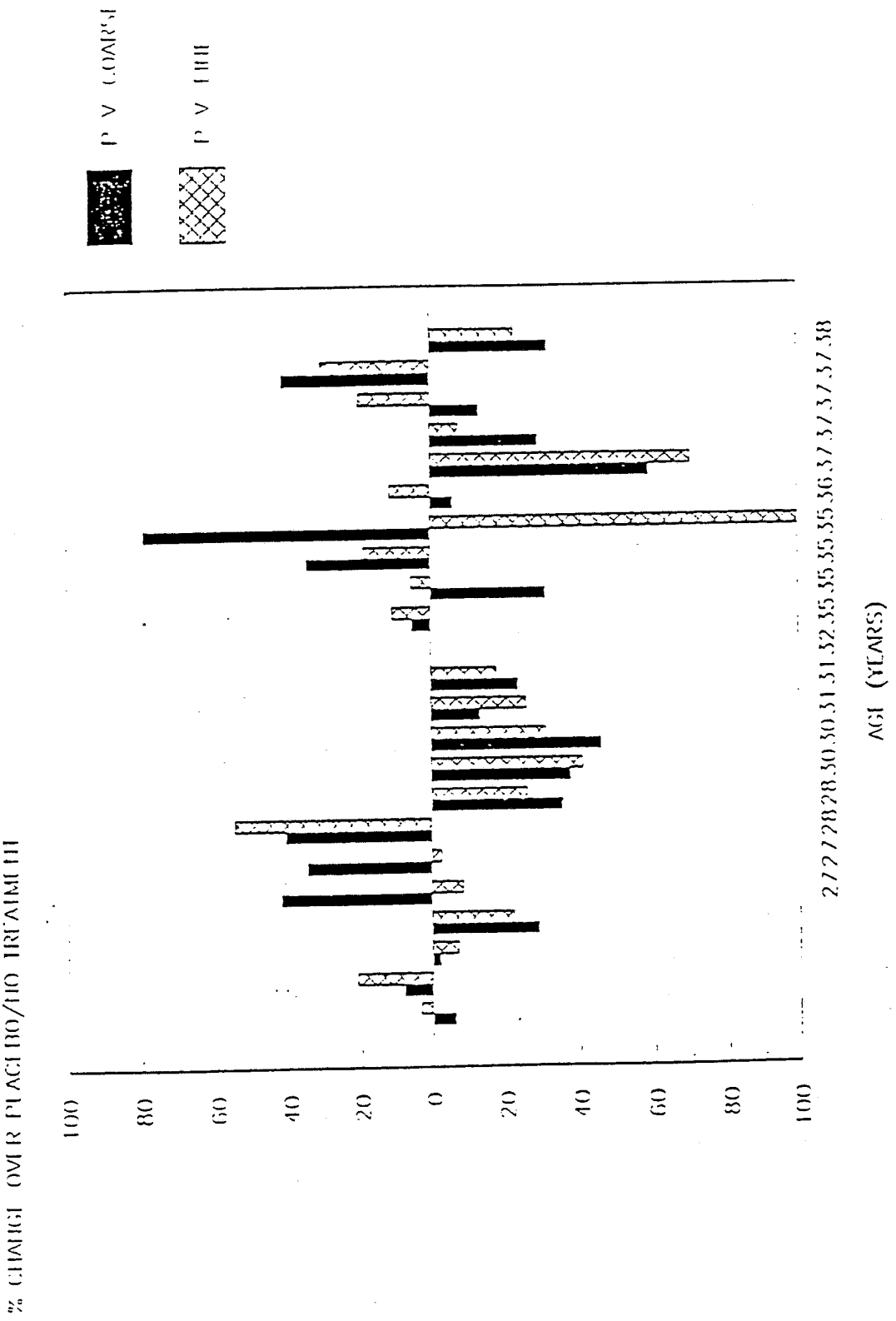


Figure 6 - Group 1

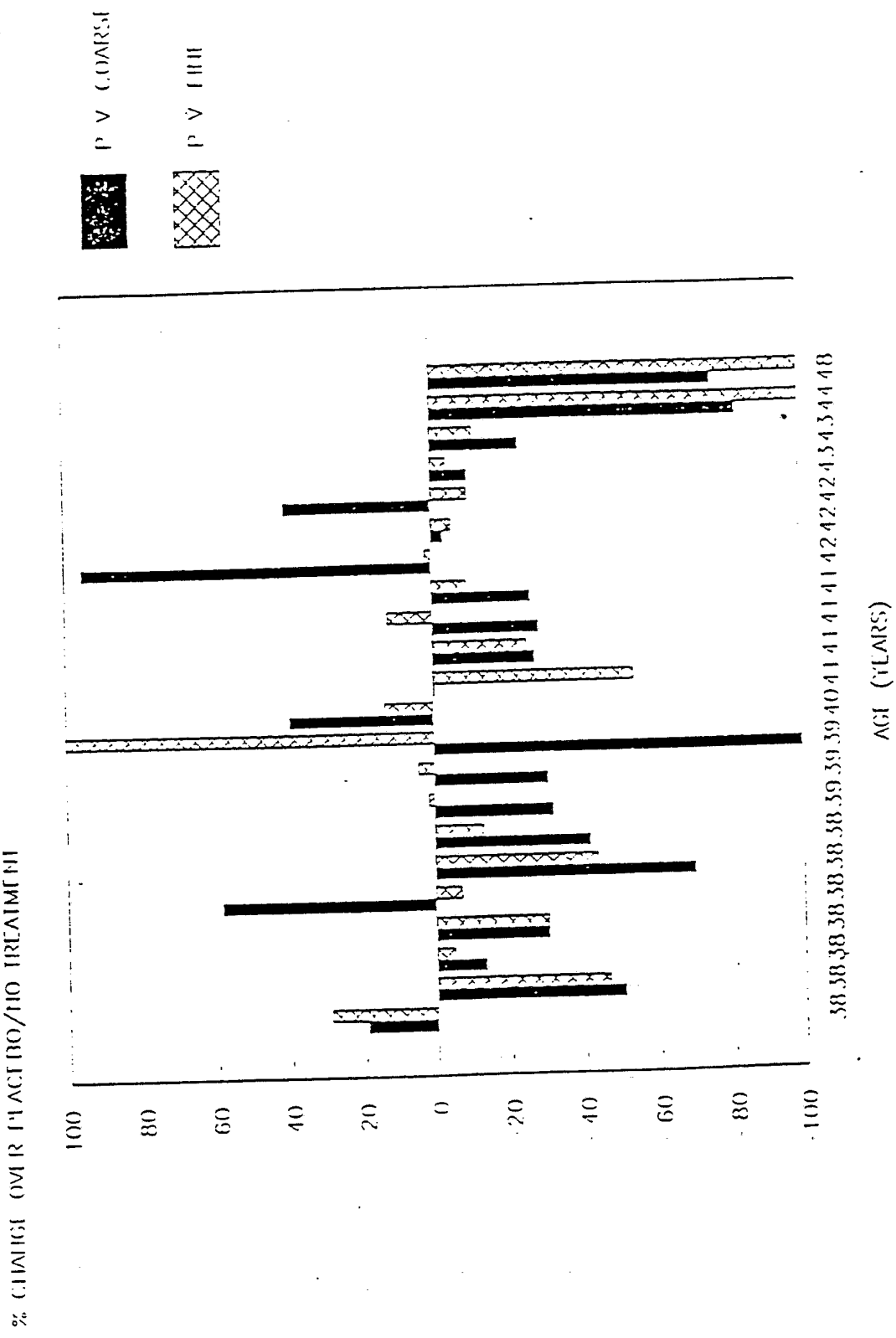


Figure 7 - Group 1

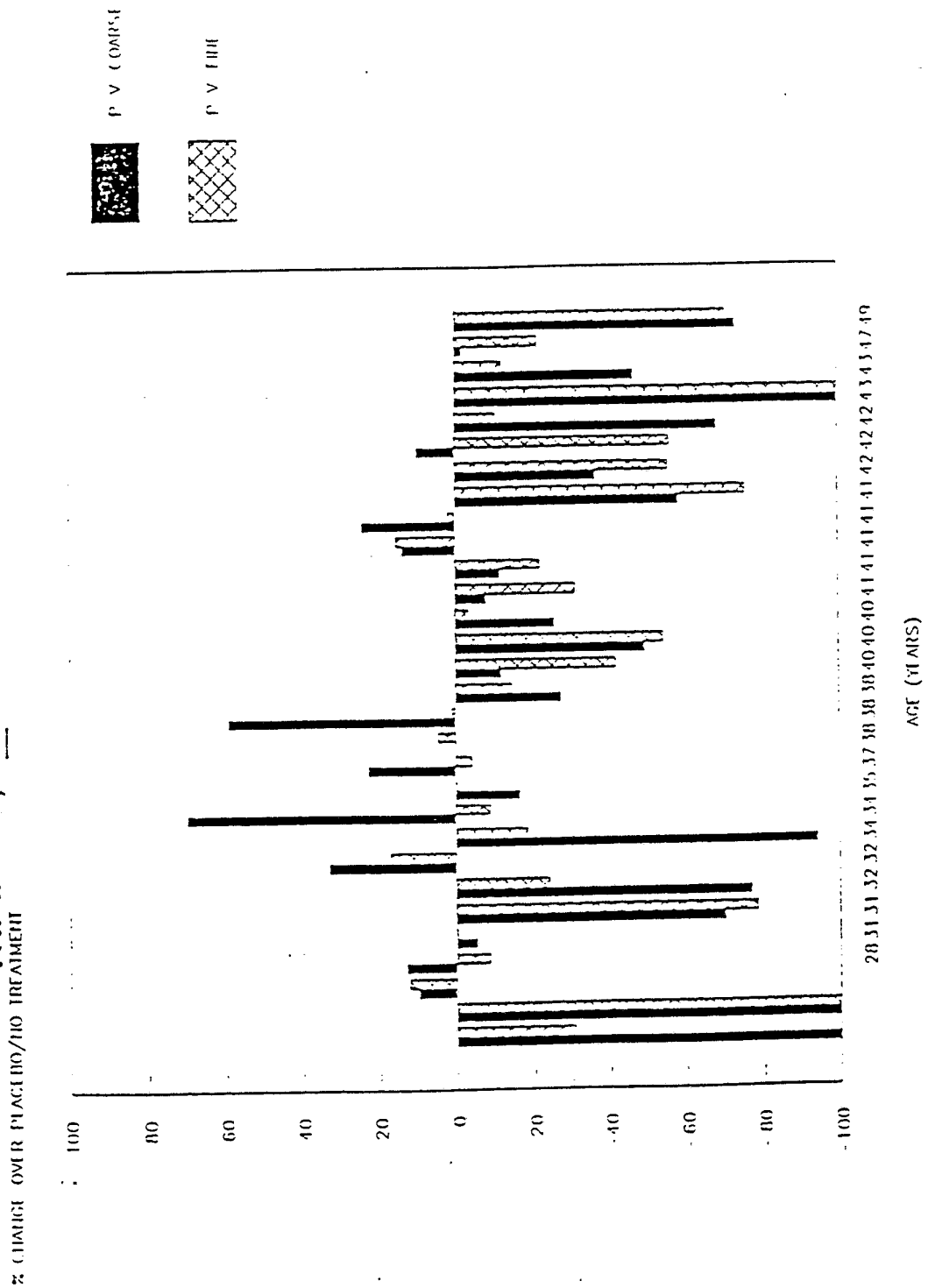


Figure 8 - Group 1

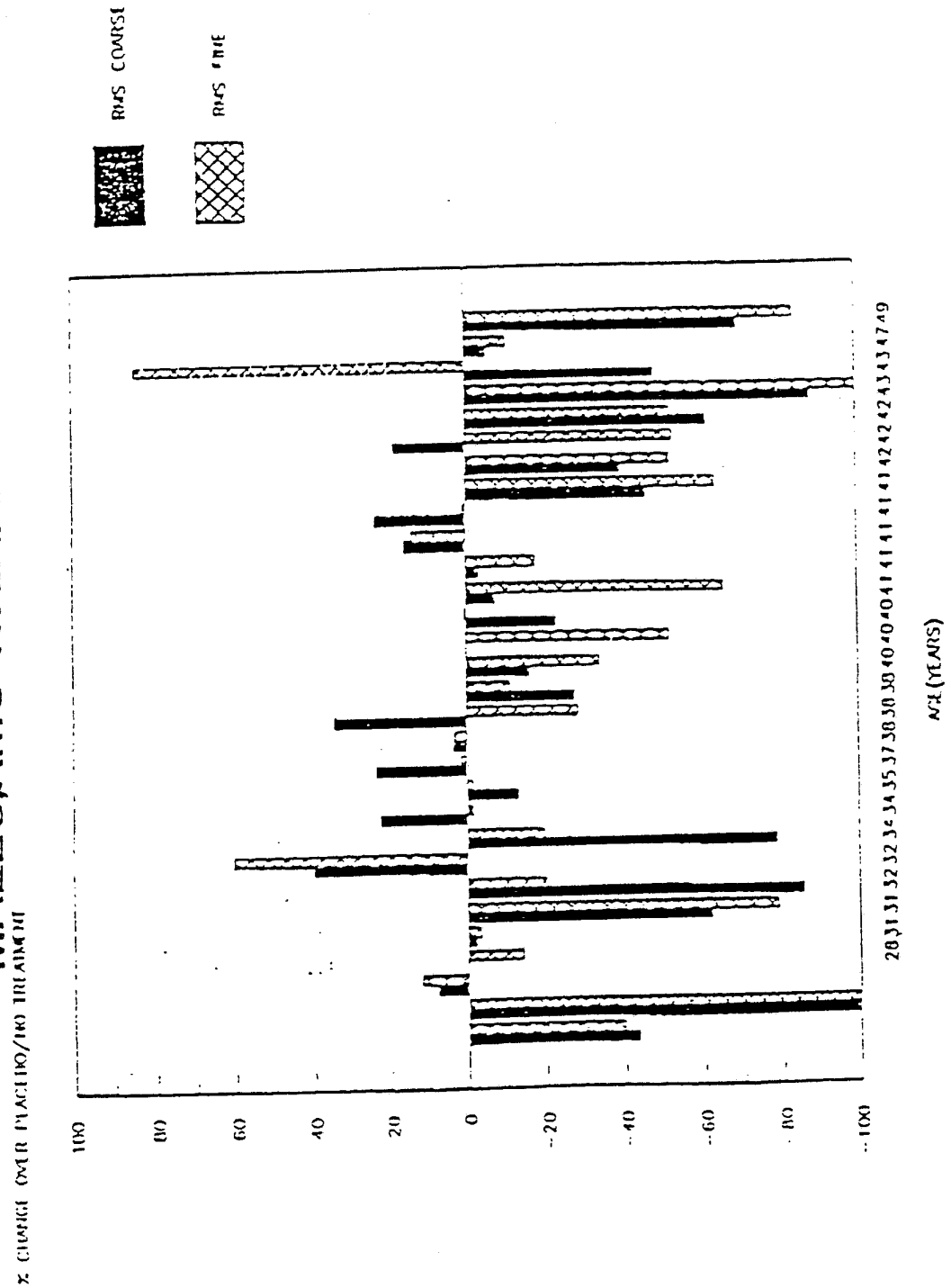


Figure 9 - Group 1

MALES,CLA WRINKLES

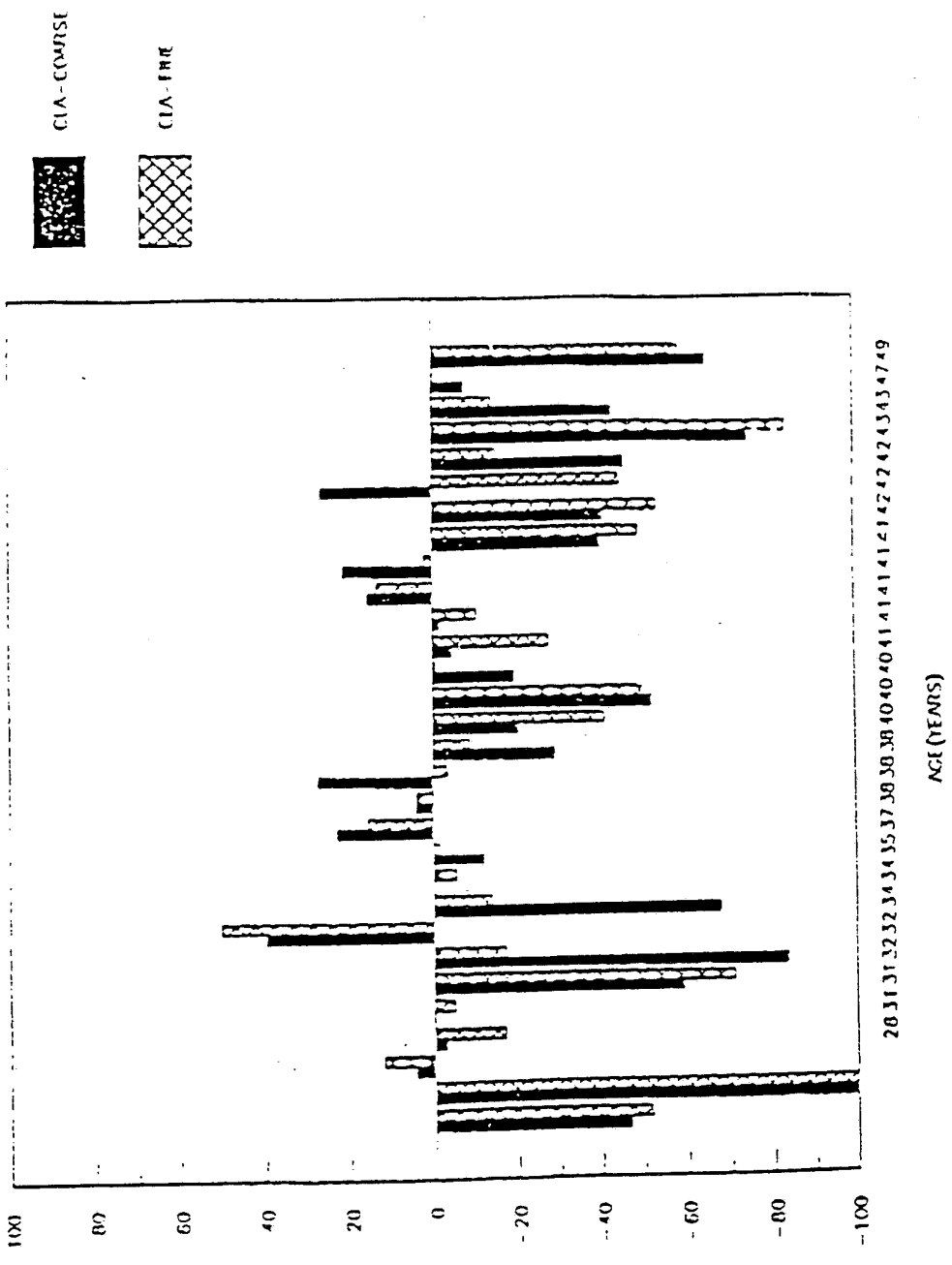


Figure 10 - Group 3

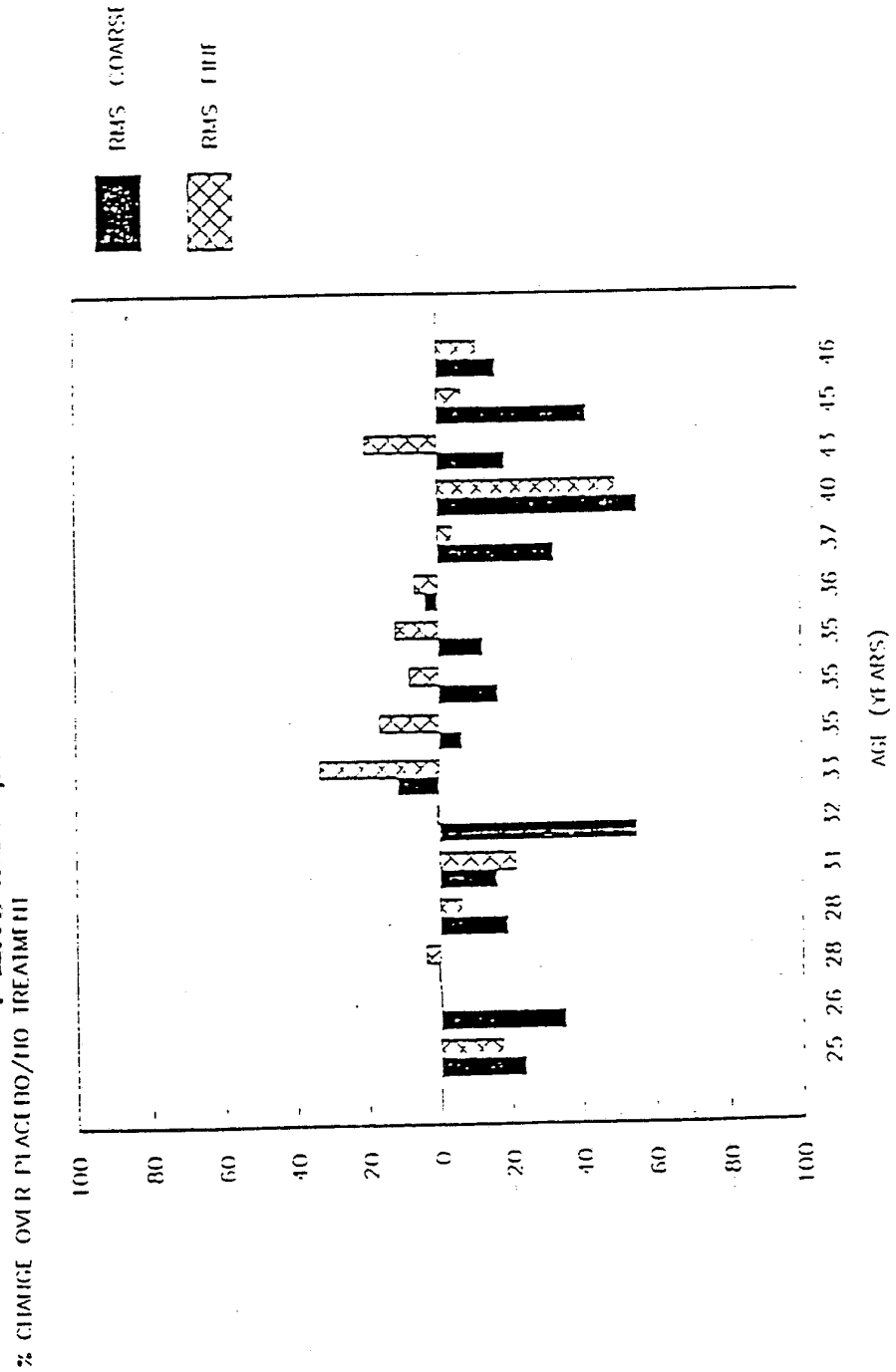


Figure 11 - Group 3

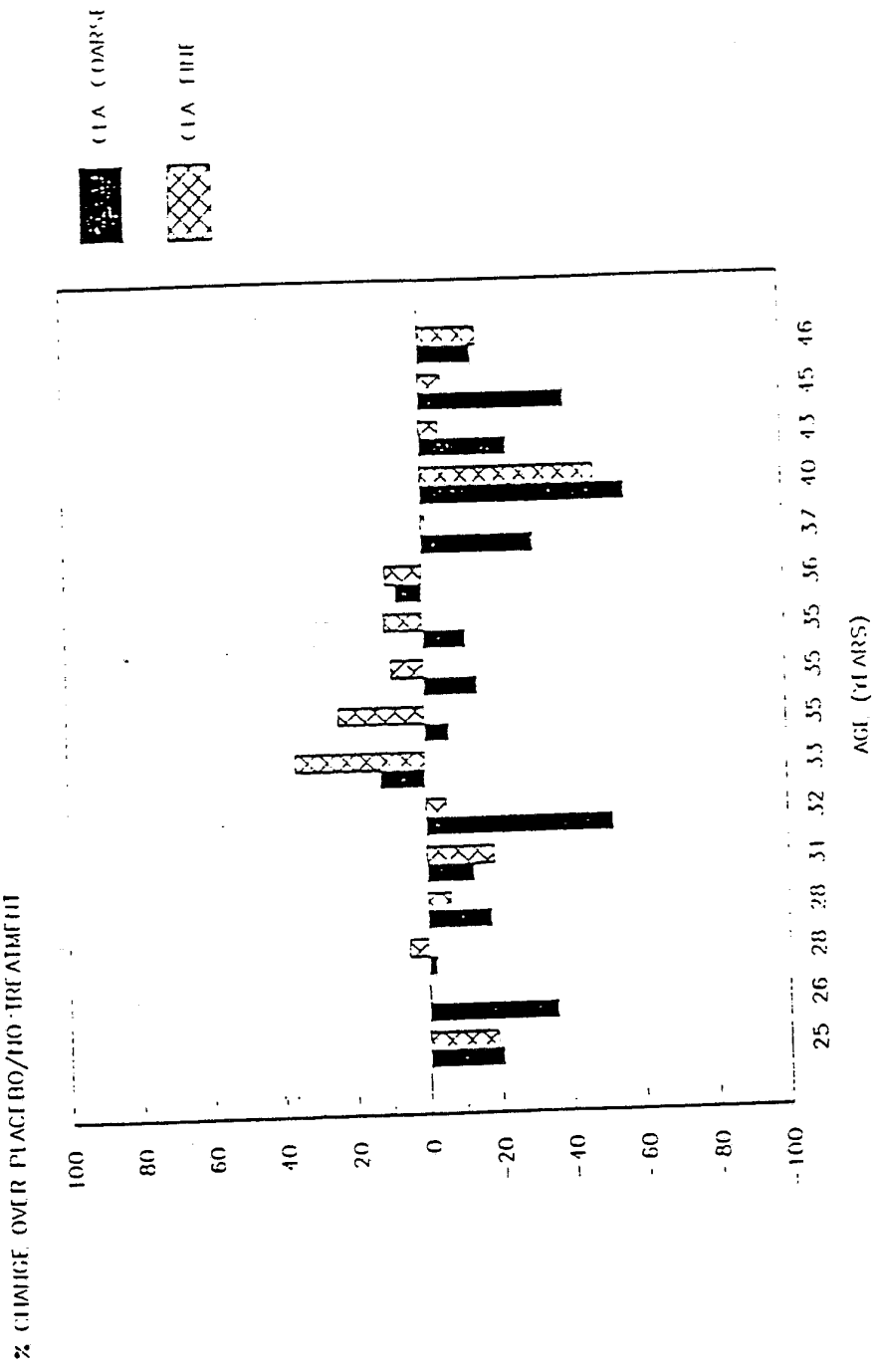


Figure 12 - Group 3

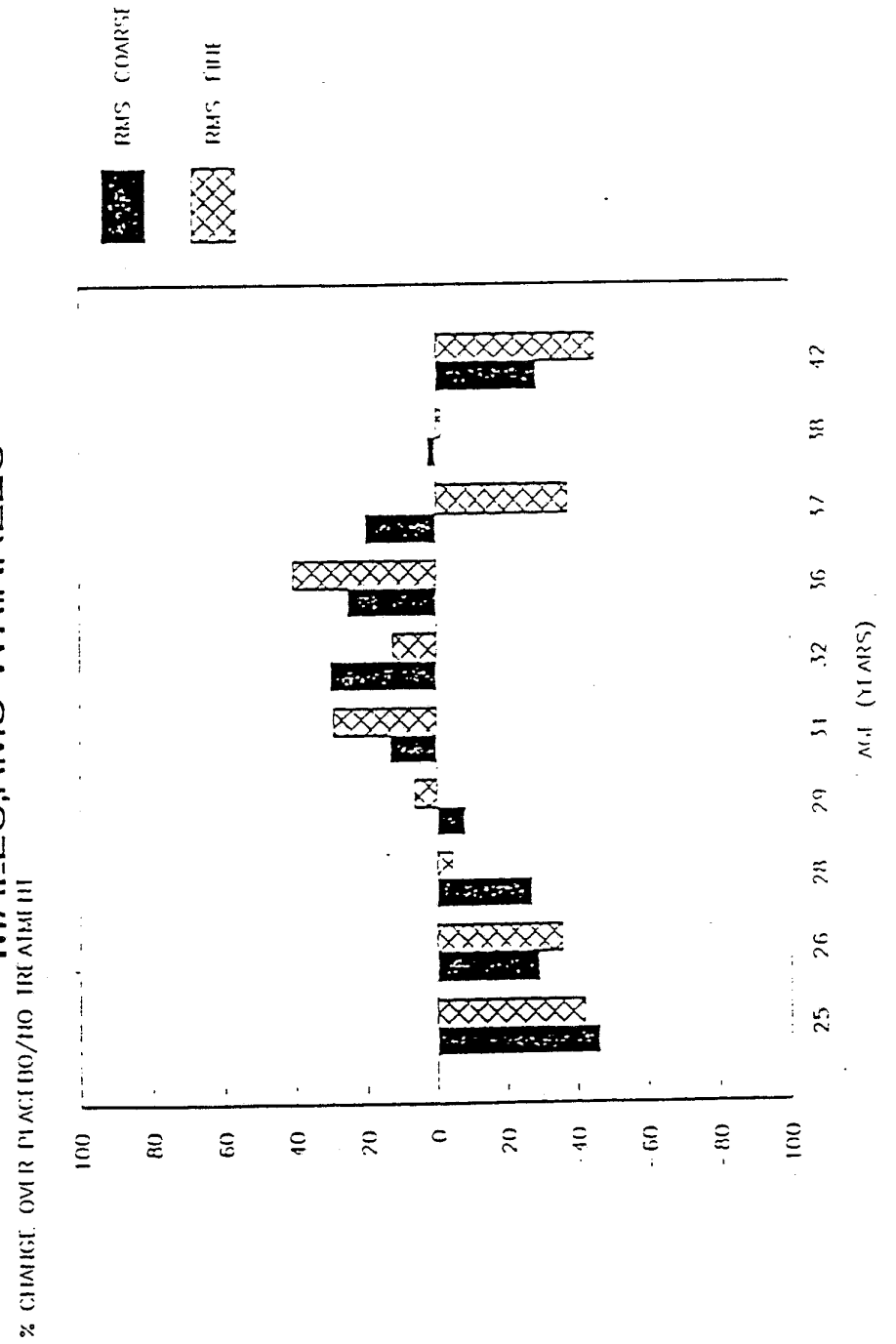


Figure 13 - Group 3

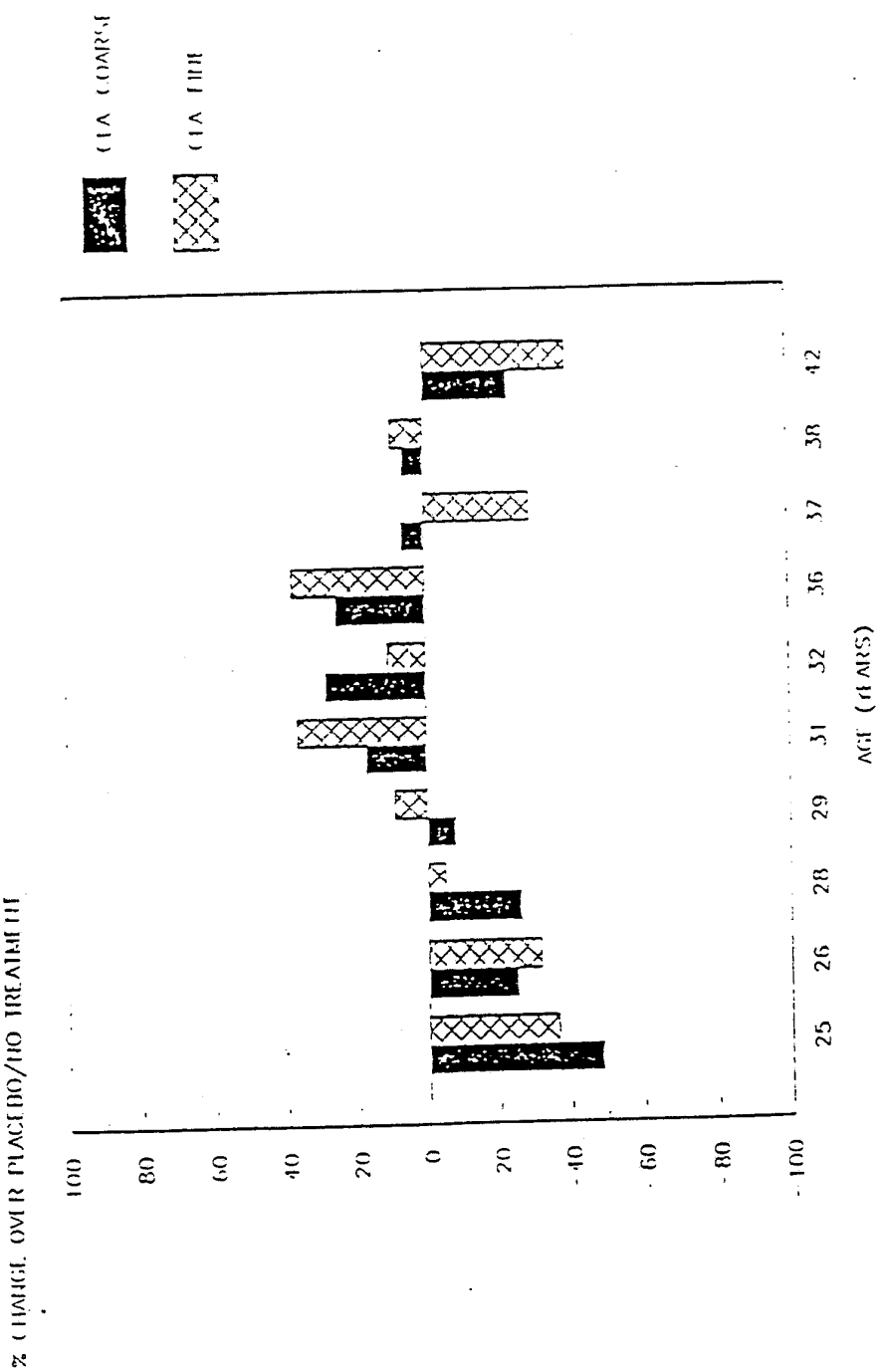


Figure 14 - Group 3

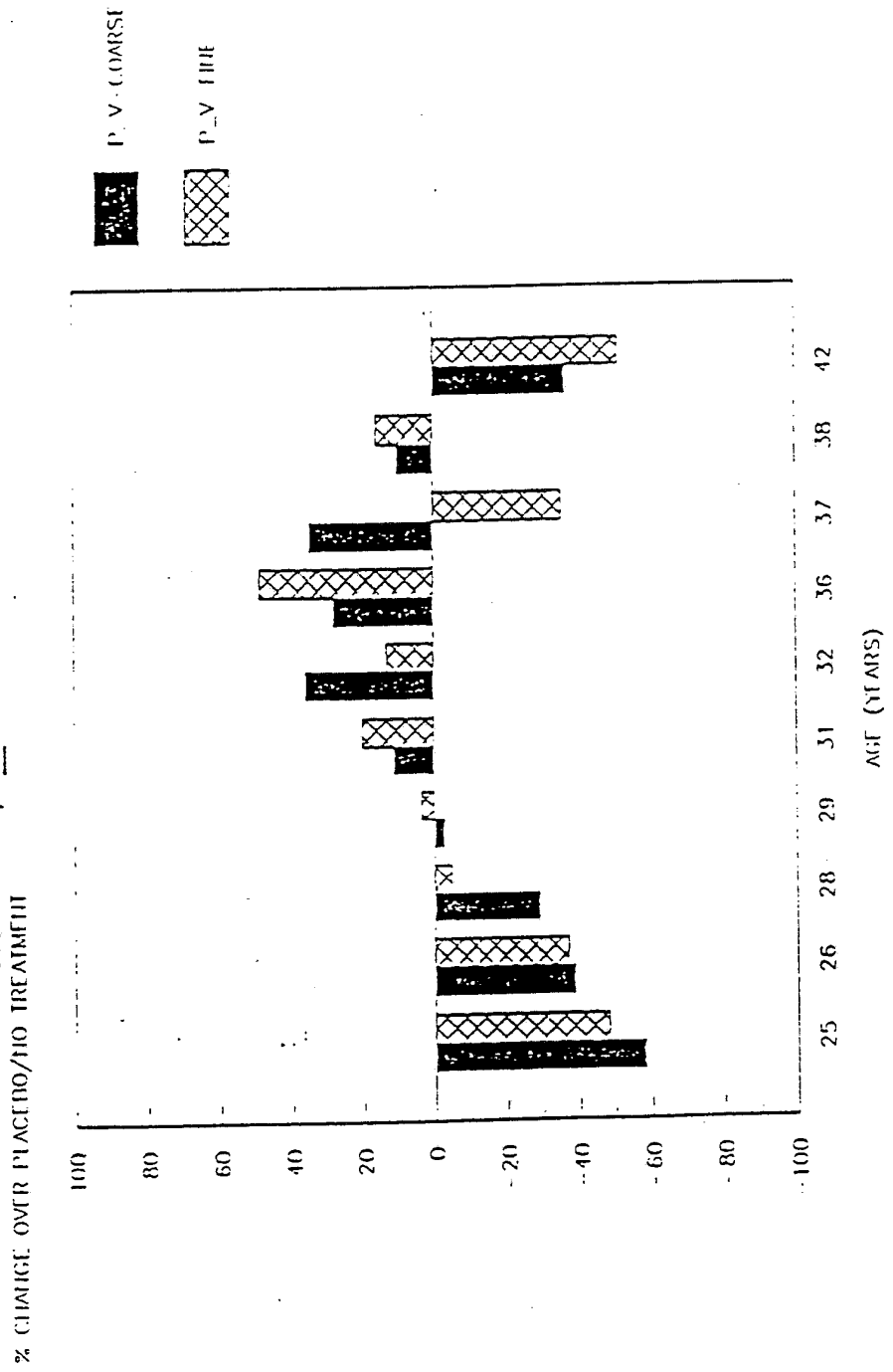
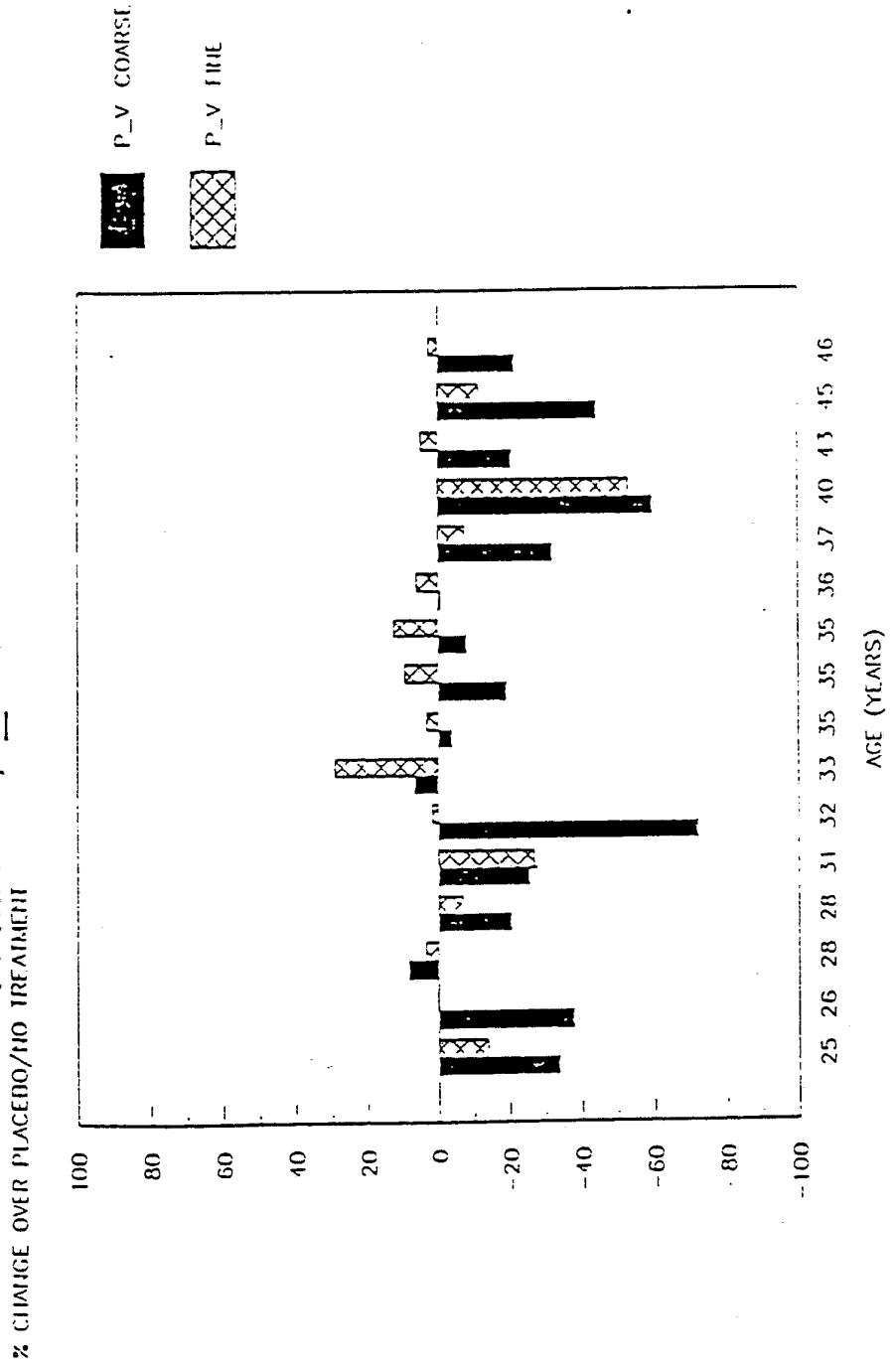


Figure 15 - Group 3



INTERNATIONAL SEARCH REPORT

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

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

Int. Cl.[5] A61K 007/48, A61K 037/12

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC	A61K 007/48, A61K 037/12

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

AU : IPC as above; JOPAL; Biological abstracts

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category*	Citation of Document, [11] with indication, where appropriate of the relevant passages [12]	Relevant to Claim No [13]
X,P	US,A, 4973473 (SCHNEIDER et al) 27 November 1990 (27.11.90). See claim 1, column 3 lines 6-39	(1, 12)
X	Patents Abstracts of Japan, C435, page 141, JP,A, 62-39512 (YAKURIGAKU CHUO KENKYUSYO K.K.) 20 February 1987 (20.2.87)	(1, 12)
X	Patents Abstracts of Japan, C-209, page 23, JP,A, 58-192812 (KOUKEN K.K.) 10 November 1983 (10.11.83)	(1, 12)

* Special categories of cited documents : [10]

"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 t 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	Date of Mailing of this International Search Report
30 January 1992	10 February 1992 (10.02.92)
International Searching Authority	**Signature of Authorized Officer**
AUSTRALIAN PATENT OFFICE	T. NIZNIK

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. ☐ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

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

1. ☐ Claim numbers ..., because they relate to subject matter not required to be searched by this Authority, namely:

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, specifically:

3. ☐ Claim numbers ..., because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4a

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

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.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL APPLICATION NO. PCT/AU 91/00492

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report	Patent Family Member	
US 4973473	US 4973473	WO 9100083