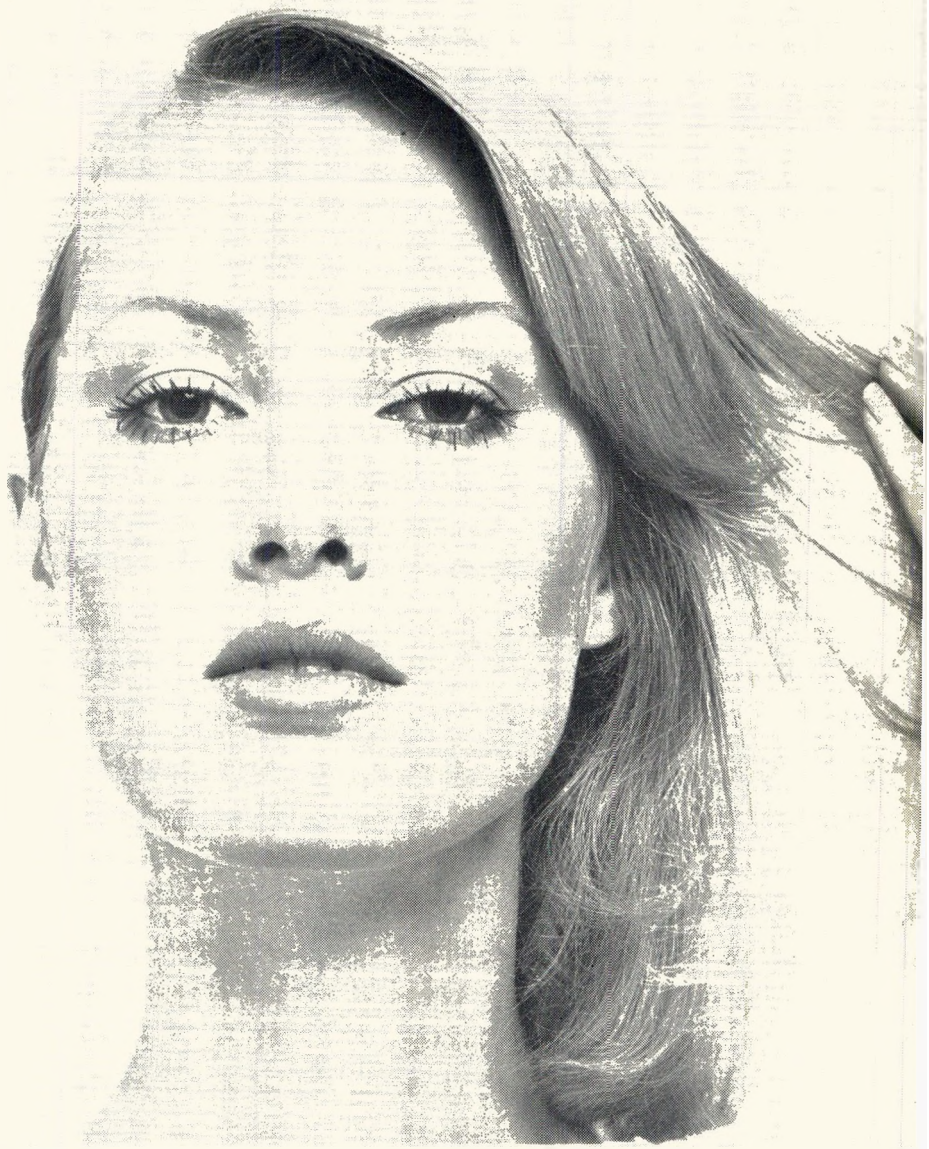
ISSN 0037-9832

VOL 28 NO 10

OCTOBER 1977

Journal of the Society of Cosmetic Chemists

Contents



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Journal of the Society of Cosmetic Chemists

This edition is published for

THE SOCIETY OF COSMETIC CHEMISTS
OF GREAT BRITAIN

by Blackwell Scientific Publications Ltd, Osney Mead, Oxford OX2 0EL
Hon. Editor: J. M. Blakeway
Roure Bertrand Dupont S.A. 55, Voie des Bans, 95100 Argenteuil (France)

VOL. 28 OCTOBER 1977 No. 10

GENERAL NOTICES

Publication dates: The 'Journal of the Society of Cosmetic Chemists' is published on the 5th of each month.

Five issues for the Society of Cosmetic Chemists of Great Britain
56 Kingsway London WC2B 6DX.

Seven issues by the Society of Cosmetic Chemists
50 East 41 Street, New York, N.Y. 10017, U.S.A.

Issue No	*Publication Date*	*Country of Origin*
1	January	Great Britain
2	February	U.S.A.
3	March	U.S.A.
4	April	Great Britain
5	May	U.S.A.
6	June	Great Britain
7	July	Great Britain
8	August	U.S.A.
9	September	U.S.A.
10	October	Great Britain
11	November	U.S.A.
12	December	U.S.A.

Advertisements: All enquiries regarding advertisements in the British Editions of the Journal should be addressed to Blackwell Scientific Publications, Osney Mead, Oxford OX2 0EL.

Subscription: All members of the Society of Cosmetic Chemists of Great Britain receive one copy of each edition free. Further copies at non-member rates. Industrial and non-member subscribers: £40; overseas £48. If payments are made by bank transfer, all charges shall be at the remitter's expense.

Missing numbers: **Journals are despatched at Printed Paper rate. Claims for missing numbers can be entertained only from subscribers in the country of origin of the particular issue, and must be made within 30 days from date of issue.** Members and subscribers are urged to give notice of change of address to the Publications Offices.

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Clinical and Experimental Dermatology

Edited by Martin Black and published quarterly at £18.00 (U.K.), £22.00 (overseas), $52.50 (U.S.A. and Canada)

Volume 2, Number 4, December 1977

Blackwell Scientific Publications Ltd

P.O. Box 88, Oxford, England

SYNOPSES FOR CARD INDEXES

The following synopses can be cut out and mounted on 127 × 76 mm index cards for reference without mutilating the pages of the Journal.

A colorimetric method for determining hydrogen peroxide in emulsions: K. C. JAMES and E. TSIRIVAS. *Journal of the Society of Cosmetic Chemists* **28** 615–620 (1977)

Synopsis—A method has been developed for the colorimetric determination of hydrogen peroxide, and is dependent on the intensity of the blue colour obtained with dichromate. The effects of a limited range of surfactants on the reproducibility of the process have been investigated, and the method used to determine hydrogen peroxide in two cosmetic emulsions.

Causes of skin colouration, origin, development and structure of pigment cells: J. A. A. HUNTER. *Journal of the Society of Cosmetic Chemists* **28** 621–627 (1977)

Synopsis—Haemoglobin, oxyhaemoglobin, melanin and carotene are pigments responsible for the colour of human skin. An abnormal skin colour is produced either by an imbalance in the proportion of these four pigments or by an abnormal pigment. Melanin is synthesised in melanocytes found usually in the basal layer of the epidermis. Within the melanocytes melanin is bound to a protein matrix and the melanosomes so formed are transferred to surrounding keratinocytes. The number of melanocytes is similar in Caucasoid and Negroid skin. Black skin is produced by increased melanocytic activity associated with the production of melanosomes which are larger than those in Caucasoid skin. Negroid melanosomes tend to be disposed individually in keratinocytes whereas those in Caucasoids are usually complexed.

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Synopsis—The versatility of Hagemann's Ester (ethyl 2-methyl-4-oxocyclohex-2-ene-1-carboxylate) as an intermediate in the synthesis of a range of alkylated 3-methylcyclohex-2-en-1-ones has been demonstrated.

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The influence of some formulation variables and valve/actuator designs on the particle size distributions of aerosol sprays: R. W. PENGILLY and J. A. KEINER. *Journal of the Society of Cosmetic Chemists* **28** 641–650 (1977)

Synopsis—Knowledge of the size and distribution of particles produced from cosmetic aerosol products is important not only from the viewpoint of product optimization but also from considerations of potential inhalation characteristics. A discussion is given of methods suitable for determination of the respirable fraction of the spray or a complete particle size distribution.

Results are presented for the particle size distributions of some aerosol formulations with differing compositions and levels of propellant. The effects of certain actuator designs and valve specifications are also presented. These results are discussed in terms of different particle formulation mechanisms due to differences in formulation, mechanical action of the valve and actuator and subsequent change in size of the particles. It is concluded that the particle size distribution of a cosmetic aerosol product only has meaning when the formulation, dispensing, and sampling details are also specified.

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A colorimetric method for determining hydrogen peroxide in emulsions

K. C. JAMES *and* E. TSIRIVAS *The Welsh School of Pharmacy, University of Wales Institute of Science and Technology, Cathays Park, Cardiff, Great Britain, CF1 3NU and P. D. Papoytsanis S.A., Kato Kifissia, Athens, Greece*

Received 10 June 1976

Synopsis

A method has been developed for the colorimetric determination of **hydrogen peroxide**, and is dependent on the intensity of the blue colour obtained with dichromate. The effects of a limited range of **surfactants** on the reproducibility of the process have been investigated, and the method used to determine hydrogen peroxide in two cosmetic emulsions.

INTRODUCTION

There are numerous methods available for determining hydrogen peroxide, but none can be applied with confidence to its estimation in emulsions. Potassium permanganate gives a fading end point in the presence of organic matter, and iodimetric methods (1), while less sensitive to organic materials, are vulnerable to surfactants (2, 3). Titration with ceric ammonium sulphate is known to be satisfactory in the presence of ethanol and diethyl ether (4) and some organic peroxides, but has not been tested in the presence of surface active materials. Many colorimetric methods have been described, for example (5–7), but most depend on general oxidation and are not specific to peroxide. Some, for example (7) depend on complexation. The oxidation of dichromate ion to the blue, ether-soluble peroxochromic acid (CrO_5) is a well known qualitative test for hydrogen peroxide, and is claimed to be specific. The reactions involved follow equations 1 and 2 (8).

$$Cr_2O_7^{2-} + H_2O = HCrO_4^- \quad (1)$$

$$H^+ + HCrO_4^- + 2H_2O_2 = CrO_5 + 3H_2O \quad (2)$$

Colorimetric methods based on these reactions, and involving extraction with either ethyl acetate (9) or tri-n-butyl phosphate in benzene (10) have been described for the estimation of chromium. The method is now investigated as a possible means of determining hydrogen peroxide in cosmetic preparations.

EXPERIMENTAL

APPARATUS AND MATERIALS

Absorbance measurements were carried out using a Unicam Spectrophotometer H 1620, Mk. 2 Digital. Hydrogen peroxide, benzene, ethyl acetate, potassium dichromate, potassium permanganate and sulphuric acid were analytical grade (Analar) reagents, (British Drug Houses Ltd). Tri-n-butyl phosphate was laboratory grade, from the same source. It was freed from pyrophosphates before use (10). Solan E (an ethoxylated lanolin) and Polawax (a non-ionic emulsifying wax) were supplied by Croda Chemicals Ltd, while Texapon N25 (a solution of sodium alkylether sulphate) and Emulgrade F (a mixture of cetostearyl alcohol, alcohol sulphate and non-ionic emulsifiers) were supplied by Henkel and Cie GmbH.

ANALYTICAL METHOD

Basic experimental conditions were taken from Sastri and Sundar (10) and modified in accord with our own observations, described below. The procedure finally adopted was as follows: 1 to 2 ml of sample were acidified with 1 ml of 0·5 N sulphuric acid and a two to three fold excess of potassium dichromate added in the form of a 0·01 M solution. The mixture was cooled to about 8°C and adjusted to 10 ml with water at the same temperature, followed by 10 ml of a 25% solution of tri-n-butyl phosphate solution in benzene (TBP/benzene). The two phases were mixed well for about 30 sec and then allowed to separate, whereapon an aliquot of the benzene solution was transferred to the spectrophotometer. The absorption against pure solvent is shown in *Fig. 1*, and indicates a maximum at 584 nm, which was used for all subsequent measurements.

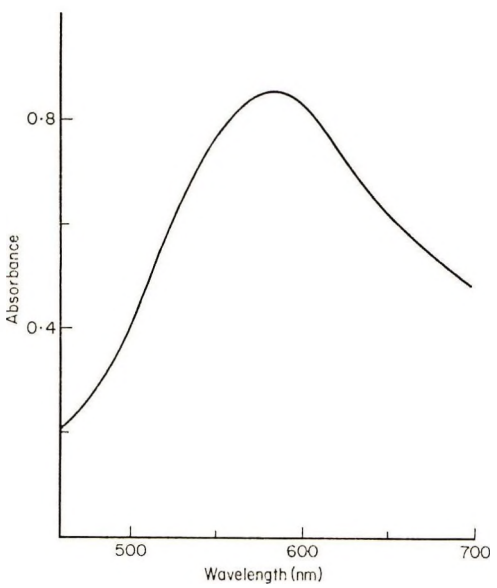

Figure 1. Absorption curve of peroxochromic acid. $[H_2O_2] = 2{\cdot}82 \times 10^{-3}$M.

Successive extractions with small volumes of TBP/benzene were impracticable, because of the known instability of peroxochromic acid in water. Single extractions with

various volumes of TBP/benzene indicated that the quantity extracted levelled off at 10 ml of extracting solvent.

Absorption measurements at 584 nm, taken at intervals after extraction, indicated that the colour was stable for 30 min in TBP/benzene, but then began to fade. This is in conflict with Tuck (11), who found that peroxochromic acid is stable in TBP/benzene for 10 to 15 h. Hydrogen peroxide decomposition is known to be catalysed by Cr (VI) salts (12), and the difference from Tuck's results is probably that he used the procedure to estimate chromium and therefore had no excess chromium in his TBP/benzene extract.

The effect of dichromate concentration on absorbance is shown in *Fig. 2.* Equations 1 and 2 indicate that 1 mole of potassium dichromate is equivalent to 4 moles of hydrogen peroxide, hence the plot levels out at approximately twice stoichiometric concentration, and the absorbance varies little beyond this, up to a threefold excess of dichromate over peroxide. A calibration curve, obtained using an excess of dichromate within this range, followed Beer's law up to 4×10^{-3} M H_2O_2 (*Fig. 3*).

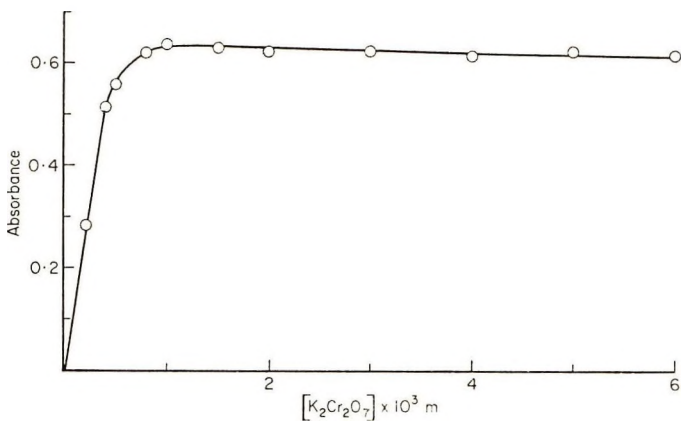

Figure 2. Effect of dichromate concentration on absorption of peroxochromic acid at 584 nm. $[H_2O_2] = 1{\cdot}96 \times 10^{-3}$ M.

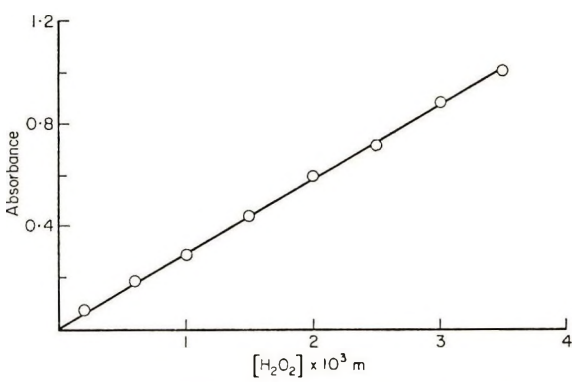

Figure 3. Calibration plot of peroxochromic acid at 584 nm.

Recovery was tested by comparing the results obtained for ten aqueous solutions varying from 3×10^{-3} to 1×10^{-2} M H_2O_2, with those obtained by permanganate titration. The mean recovery was 97·5 ± 0·5% ($P' = 0{\cdot}01$) of the permanganate results.

The low figure is probably due to incomplete extraction, but is reproducible and therefore easy to correct.

APPLICATION TO HYDROGEN PEROXIDE EMULSIONS

The effects on the method of a small selection of surfactants, cetrimide, sodium lauryl-ether sulphate (Texapon N25) and an ethoxylated lanolin derivative (Solan E) were investigated by incorporating each in turn into a hydrogen peroxide solution of known concentration. Results obtained with various concentrations of surfactant are shown in *Table I*. Solan E had no effect on absorbance for concentrations up to at least $2{\cdot}75 \times 10^{-2}\%$, but with sodium lauryl-ether sulphate, the absorbance began to fall when the surfactant concentration exceeded $8 \times 10^{-3}\%$. In the presence of cetrimide, the colour began to fade immediately on extraction with the TBP/benzene solution, and the rate of decline increased with increasing cetrimide concentration. The results with cetrimide in *Table I* were obtained under carefully controlled conditions, and exactly 9 min after extraction. Even then, a lower absorbance was obtained than with hydrogen peroxide alone, but the result was nevertheless constant over a tenfold range of cetrimide concentration.

Table I. Effects of surfactants on absorbance. Initial concentration of hydrogen peroxide $= 1 \times 10^{-2}\%$

Cetrimide		Sodium laurylether sulphate		Solan E	
% Surfactant	Absorbance	% Surfactant	Absorbance	% Surfactant	Absorbance
w/v $\times 10^3$		w/v $\times 10^3$		w/v $\times 10^3$	
0·0	0·879*	0·0	0·894	0·0	0·842
2·5	0·822	1·0	0·882	2·5	0·865
5·0	0·813	2·0	0·872	5·0	0·847
7·5	0·805	3·0	0·890	7·5	0·840
10·0	0·819	4·0	0·881	10·0	0·845
12·5	0·814	5·0	0·902	12·5	0·860
15·0	0·832	6·0	0·897	15·0	0·870
17·5	0·820	7·0	0·883	17·5	0·838
20·0	0·822	8·0	0·895	20·0	0·842
22·5	0·828	9·0	0·869*	22·5	0·845
25·0	0·825	10·0	0·853*	25·0	0·858
27·5	0·818	11·0	0·842*	27·5	0·848
Mean absorbances	0·820 ± 0·007		0·888 ± 0·010		0·850±0·009

* Not considered in determination of mean.

The formula given in *Table IIa* has been recommended for hair bleaching emulsions (13). Five such preparations were made containing from 3 to 6% hydrogen peroxide in precisely known quantities. Aliquots were taken and subjected to the analytical procedure described above. Results are given in *Table IIb*, and show a mean recovery of $101 \pm 3{\cdot}4\%$ ($P' = 0{\cdot}01$). A second recommended formula (14), given in *Table IIc*, yielded duplicate recoveries of 99·2 and 97·2%. The difference between the two sets of results is assumed to be due to the effect of the emulsion constituents on the distribution coefficient of peroxochromic acid between the aqueous phase and the TBP/benzene solution.

Table II. Determination of hydrogen peroxide in cosmetic emulsions

(a)

Polawax	5·0 g
Solan E	5·0 g
Hydrogen peroxide and water, to 100 g	

(b)

Weight taken x 10^2	Absorbance	$\%H_2O_2$ Actual	$\%H_2O_2$ Found	% Recovery
1·519	0·414	3·02	3·07	101·6
1·339	0·454	3·82	3·80	99·4
1·197	0·508	4·61	4·73	102·6
1·051	0·520	5·43	5·58	102·7
0·983	0·517	6·07	6·03	99·3

(c)

Texapon N25	2 to 2·5 g
Emulgrade F	0·84 to 2·0 g
Citric acid	1·2 g
Water to hydrogen peroxide	100 g

(d)

0·950	0·431	2·58	2·56	99·2
0·995	0·428	2·50	2·43	97·2

It thus appears that the analytical procedure described can be used for the analysis of hydrogen peroxide emulsions, subject to prior standardisation of the method to the particular formula. Preparations containing cationics should be treated with caution however.

The potential of ethyl acetate as extracting solvent was also investigated. It could be used satisfactorily in the determination of hydrogen peroxide in aqueous solutions, but the results were sensitive to the presence of every surface active agent examined.

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J. Soc. Cosmet. Chem. **28** 621–627 (1977)

Causes of skin colouration, origin, development and structure of pigment cells

J. A. A. HUNTER *Department of Dermatology, The Royal Infirmary, Edinburgh*

Presented at the Joint Symposium with the Pharmaceutical Society of Great Britain, "Cosmetic and Pharmacological Aspects of Colour" 9–11 November 1976, Stratford upon Avon

Synopsis

Haemoglobin, oxyhaemoglobin, **melanin** and **carotene** are **pigments** responsible for the **colour** of human **skin.** An abnormal skin colour is produced either by an imbalance in the proportion of these four pigments or by an abnormal pigment. Melanin is synthesised in **melanocytes** found usually in the basal layer of the **epidermis.** Within the melanocytes melanin is bound to a protein matrix and the melanosomes so formed are transferred to surrounding keratinocytes. The number of melanocytes is similar in Caucasoid and Negroid skin. Black skin is produced by increased melanocytic activity associated with the production of melanosomes which are larger than those in Caucasoid skin. Negroid melanosomes tend to be disposed individually in keratinocytes whereas those in Caucasoids are usually complexed.

INTRODUCTION

During the last decade considerable progress has been made in understanding mechanisms of skin colouration, particularly the formation and distribution of melanin. In this paper an attempt will be made to review the topic and to emphasise views which have been generally accepted.

SKIN PIGMENTS

Human skin varies in thickness from about 3 to 5 mm and consists of three main layers: a stratified squamous epithelium on the surface, called the epidermis; a connective tissue dermis, and an underlying fatty layer. Combinations of four pigments (*Table I*) are responsible for the various colours of human skin.

Table I. Pigments concerned in normal skin colour

Haemoglobin
Oxyhaemoglobin
Melanin
Carotene

The pink appearance of untanned Caucasoid skin is due to the reddish pigment haemoglobin in the small blood vessels of the superficial dermis. If a sun tan is acquired this pink colour is partly obscured by a brown pigment, melanin, in the overlying epidermis. Melanin is, of course, also responsible for the various shades of brown seen in Negroids. Other hues are produced by the combination of these pigments with the fourth one, carotene, a yellow substance found in the subcutaneous fat and epidermis. There is no blue pigment, and when this colour is seen, it is the result of an optical effect (1).

Abnormal skin colour may either be produced by an imbalance in the proportion of these four pigments, as seen for example, in cyanosis, diffuse melanosis and carotenaemia, or may be caused by an abnormal pigment (*Table II*).

Table II. Some pigments responsible for abnormal skin colour

Haemoglobin products
Methaemoglobin
Sulphaemoglobin
Carboxyhaemoglobin
Bilirubin and Biliverdin
Haemosiderin
Metals
Gold, Silver
Drugs
Mepacrine, Clofazimine, Chlorpromazine
Tattoo Pigments

Although melanin is therefore only one of many pigments, the rest of this paper will be devoted solely to the study of mechanisms involved in pigmentation due to melanin. In emphasising structural aspects an attempt will be made to set the scene of melanin formation and disposal. Later papers will both amplify some of the points mentioned here only briefly and expand the general theme to include discussions on the biochemistry, control and significance of melanin pigmentation.

CELLULAR SITE OF MELANIN SYNTHESIS

The pioneer work of Bloch (2) indicated that certain branched cells in the epidermis now called melanocytes, contained an oxidising factor (dopa-oxidase) which catalysed the oxidation of the colourless dihydroxyphenylalanine (dopa) to an insoluble dense substance, melanin. Improvements in Bloch's dopa technique (3) led the Canadian Masson (4) to propose that the dopa positive melanocyte was the only melanin producing cell in the epidermis. Fitzpatrick, Becker, Lerner and Montgomery (5) modifying Bloch's method by using tyrosine instead of dopa as a substrate, demonstrated the presence of tyrosinase in melanocytes. Most workers today consider tyrosinase and dopa-oxidase to be identical; the enzyme catalysing both tyrosine and dopa in the initial steps of melanin formation. Billingham (6) showed that the branches of melanocytes, seen in the epidermal basal layer, travelled along the intercellular spaces between ordinary epidermal cells (keratinocytes), split frequently, and terminated in the form of 'caps' or 'end buttons' closely applied to the walls of keratinocytes. He felt that melanin granules were manufactured within the melanocyte and passed to the surrounding

epidermal cells across these end caps. Some years later Cruickshank and Harcourt (7) were able to confirm this process of pigment donation *in vitro* in elegant cinematographic studies. Fitzpatrick and Breathnach (8) suggested the term 'Epidermal Melanin Unit' (*Fig. 1*) to describe a structural, as well as functional, use of the melanocyte and surrounding keratinocytes. Its use should emphasize the fact that pigmentary processes involve not only the melanocyte but also the surrounding keratinocytes, which acquire the pigment secondarily.

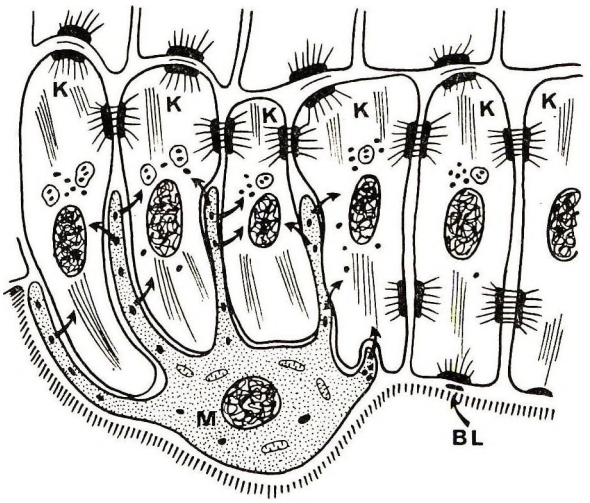

Figure 1. The epidermal melanin unit. Dendritic processes of a basal cell layer melanocyte (M) wind between keratinocytes (K). Pigment granules, melanosomes, produced in the melanocyte are transferred to the keratinocytes via the dendritic processes (arrows).
BL : basal lamina.

ORIGIN OF THE MELANOCYTE

Experiments on embryonic mice led Rawles (7) to conclude that melanocytes arise from the neural crest (a strip of specialised ectoderm flanking each side of the neural

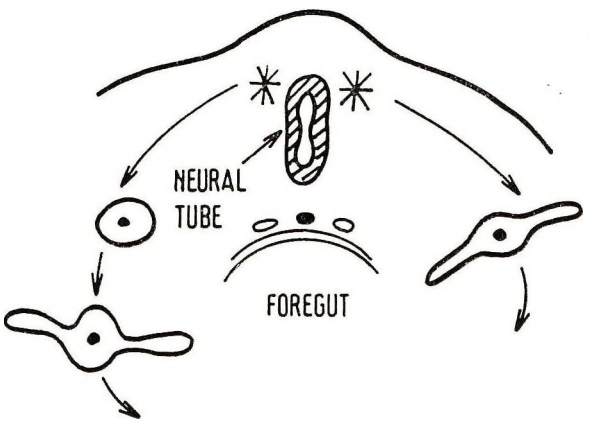

Figure 2. Origin of the melanocyte. Migration (arrow) of embryonic neural crest cells (*) to the epidermis, mucous membranes, retina and central nervous system.

plate) and not from the neighbouring epidermal cells. Cells indistinguishable from mesenchymal cells, migrate from the neural crest and undergo differentiation into cells producing pigment when they reach the epidermis. This occurs as early as the fourteenth week in the human (Breathnach and Wyllie (10)). Once in the epidermis the melanocytes form a self-replicating population of cells, which retain their ability to migrate, even in adult epidermis.

Conditions like neurofibromatosis, where pigmentary abnormalities are associated with nerve and suprarenal tumours, are experiments of nature which serve as a reminder of the pleuri-potentiality of neural crest cells.

FINE STRUCTURE OF THE MELANOCYTE

At the ultrastructural level the melanocyte is a distinctive cell. It is distinguished from neighbouring keratinocytes by its dendritic nature, its lack of tonofibrils, and desmosomes are absent (*Fig. 1*). It is seen most often in the basal layer. Unlike the keratinocyte, mitochondria are abundant. Microfibrils, as distinct from tonofilaments, are seen in the cytoplasm. Unlike tonofilaments they show no tendency to form bundles and are often seen as parallel arrays of fine filaments. The Golgi apparatus is usually prominent and the endoplasmic reticulum well developed (*Fig. 3*).

The cell has a smooth plasma membrane which shows occasional thickened areas when apposed to the basal lamina. There are however no hemidesmosomal attachments to the basal lamina.

The characteristic organelle of the melanocyte is the melanosome (*Figs 3*, *4*, and *5*). These are numerous in melanocytes of negroids and caucasoid individuals with a dark complexion though they are seen without difficulty in the melanocytes of those with a fair skin. They are ovoid or rod shaped bodies measuring 0·4–1·0 μm in length and 0·1–0·5 μm in diameter. Definition of melanosome (11):

'A melanosome is an organelle that is surrounded by a unit membrane and contains a highly organised internal structure of longitudinally orientated strands of concentric lamellae that have a regular pattern of dense particles with a characteristic periodicity. The organelles may be spherical or ellipsoid and often contain tyrosinase.'

Drochmans (12) studied high resolution pictures of melanosomes and considered that the first stage in formation of the melanosome was the deposition of a protein matrix composed of coiled filaments (*Fig. 4*)

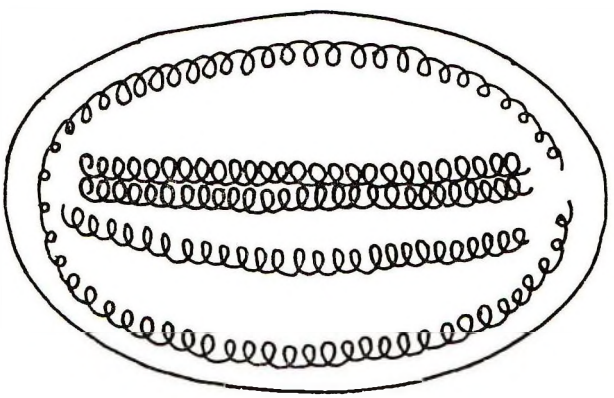

Figure 4. Stage II melanosome (after Drochmans).

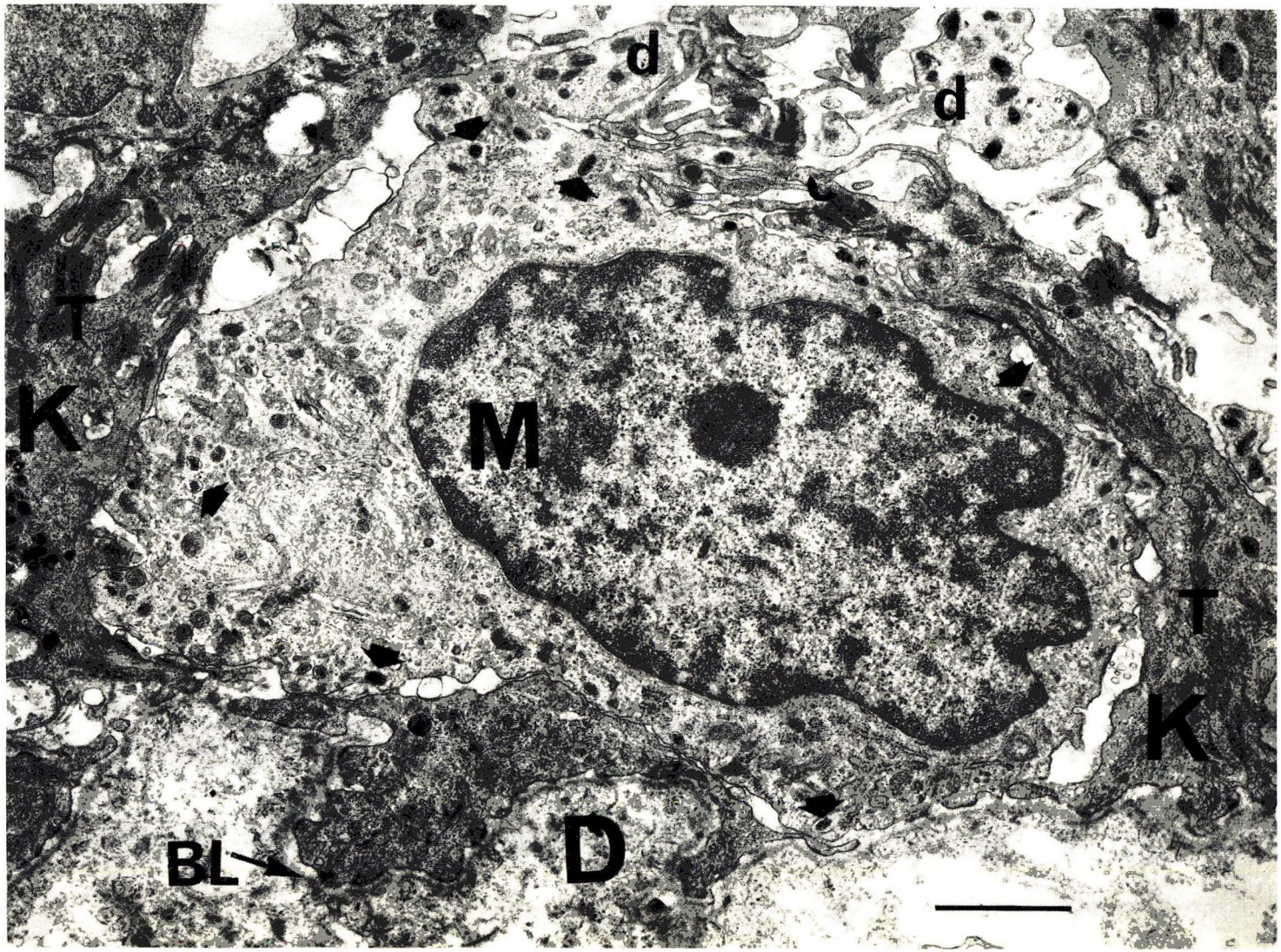

Figure 3. Human Melanocyte (M). The cell contains melanosomes (arrowed) but no tonofibrils (T). Tonofibrils are seen in surrounding keratinocytes (K). d: dendritic processes of melanocyte; BL: basal lamina; Broad arrows: desmosomes; D: dermis; Bar: 1 μm.

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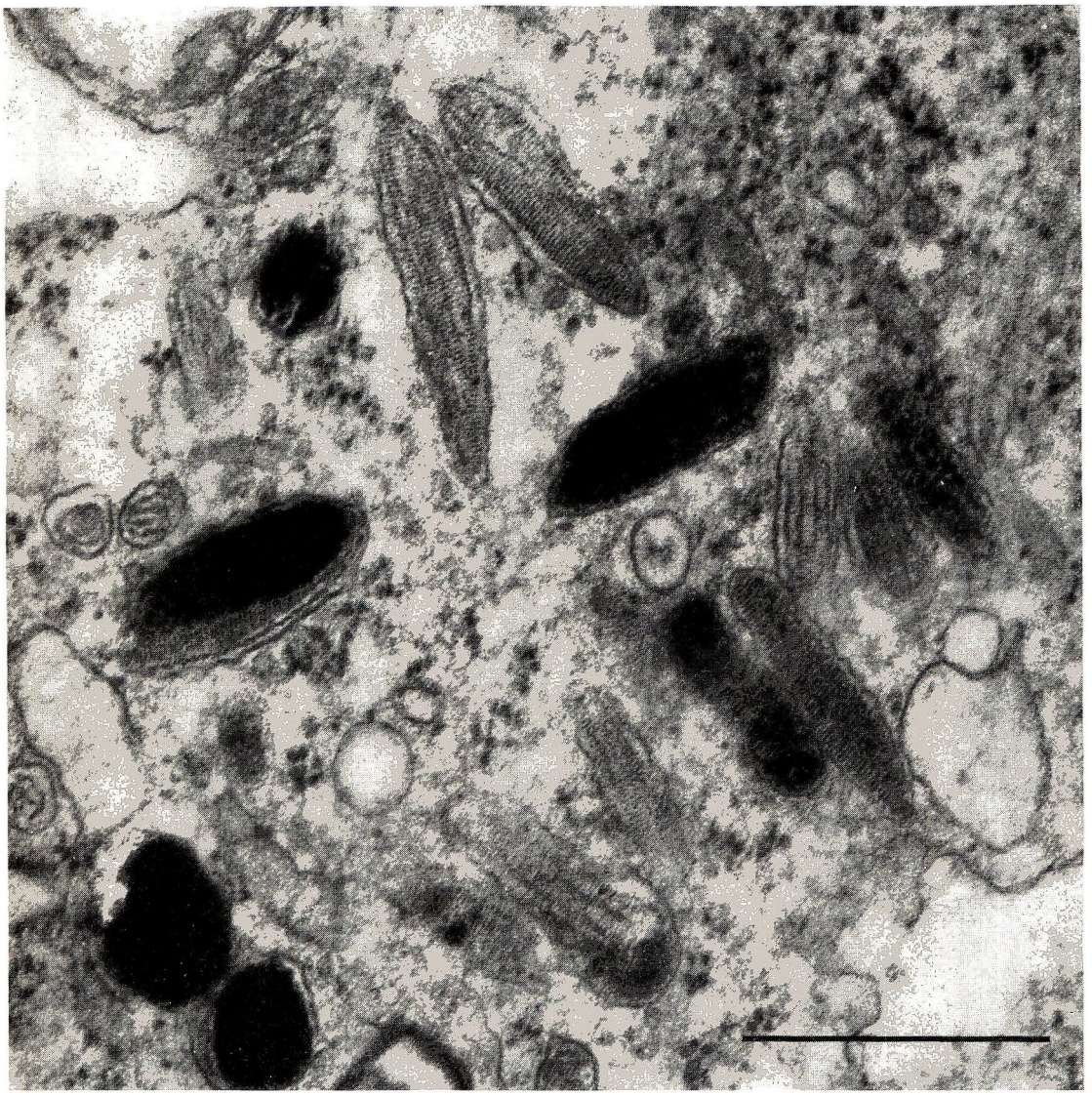

Figure 5. Human Melanosomes. All stages (see text) are seen. Bar: 0·5 μm.

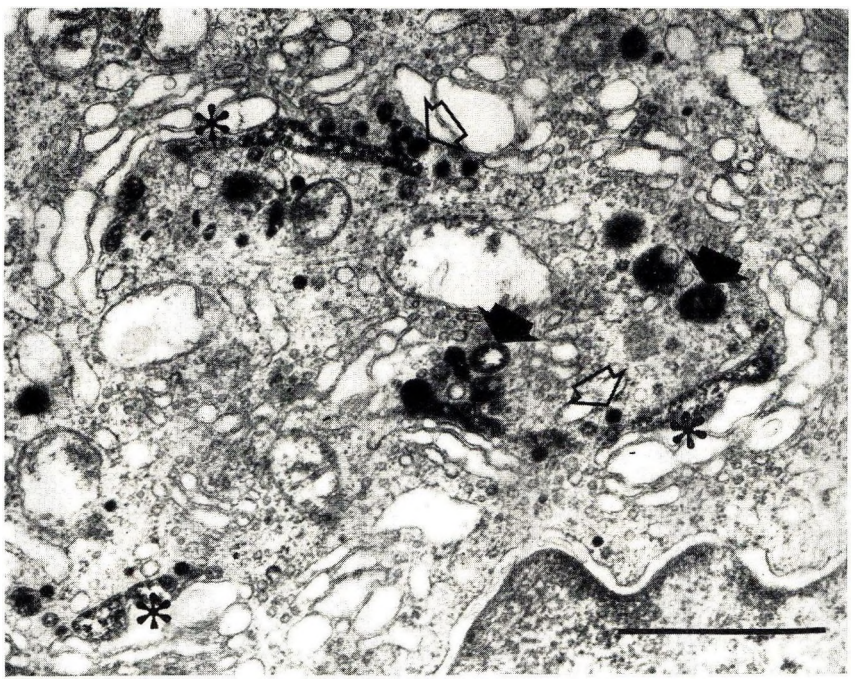

Figure 6. Human malignant melanocyte. Ultrastructural dopa reaction. The tissue was incubated in dopa after partial fixation in glutaraldehyde. Dense reaction product indicates the inter-cellular localization of tyrosinase in the Golgi saccules (*), endoplasmic reticulum near the Golgi apparatus (open arrows) and Stage I melanosomes (broad arrows).
Bar: 1 μm.

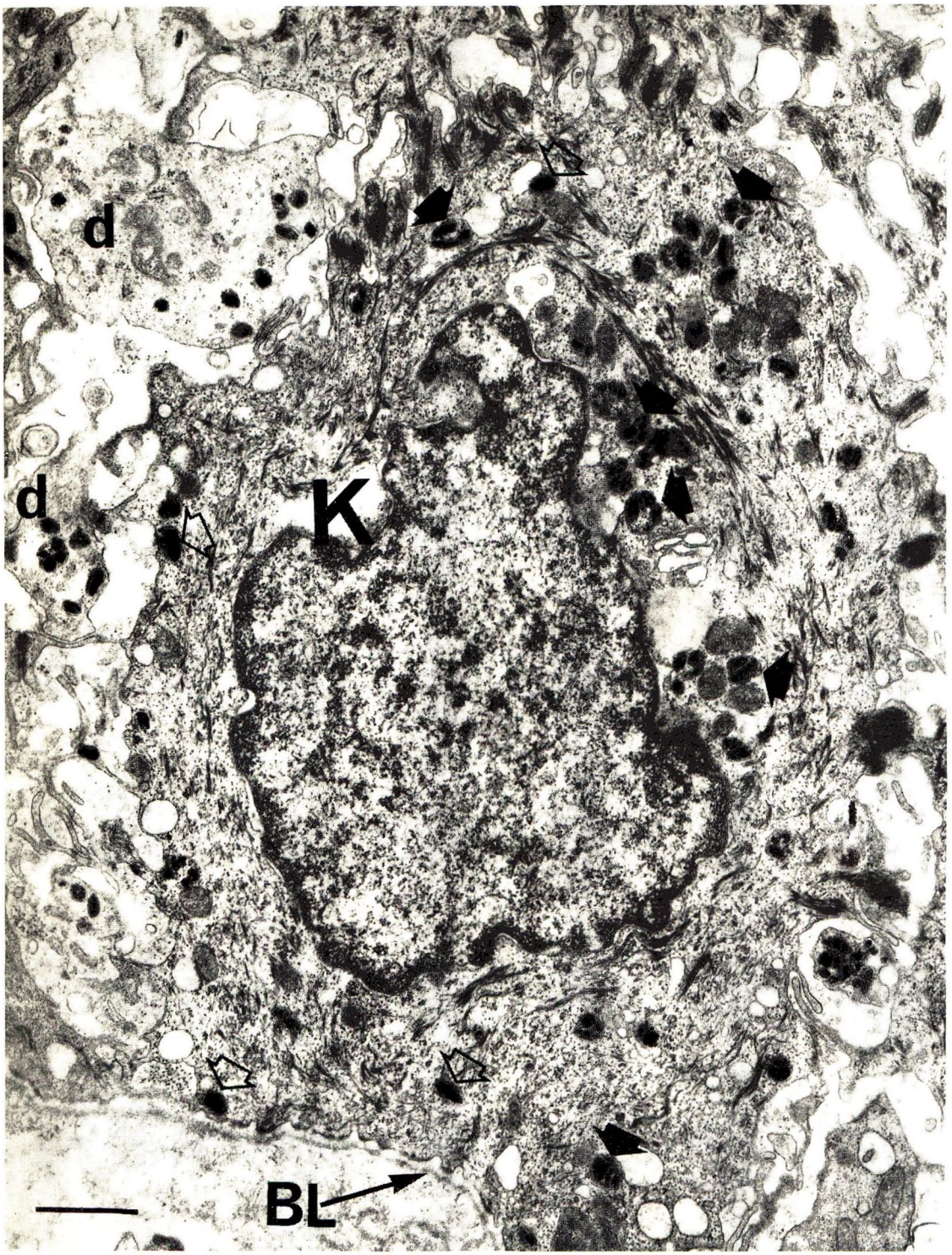

Figure 7. Melanosomes within Caucasoid keratinocyte. Basal layer keratinocyte (K) contains many complexed melanosomes (arrows) and a few single ones (open arrows). BL: basal lamina; d: dendritic process of melanocyte; Bar: 1 μm.

He felt that cross-linking of these filaments both at the periphery and at the centre of the melanosome was responsible for the transverse striations seen in micrographs. After formation of the protein matrix, melanin deposition gradually occurs, and the pigment accumulates on the inner membranes obscuring the characteristic periodicity of the structure. Finally the organelle becomes a uniformly dense particle without discernible internal structure.

Four stages in the development of the melanosome are recognized (13):

Stage I. A spherical, membrane delineated vesicle may be called a melanosome if it:

(i) is shown to contain tyrosinase by electron microscopy combined with histochemistry or

(ii) contains filaments that have a distinct periodicity of 100Å.

Stage II. The organelle is oval and shows numerous membranous filaments, with or without cross linking, having a distinct periodicity.

Stage III. The internal structure, characteristic of Stage II has become partially obscured by electron-dense melanin.

Stage IV. The oval organelle is electron-opaque without discernible internal structure in routine preparations.

Stage I melanosomes are seen as spherical vesicles near the Golgi apparatus. The other stages are usually seen scattered singly throughout the cytoplasm (*Fig. 5*) though there is a preponderance of Stage III and Stage IV melanosomes in the dendritic processes. If preservation is good a distinct unit membrane can be seen surrounding the internal structure of the organelle (*Fig. 4*). Occasionally complexed melanosomes are also seen in normal melanocytes.

Intracellular site of melanin synthesis

Information obtained from electron microscopy, electron microscopic cytochemistry, autoradiography and cell particle fractionation supports the view that tyrosinase is synthesised on the ribsosomes. It is then transferred via the rough endoplasmic reticulum to the Golgi apparatus from where it is channelled via tubular elements to a focal dilatation of the smooth endoplasmic reticulum in which the coiled melanosomal matrix has independently formed. Melanisation of the structural protein can then take place and once this is completed the connection with tubular system is severed (14, 15, 16).

RACIAL DIFFERENCES IN PIGMENTATION

It seems extraordinary that it was not until the late nineteen sixties that Man began to understand why Negroes were black and Caucasoids white. The work of Szabo, Wolff and their colleagues (17, 18, 19) has clarified the problem and is worth summarising.

There is no difference in the number of melanocytes between Negroes and Caucasoids (20). There are, however, fewer melanosomes in the melanocytes and keratinocytes of Caucasoids and Mongoloids. Of those present in the melanocyte most are in Stages I, II and III. Those in the keratinocytes are in Stage IV but tend to be grouped in membrane-limited organelles to form 'melanosome complexes'. The appearance is different in Negroids and Australian aborigines. Here there are more melanosomes in the melanocytes and keratinocytes and a high proportion of melanosomes are seen at the IVth stage of

development. Most of the melanosomes in keratinocytes appear disposed individually rather than in complexes (*Fig. 5*) (17). Wolff and Konrad (18, 19) have shown, both experimentally (using latex beads in guinea pig skin) and in human pigmentary disorders, that the complexing of melanosomes in keratinocytes is a size-dependent phenomenon. Particles of 0·1 μ tended to be complexed whilst those with a diameter of 0·8 μm were not.

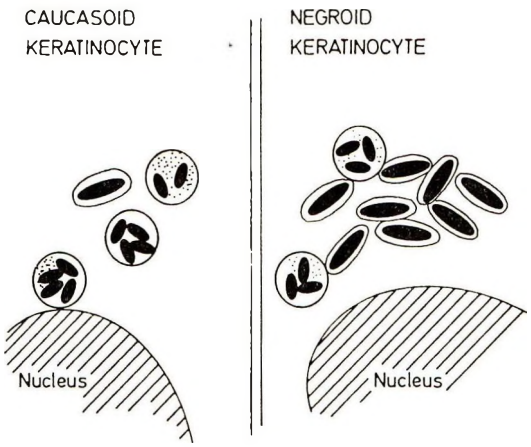

Figure 8. Racial differences in melanosomal packaging. The smaller melanosomes in the Caucasoid keratinocyte are usually complexed whereas the larger ones in the Negroid tend to be disposed individually.

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Alkyl substituted 3-methylcyclohex-2-en-1-ones

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Presented at the Joint Symposium with the British Society of Perfumers, "The future of perfumery" 4 April 1977, Stratford-upon-Avon.

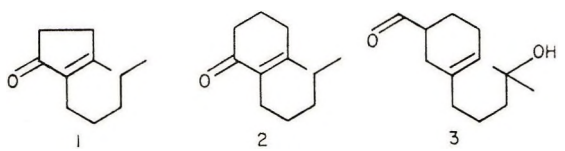
Synopsis

The versatility of Hagemann's Ester (ethyl 2-methyl-4-oxocyclohex-2-ene-1-carboxylate) as an intermediate in the synthesis of a range of alkylated 3-methylcyclohex-2-en-1-ones has been demonstrated.

The effects of the substitution pattern and of the chain length of the alkyl substituent on the odour of these ketones are discussed and some comparisons drawn with their cyclopentenone analogues (dihydrojasmones).

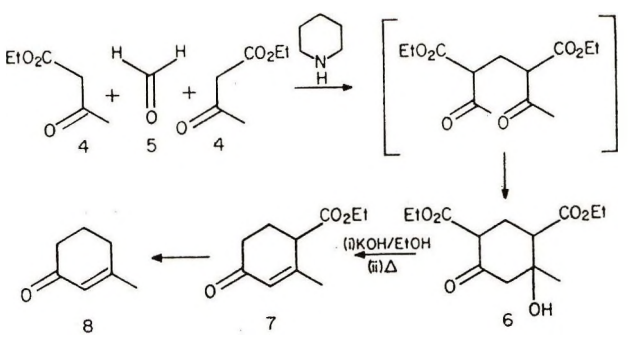
The correlation of structure with odour is a continuing challenge to the perfumery chemist. It is one which has stimulated considerable research over the last 20 years and one to which there has been, as yet, no definitive answer.

Dihydrojasmone [1] and Lyral [3] are chemicals extensively used in our industry. When these compounds are drawn in the orientation shown, it can be readily appreciated that a 2-alkyl-methylcyclohex-2-en-1-one [e.g. 2] exhibits structural features common to both, and consequently could well possess an interesting odour.



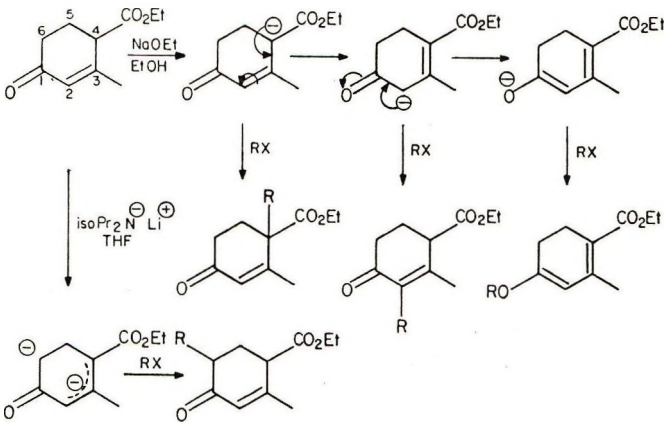
1 2 3

The preparation of these materials utilised Hagemann's Ester [7] as the starting material. This compound was prepared by the base catalysed condensation of formaldehyde [5] with ethyl acetoacetate [4] in a molar ratio of 1:2; this produced the diester [6] as the first isolable intermediate (1).

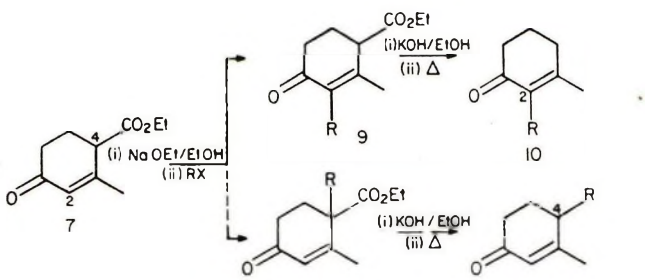


Careful hydrolysis and decarboxylation under basic conditions removed the β-ethoxycarbonyl group to yield Hagemann's Ester [7] in 61% yield. Use of acidic reaction conditions to effect hydrolysis and decarboxylation produced material contaminated with 3-methylcyclohex-2-en-1-one [8].

Hagemann's Ester [7] is a vinylogous β-keto-ester i.e. a double bond has been introduced between the ester group and the carbonyl function; consequently the corresponding ambidentate anion should be capable of reaction at the O-atom, C–2 and C–4. Furthermore, if dianion formation can be induced [2], the position (C–6)* analogous to the methyl group of ethyl acetoacetate should be activated. By altering the reaction conditions, therefore, it should be possible to alkylate at different sites round the ring.



When Hagemann's Ester [7] was treated with sodium ethoxide in ethanol, followed by an alkyl halide, alkylation occurred predominantly at the 2-position (3) to yield the substituted product [9]. In the present study, alkylation has been carried out using a

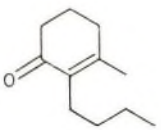
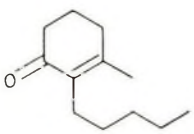
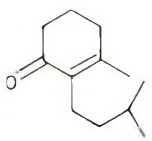
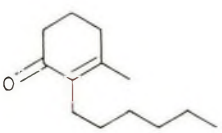
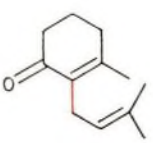


series of straight chain primary bromides (butyl, pentyl, hexyl), and one substituted primary bromide (iso-amyl), all of which gave satisfactory yields of alkylated keto-esters [9]. When a secondary halide (sec-amyl bromide) was used, a much lower yield of alkylated product was obtained (4). The one allylic halide used (3-methylbut-2-enyl chloride =prenyl chloride) reacted appreciably faster, and produced the highest yield of alkylated ester.

* It should be pointed out that Hagemann's Ester [7] and related β-keto-esters have been deliberately numbered as substituted cyclohexenones – so ensuring that the numbering of the C-atoms is self-consistent.

Hydrolysis of the ester function was accomplished by refluxing with 10% alcoholic potassium hydroxide; slow distillation of the carboxylic acid produced resulted in decarboxylation to the desired 2-alkyl-3-methylcyclohex-2-en-1-one [10] (*Table 1*).

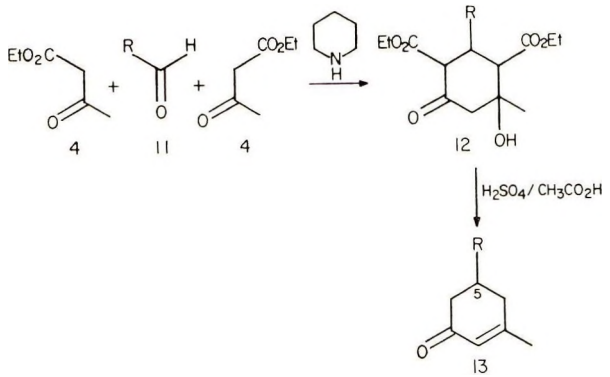
Table I 2-Alkyl-3-methylcyclohex-2-en-1-ones

Compound	Bp.	Yield (%) (from Hagemann's Ester)	Odour
	69° / 0·7 mm	39	Very strong, minty, some phenolic / chemical notes.
	81° / 0·4 mm	44	Less minty, some salicylate / benzoate characteristics.
	84° / 0·7 mm	39	Practically no minty notes; increasing amyl salicylate character.
	90° / 0·5 mm	49	No minty notes, faint amyl salicylate character; some fatty, buttery, jasmonyl character.
	97° / 0·5 mm	63	Some herbal, almost celery, notes together with amyl salicylate character.

A small amount of alkylation in the C–4 position accompanies the C–2 alkylation (5), especially when the alkylating group is small (methyl) or a β-halo-ester. However, it is claimed that the 4-alkyl ester is not hydrolysed by dilute alcoholic potassium hydroxide (5) and in our work no trace of isomeric ketones was found contaminating ketones of type [10].

The most characteristic feature of the compounds of the 2–series [10] (when compared with the members of the other series) is the absence of the vinylic proton at C–2. This can clearly be seen in the n.m.r. spectra where there is no peak at δ5·6–5·8. Furthermore, in the u.v. spectra, the compounds of the 2–series have $\lambda_{max} \simeq 235 m\mu$: the members of the other series have $\lambda_{max} \simeq 224 m\mu$.

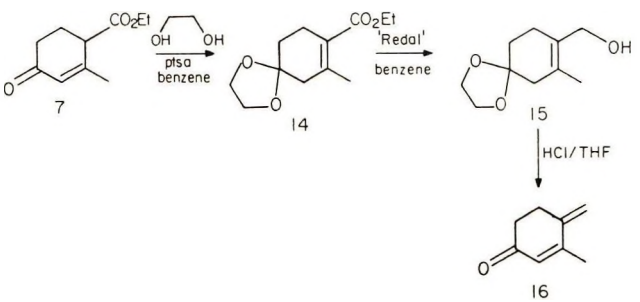
A simple modification of the condensation reaction has allowed the preparation of a series of 5-alkyl-3-methylcyclohex-2-en-1-ones. When an aliphatic aldehyde [11] was substituted for formaldehyde and condensed with two equivalents of ethyl acetoacetate, the initial product was the β-hydroxyketone [12] (6).



As mentioned earlier, in the case where R=H, the removal of both ethoxycarbonyl groups is best carried out under acidic conditions. The same pattern of behaviour is followed by the 5-substituted compounds – on treatment with concentrated sulphuric acid in glacial acetic acid – 5-alkyl-3-methylcyclohex-2-en-1-ones [13] (6) were prepared without difficulty (*Table II*).

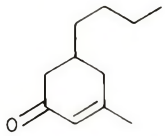
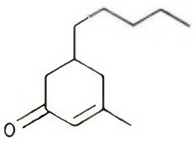
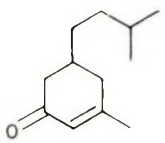
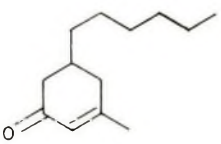
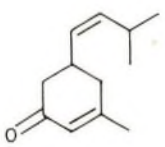
The preparation of the 5-prenyl substituted cyclohexenone requires the β, γ-unsaturated compound 4-methylpent-3-en-1-al as the aldehydic component. We have been unable to prepare this material (7) in a pure state. Consequently the condensation of the α, β-unsaturated aldehyde, 4-methylpent-2-en-1-al (8) with two equivalents of ethyl acetoacetate to produce an isomeric ketone has been investigated. Only a low yield of the substituted cyclohexenone could be expected (and indeed was obtained) as the most likely mode of reaction involves a Michael condensation of the α,β-unsaturated aldehyde with the anion from ethyl acetoacetate.

The production of 4-alkyl-3-methylcyclohex-2-en-1-ones from Hagemann's Ester [7] has been investigated by two routes. The first of these is the 'Dienone Route'.

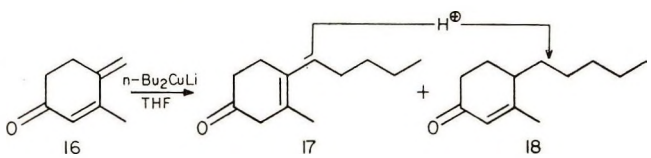


The transformations from Hagemann's Ester [7] to the dienone [16] are well-documented as far as the alcohol [15] (9), but there are little experimental data in the literature for the final stage (10). In our hands, 3-methyl-4-methylenecyclohex-2-en-1-one could be obtained in 45% overall yield from Hagemann's Ester. 1, 6-Addition of organometallic reagents to dienones is a relatively little investigated procedure. However,

Table II. 5-Alkyl-3-methylcyclohex-2-en-1-ones

Compound	Bp.	Yield (%)	Odour
	91°/1·2 mm	55	Strong, dry, celery and nutty (walnut) reminiscent of dihydrojasmone.
	94°/0·6 mm	53	Less intense, some celery notes; some dihydrojasmone character present.
	110°/1·6 mm	47	Weakest of series, faint jasmine character.
	113°/1·3 mm	45	Fatty, almost aldehydic (reminiscent of Adoxal), soft floral background.
	78°–79°/1·0 mm	5	Oily, nutty, slight dihydrojasmone character.

the ready 1,4-addition of organocuprates to α, β-unsaturated carbonyl compounds (11) has become well established in the last few years. In fact, Marshall *et al.* (12) have recently investigated the regioselectivity of lithium dimethylcuprate addition to alicyclic dienones and shown that 1,6-addition is the preferred mode of reaction. Thus treatment of dienone [16] with lithium di-n-butylcuprate yielded a mixture of isomeric ketones [17, 18] in which the β,γ-isomer [17] was the predominant compound.

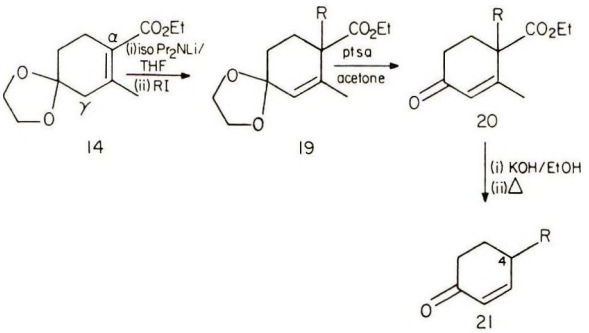


16 17 18

Treatment of this mixture with acidic reagents, either hydrochloric acid in acetone, or preferably, passage through a column of acidic alumina, caused isomerization of enone [17] to the fully conjugated isomer [18] which was isolated in 49% yield from the dienone [16].

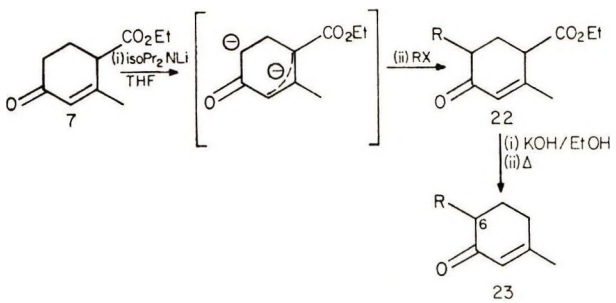
While work on the dienone route was in progress, improved methodology for the alkylation of α,β-unsaturated esters at the α-position (13) was reported. This suggested a route, both more direct and bearing great similarity to our earlier work, to the ketones of the 4-series – the 'Ketal Route'.

The ketal ester [14] derived from Hagemann's Ester is an α,β-unsaturated ester, and alkylation should be possible at the α-position to yield alkylated ketal ester [19]. Reaction at this α-centre should be enhanced by the steric hindrance to the γ-site from the adjacent spiro-centre. Evidence to support this view has been obtained from the methylation of ester [19] at the α-position in high yield (14).



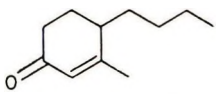
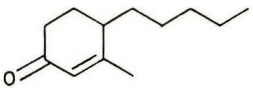
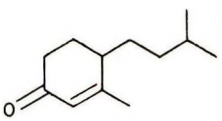
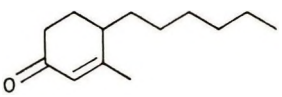
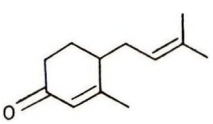
The ketal-ester [14] was treated with an excess of lithium di-iso-propylamide in order to form the anion which was then alkylated with the appropriate iodide. The alkylated ketal-ester [19] which resulted was hydrolysed to the corresponding keto-ester [20] with p-toluenesulphonic acid in aqueous acetone. Hydrolysis could be accomplished only on prolonged refluxing with dilute ethanolic potassium hydroxide; distallation of the resulting carboxylic acid produced the desired 4-alkyl-3-methylcyclohex-2-en-1-one [21] (*Table III*). At the same time a small quantity of the isomeric 6-alkyl-3-methylcyclohex-2-en-1-one was produced and care was required to remove this material from the main product. The mechanism of its formation has not been established.

Ethyl acetoacetate can be alkylated at the terminal methyl group rather than at the internal methylene group under conditions where dianion formation is induced (2). In an analogous fashion, dianion formation utilizing Hagemann's Ester [7] should furnish alkylation at the 6-position, and so permit entry into the fourth and final series of substituted cyclohexenones.



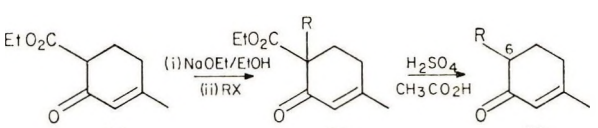
Unfortunately, the specificity of this reaction is poor. After hydrolysis and decarboxylation, the product, which is obtained in 50% yield from Hagemann's Ester, is a

Table III. 4-Alkyl-3-methylcyclohex-2-en-1-ones

Compound	Bp.	Yield (%)	Odour
	82°/1·4 mm	34	Soft, nutty with a lemon note.
	72°/0·15 mm	43	Soft, nutty, some floral character; lemon note still present.
	75°/0·4 mm	39	Soft, floral, some 'tea-leaf' character; lemon note retained.
	84°/0·1 mm	40	Soft, dry, reminiscent of mustard; slight lemon character.
	82°/2·0 mm	27	Soft, herbal-floral, faintly nutty.

~2:1 mixture of the desired 6-alkyl compound [23] together with a smaller quantity of the 4-isomer.

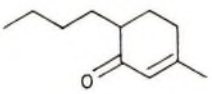
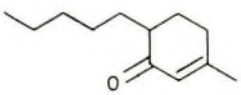
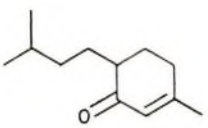
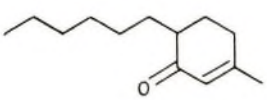
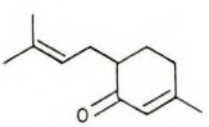
To obtain the 6-alkyl series of compounds, an isomer [24] of Hagemann's Ester has been prepared (15) which, for convenience, has been called isoHagemann's Ester. Theoretical considerations suggest that this molecule, both a β-keto-ester and an α,β-unsaturated ketone, should alkylate at the 6-position. In practice this has been confirmed only by an isolated observation of Wichterle, Prochazka & Hofman (16).



24 25 23

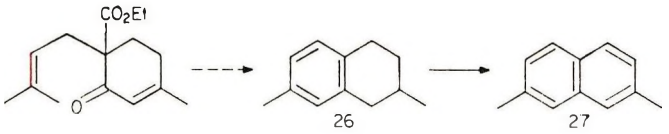
Alkylation of isoHagemann's Ester [24] via its sodium enolate proceeded without complications, and the alkylated esters [25] were easily isolated. Apart from the prenylated compound, hydrolysis and decarboxylation proceeded best under acidic conditions

Table IV. 6-Alkyl-3-methylcyclohex-2-en-1-ones

Compound	Bp	Yield (%) (from isoHagemann's Ester)	Odour
	110°/6·0mm	50	Herbal, celery; celery character develops and predominates on dry out.
	106°/3·0mm	51	Faint; celery character again developing on dry out.
	108°/3·5 mm	33	Faint, celery, some nutty character.
	81°/0·1 mm	48	Herbal, celery character almost entirely lost; nutty, almost lactone notes present, reminiscent also of jasmonyl.
	77°/0·3 mm	34	Much greener and more floral than rest of series; faint herbal, celery character.

to yield ketones readily established as 6-alkyl-3-methylcyclohex-2-en-1-ones [23] (*Table IV*). The possible presence of the isomeric 2-alkyl compounds, produced from the Hagemann's Ester [7] invariably present in isoHagemann's Ester [24] (17) was thereby surmounted as 2-alkylated Hagemann's Esters [9] are not readily decarboxylated under acidic conditions (1).

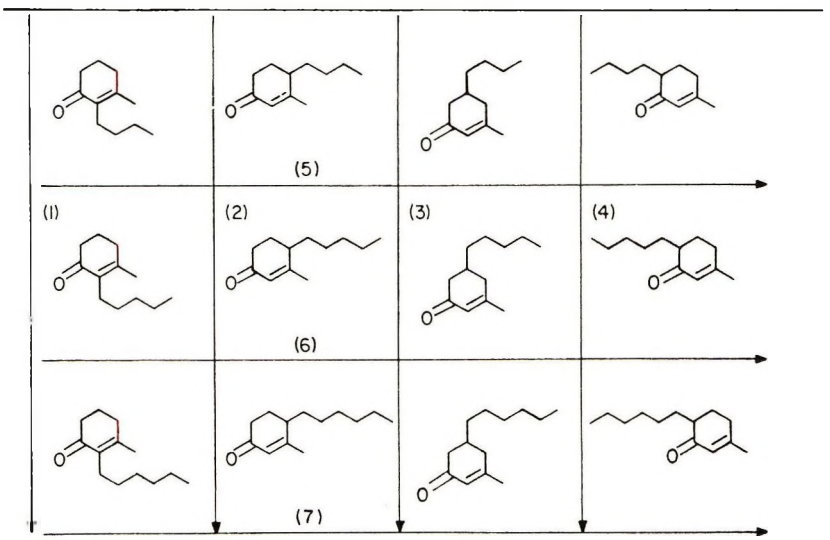
This general pattern was not followed when prenyl chloride was used as the alkylating agent. Although the alkylation stage proceeded smoothly due to the high activity of the allylic halide, hydrolysis and decarboxylation under the usual acidic conditions led to a mixture of three products in the ratio 16:1:3. The smallest component possessed the empirical formula ($C_{12}H_{18}O$) and its mass spectral breakdown pattern was consistent with the desired 6-prenyl-3-methylcyclohex-2-en-1-one. The intermediate component was a highly unsaturated hydrocarbon ($C_{12}H_{12}$), the u.v. spectrum of which established its structure as 2,7-dimethylnaphthalene [27]. The presence of this material was primarily responsible for the easy identification of the major component, another hydrocarbon ($C_{12}H_{16}$), as 2,7-dimethyltetralin [26] (18). Both hydrocarbon components result from acid-catalysed cyclisation.

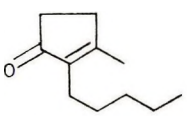


Recourse to basic hydrolysis followed by thermal decarboxylation did give a moderate yield of 6-prenyl-3-methylcyclohex-2-en-1-one.

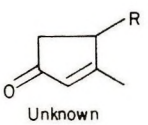
In the n.m.r. spectra of the compounds of the 4-, 5-, and 6-series, the proton on the ring double bond occurs at δ5·6–5·8 and generally shows fine splitting caused by the methyl group on the double bond which itself produces a doublet ($J \simeq 1$ cps) centred at δ1·9. The mass spectra of the compounds of the 6-series [23] are all very similar, the base peak in each case being m/e 110; they can thus be differentiated from the members of the 5-series [13] all of which exhibit a base peak at m/e 82. In contrast, 4-substituted α,β-unsaturated ketones are reported (19) to show a prominent ion at m/e M–42 due to

Table V.

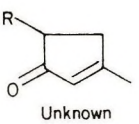




Dihydrojasmone
intensely floral and fresh with fruity and somewhat myrrh-like undertone.

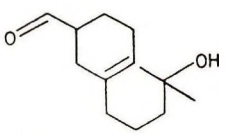


Unknown

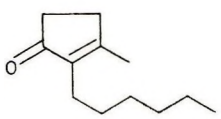


Unknown

(R=n-butyl, n-pentyl, n-hexyl)



Lyral
soft, delicate, floral (muguet); extremely tenacious.



Warm, spicy, sweet-floral and diffusive, yet quite tenacious odour.

the elimination of ketene, but this behaviour has not been demonstrated by the compounds of type [21].

From a chemical point-of-view Hagemann's Ester has been demonstrated as a versatile intermediate in the synthesis of alkylated 3-methylcyclohex-2-en-1-ones. In contrast, it is difficult to draw any wide ranging conclusions from a perfumery standpoint. Although it is possible to outline a number of generalisations (*Table V*) where, e.g. line (1) represents decreasing mintiness and increasing salicylate character and line (5) represents decreasing softness and florality, none of the compounds depicted possess odour characteristics which approach closely to those of dihydrojasmone and Lyral.

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The influence of some formulation variables and valve/actuator designs on the particle size distributions of aerosol sprays

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Received 23 February 1977

Synopsis

Knowledge of the size and distribution of **particles** produced from cosmetic **aerosol** products is important not only from the viewpoint of product optimisation but also from considerations of potential inhalation characteristics. A discussion is given of methods suitable for determination of the respirable fraction of the **spray** or a complete **particle size distribution**.

Results are presented for the particle size distributions of some aerosol formulations with differing compositions and levels of propellant. The effects of certain actuator designs and valve specifications are also presented. These results are discussed in terms of different particle formation mechanisms due to differences in **formulation**, mechanical action of the **valve** and **actuator** and subsequent changes in size of the particles. It is concluded that the particle size distribution of a cosmetic aerosol product only has meaning when the formulation, dispensing, and sampling details are also specified.

INTRODUCTION

The production of particulate material from a pressurised pack is a complex sequence of events, much of which is little or poorly understood. Knowledge of the size and distribution of particles produced from cosmetic aerosol products is important for product optimisation and consideration of potential inhalation characteristics.

Much of the information in the literature on aerosol spray particle size appears at first sight to be contradictory. For example, in the case of hairspray products, Brunner *et al.* (1) found that 50% by weight of the particles were 30 μm or more, whereas Ripe *et al.* (2) found that, of the hairsprays they examined, 49% of the particles had a diameter of less than 15 μm. These differences may be due to many factors, including variations in sampling and sizing techniques (as suggested by Cambridge (3)), and widely differing formulation/valve-actuator systems. These variables are known to exert a large influence on spray particle size. The object of this paper is to consider some of the methods that have been applied to determining the particle size distributions of aerosol sprays, and to examine the influence of some formulation and hardware design variables on the particle size of some model aerosol systems, with a view to presenting a more unified picture of some of the important variables.

CLASSIFICATION OF PARTICLE SIZING TECHNIQUES

It is convenient to classify methods suitable for sizing aerosol sprays into three basic categories:

(i) The particles are collected and then physically examined. Methods suitable for collection include air elutriation, centrifuging, thermal precipitation, electrostatic precipitation, sedimentation and impaction. Analysis may be by counting (optical or electron microscopy), weighing or other means. These methods have obvious limitations for studying volatile systems (which is the usual case for cosmetic aerosols).

(ii) The particles are passed into a probe which is connected to a sensing device. Commercial light scattering counters utilise this principle.

(iii) The aerosol is examined without the use of physical sampler or probe (e.g. photography, holography and some light scattering methods).

ADVANTAGES AND DISADVANTAGES OF SIZING TECHNIQUES

A cursory examination of aerosol sizing literature will immediately reveal that no single sizing method will supply all the information to completely characterise an aerosol spray. For the aerosol technologist or cosmetic chemist, the sizing exercise is frequently one of compromise: how to obtain size data accurately, covering the size range of interest without resort to excessive expenditure on equipment or lengthy analysis time. A selection of sizing methods that have been applied to aerosol sprays, together with their strengths and weaknesses is summarised in *Table I.*

Table I. Summary of particle sizing methods

Method	Size range (μm)	Major problems
Optical microscopy	0·2–300	0·2 μm limit of resolution Spreading of larger droplets
Cascade impactors	0·2–20	Wall losses/disaggregation Rebound/re-entrainment Limited size data
Light scattering counters	0·1–20	Refractive index, shape, sensitivity, coincidence, cross-sensitivity, calibration isokinetic sampling
Holography	3–1000	Lower limit 3 μm Two stages in sizing: formation and reconstruction. Analysis time.
Photography	5–1000	Small depth of field Automation difficult but possible. Difficulty in three dimensions.

Optical microscopy provides a convenient and simple but tedious method for a complete analysis of particle size distribution down to 0·2 μm. The method has been applied by Tregan and Lefebvre (4), and by Rance (5) who used an image-splitting analyser for more rapid counting. For large liquid particles or non-volatile droplets the problem of droplet spread can be partially overcome by the additional techniques

described in references (6) and (7), but both these techniques can be used with only limited success.

Cascade impactors are air sampling devices consisting of high-velocity air jets in cascade (i.e. in series) with each jet directing the air against a collecting plate at a progressively higher velocity. After calibration with suitable monodisperse aerosols, size–number distributions can be determined by microscope counting of the particles, or size–weight distributions can be obtained by weighing. Sciarra, McGinley and Izzo (8) have used the cascade impactor for estimation of the weight percentage of particles below 10 μm for hairspray formulations having different valve characteristics. Size distributions have to be constructed from a limited number of points, typically a maximum of five. A recent analysis of impactor data (9) has enabled development of smooth distribution curves from the masses of particles collected at different stages of a multistage impactor.

Light scattering methods can be particularly useful in monitoring particle size distributions from aerosol sprays. The main difficulty is that the intensity of the scattered light pulse not only depends on particle size but, for a given light source and scattering/measuring configuration, the intensity is also a function of other variables such as refractive index and particle shape. Jaenicke (10) has examined the additional problems of coincidence (the simultaneous occurrence of more than one particle at a time in the sensing volume) and cross-sensitivity (counting of particles in channels adjacent to that corresponding to the correct particle size).

All aerosol particle counters need to be calibrated with standard aerosols of known size before use. Typical aerosols are produced by atomisation of suspensions of polystyrene latex spheres. This only provides calibration data at a limited number of points in the size range of interest. Moreover, inaccuracies can arise if the refractive index of the measured aerosol is greatly different from that of the polystyrene latex.

With probe systems correct sampling is essential, i.e. it is necessary to obtain a representative sample of the aerosol in terms of size and distribution. This can only be accomplished by isokinetic sampling and it is particularly relevant for cosmetic aerosols, in which particles can possess appreciable momentum. The general problems concerning representative aerosol sampling have been reviewed by Fuchs (11).

The measurement techniques employed in the present work have used a compromise of light scattering coupled with optical array imaging to enable a total size range of 0·3–300 μm to be covered.

ANALYSIS AND DEFINITION OF SIZE PARAMETERS

The analysis of size data can present problems, not only of handling the large volume of information, but also of interpretation of the data. In an ideal situation, the aerosol distribution can be represented by an analytic function, $f(D)$ of the form

$$df = f(D)\, dD \tag{1}$$

with the condition

$$\int_0^\infty f(D)\, dD = 1 \tag{2}$$

where df is the number of particles having radii between D and $D + dD$. Transformation of the size parameters can then be obtained in both number and weight terms. The most common choice of function is based on log–normality to describe the distribution:

$$F = \int_{\infty}^{\ln D} \frac{1}{(2\pi)^{\frac{1}{2}} \ln \delta g} \exp\left[-\frac{(\ln D - \ln Dn)^2}{2 \ln^2 \delta g} \right] d(\ln D) \qquad (3)$$

where F is the cumulative number of particles with logarithms of diameters less than $\ln D$.

δg is the geometric standard deviation
Dn is the number median diameter.

Many authors have applied the criterion of log–normality in terms of obtaining straight lines on logarithmic–probability scales. Parameters such as the number-median or mass–median diameter can then be read off at the 50% cumulative percentage point. An additional test for log–normality is to apply the Hatch–Choate (12) equation to test for transformation between number median diameter (Dn) and mass median diameter (Dm):

$$\ln (Dn) = \ln (Dm) + 3 \ln^2 \delta g \qquad (4)$$

However the information obtained by the measurement technique usually represents a limited range of the total sizes produced in reality. Thus the criterion of linear logarithmic–probability plots for log–normality can often be quite spurious. Vos and Thomson recently queried the validity of calculating a mass median diameter whose magnitude was considerably outside the range of measurement (13). In the opinion of the present authors, such a parameter, calculated from extrapolated data, has little value in characterising aerosol sprays.

The above discussion has been concerned with spherical particles whose sizes can be completely defined by one parameter – the diameter. In the case of non-spherical material, however, the situation becomes more complex since the kinetic behaviour of such particles in air can differ greatly from the corresponding behaviour of spheres. In such cases it is important to be able to determine the aerodynamic rather than the geometric diameters of the particles. The aerodynamic diameter of a particle may be defined as the diameter of a unit density sphere having the same settling velocity as the particle in question. The outstanding advantage of cascade impactors and other air segregation systems is that they size aerodynamically. However, any prediction of aerodynamic behaviour (e.g. lung deposition – see below) must be made with care since the diameters recorded by a particular air segregation device are only relative to the airflow velocity and, consequently, to the particle orientation prevailing under the conditions of measurement.

THE RELATIONSHIP BETWEEN PARTICLE SIZE AND HUMAN INHALATION

Deposition of particulate material in the respiratory tract represents the primary stage in any consideration of human inhalation. Many theoretical models have been made of aerosol deposition in the respiratory tract (14–17) and the general results of such calculations have been substantiated by experimental tests. In general, only those particles with aerodynamic diameters less than about 10 μm are likely to pass into the lower respiratory tract. This can be complicated, however, by the effects of particle density, shape, airflow patterns within the lung, and the hygroscopicity and volatility of the material under consideration. Air samplers are available (18) which are designed to separate air-borne material into fractions likely to penetrate to the depths of the human

lung (e.g. for use in the mining industry). An estimation of the inhalation hazard of an aerosol spray cannot be made by merely determining the particle size distribution or the respirable fraction, since the relative toxicity of the sprayed material must be considered. Although particle size parameters are of use in rapid screening of the potential inhalation characteristics of aerosol products, they need to be interpreted with the guidance of a toxicologist and they cannot replace biological testing.

METHODOLOGY FOR THE PRESENT STUDY

The purpose of the present study is to show the effect of some formulation and hardware variables on the particle size of some model aerosol systems. The particle sizes were determined by means of laser light scattering and optical array imaging systems (designed and supplied by Particle Measuring Systems Inc., Boulder, Colorado, USA) and calibrated with monodisperse polystyrene latices. The principle of operation of these two systems has been published elsewhere (19). These systems are ideally suited for rapidly determining the airborne size distributions of aerosol sprays and they are illustrated in *Figs 1–3*. As the measurements are made on airborne particles, rather than captured particles, they are of particular value for studying cosmetic aerosols containing substantial amounts of volatile materials (e.g. propellants). To the authors' knowledge this is the first published measurement of this type by this method.

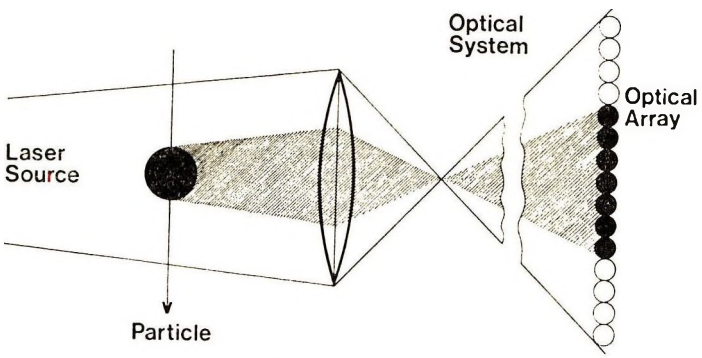

Figure 1. The optical array system.

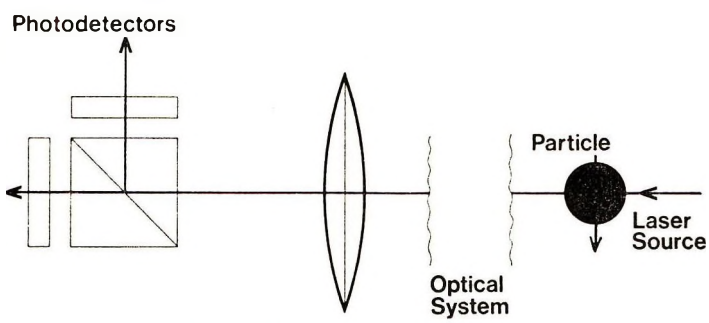

Figure 2. The light scattering system.

The effective range of the light scattering system was 1·7–14 μm and two measurement ranges of the optical array system were employed (3·3–50 and 20–300 μm). Each range was subdivided into fifteen separate size channels, from which number/size channel information was obtained.

The particle size distributions were recorded by spraying the aerosol for five seconds into the appropriate probes. With the actuator orifice and the axis of the laser beam in one horizontal plane, distances were selected at 28 and 48 cm from the actuator orifice to the laser beam axis. This was because of experimental convenience and because the distributions could be expected to exhibit significant differences due to evaporation of the volatile components of the particles. The prevailing conditions of measurement were 20°C and 50% Relative Humidity.

Two model aerosol formulations were selected for this work, based on 15/85 and 35/65 product/propellant ratios. The formulations are detailed in *Table II*. The valve/actuator systems selected are listed in *Table III*; these were selected to include a range of valve/actuator variables used in aerosol formulation studies. These variables included the size of the valve housing orifice and the presence or absence of a vapour phase tap in the valve. The actuators employed were a mechanical break-up (four-channel swirl chamber) system and a standard 0·015-inch spray orifice button. The particle sizing systems were calibrated with monodisperse polystyrene latices (0·5–2 μm diameter) and with glass beads (50–300 μm diameter).

Table II. Aerosol formulations

(a) 35/65 *Product/Propellant System*	% w/w
'Resyn' 28–2930 *	1·10
Amino-methyl propanediol †	0·11
Ethanol	33·79
Fluorotrichloromethane (3) ‡	42·20
Dichlorodifluoromethane (3) ‡	22·80
	100·00

(b) 15/85 *Product/Propellant System*	% w/w
'Resyn' 28–2930 *	1·10
Amino-methyl propanediol †	0·11
Ethanol	13·79
Fluorotrichloromethane ‡	55·25
Dichlorodifluoromethane ‡	29·75
	100·00

* National Starch and Resin Corporation Inc.
† British Drug Houses Laboratory Reagent.
‡ Imperial Chemical Industries (Mond Division).

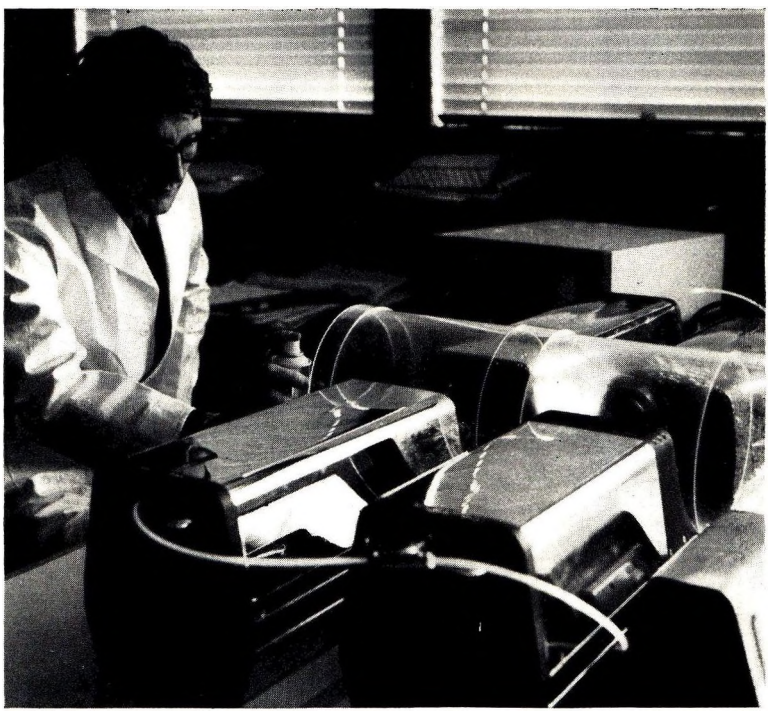

Figure 3. The complete measuring system.

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Table III. Valve/actuator systems *

Hardware † combination	Valve housing orifice (inches)	Vapour phase tap (inches)	Actuator ‡ type
1	0·025	—	1303 (Four-channel)
2	0·025	—	015 Standard
3	0·080	—	1303 (Four-channel)
4	0·080	—	015 Standard
5	0·025	0·013	1303 (Four-channel)
6	0·025	0·013	015 Standard

* Stem orifice 0·020 inches in all systems.
† All valve/actuator systems ex. Metal Box Company Limited, UK.
‡ The 1303 actuator has a four-channel swirl chamber for mechanical break-up of aerosol droplets.

RESULTS

The number/size information obtained for each spray was analysed as follows: the particle size information was computed on a mass basis and plotted on a logarithmic probability scale. From these plots the mass median diameter (the diameter above and below which lies 50 % of the mass of the particles) was read off. The mass-median diameter was obtained in order to represent the coarseness of the spray. Typical cumulative size distribution curves are given in *Fig. 4* (hardware combinations: 0·020 inch stem, 0·025 inch housing, 0·013 inch vapour phase tap and 1303 actuator).

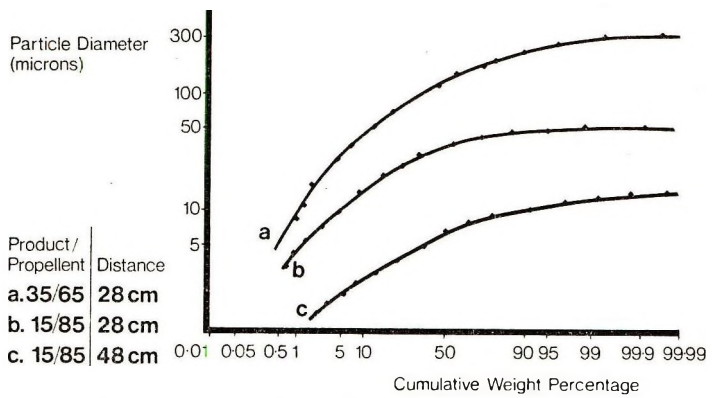

Figure 4. The particle size distributions of aerosol systems studied.

The condition of straight line plots as a criterion for log-normality was not applied because the data were limited by the extremes of the size ranges used and it had been assumed that all particles in a channel were equal in size to the mid point of that channel. Such assumptions can be further complicated by the unequal widths of the channels on some size ranges. An improved method of data analysis would be to describe the information obtained by the distribution function, from which parameters can be derived that can characterise the data. Raabe (20) has described the use of the log-normal function in particle size analysis, together with a maximum likelihood method for fitting and testing the fit of a log-normal function to grouped particle size data.

The size data for the 15/85 product/propellant aerosol are listed in *Tables IV and V.* Four repeat measurements of each valve/actuator combination gave a maximum variation of + 5% in the computed mass–median diameters, and the values quoted are the arithmetic means of these results.

Table IV. Mass–median diameters of 15/85 product propellant system at 48 cm from actuator (for fuller details see Tables 1 and 2)

Housing (inches)	Vapour phase tap (inches)	Actuator	Mass–median diameter (μm)
0·025	—	Four-channel	9
0·025	—	Standard	10
0·080	—	Four-channel	11
0·080	—	Standard	10
0·025	0·013	Four-channel	8
0·025	0·013	Standard	10
0·080	0·013	Standard	10
0·080	0·013	Four-channel	9

The effect of evaporation of the volatile components of the spray can have a large influence on the particle size distribution as can be seen from a comparison of mass–median diameters derived from data at 28 and 48 cm from the actuator, where the diameters can change by a factor of three over a distance of 20 cm. These differences in mass–median diameter are most likely due to evaporation of the ethanol solvent in the formation, which has evaporated subsequently to the explosive vaporisation of the propellant. For example, a 40 μm diameter drop of the complete resin/solvent/propellant composition in *Table IIb* will have evaporated to a drop of approximately 20 μm diameter on loss of propellant and a drop of 9 μm diameter on subsequent loss of solvent. This calculation assumes no condensation, disruption or agglomeration of the particles in flight and is based purely on the proportions of the constituents present in the formulation.

The effect of a vapour phase tap is, in addition to reducing the discharge rate of the system (21), to reduce the particle size of the spray. The effect of the vapour phase tap is most marked at the higher product/propellant ratio of 35/65 (*Table VI*). For finer sprays (15/85 product/propellant aerosol), the vapour phase tap effect is small at 28 cm (*Table V*), and is negligible and difficult to detect if measurements are made at increasing distances from the actuator (e.g. 48 cm, *Table IV*).

Table V. Mass–median diameters of 15/85 product propellant system at 28 cm from actuator (for fuller details see Tables 1 and 2)

Housing (inches)	Vapour phase tap (inches)	Actuator	Mass–median diameter (μm)
0·025	—	Four-channel	33
0·025	—	Standard	38
0·080	—	Four-channel	33
0·080	—	Standard	35
0·025	0·013	Four-channel	28
0·025	0·013	Standard	32
0·080	0·013	Four-channel	30
0·080	0·013	Standard	30

The housing orifice appears to play a part in control of the particle size: for the 35/65 product/propellant aerosol (*Table VI*), the larger the housing orifice, the coarser the spray. Finally, the effect of the actuator (mechanical breakup or standard) can also have a marked effect on the particle size.

Table VI. Mass–median diameters of 35/65 product/propellant system at 28 cm from actuator (for fuller details see Tables 1 and 2)

Housing (inches)	Vapour phase tap (inches)	Actuator	Mass–median diameter (μm)
0·025	—	Four-channel	200
0·025	—	Standard	200
0·080	—	Four-channel	205
0·080	—	Standard	210
0·025	0·013	Four-channel	125
0·025	0·013	Standard	180
0·080	0·013	Four-channel	195
0·080	0·013	Standard	120
0·018	—	Four-channel	187
0·018	—	Standard	194
0·018	0·013	Four-chanenl	112
0·018	0·013	Standard	143
0·032	—	Four-channel	200
0·032	—	Standard	202
0·032	0·013	Four-channel	134
0·032	0·013	Standard	163

The total result of these variables – distance from actuator, product/propellant ratio, actuator type, valve dimensions – is a complex set of interactions that can have a marked influence on the particle size of the spray. The general conclusions derived in the foregoing paragraph might have to be reassessed if a different formulation type was considered (e.g. compressed gas propellant, or solid suspension formulation). It is therefore considered that any study of the particle size of aerosol systems needs to be considered in relation to the total package (hardware and formulation) and the distance from the sprayhead. Moreover, it is necessary to point out, therefore, that an aerosol particle size distribution or parameter cited without reference to the formulation, valve/actuator design, and conditions of sampling has little value.

SUMMARY AND CONCLUSIONS

Knowledge of aerosol particle size distributions is important not only from the viewpoint of product optimisation but also from considerations of potential inhalation characteristics. The determination of particle size can present problems from the viewpoint of measurement and of data analysis and interpretation. No single measurement technique will provide all the information on particle size for all product types.

The results presented have shown large decreases in particle size, as reflected by mass–median diameter, with increasing distance from the actuator and with increases in propellant level. Variations in valve orifices and in the type of actuator employed present a secondary but significant influence on mass–median diameter. The mass–median diameter falls with reduction in the size of the housing orifice, with the presence

of a vapour phase tap, and with a mechanical break-up insert in the actuator. The particle size distribution of a cosmetic aerosol product only has meaning when the formulation, dispensing, and sampling details are specified.

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Cosmetics and the future

R. J. L. ALLEN*

The 1977 Medal Lecture by Professor R. J. L. Allen, delivered before the Society of Cosmetic Chemists of Great Britain on 3 March 1977, with D. F. Williams Esq., President of the Society in the Chair.

When, early last year, your President was kind enough to suggest that I should give the 1977 Medal Lecture my first reaction was to disqualify myself. My background is in biochemistry, nutrition and food science, and it appeared to me improbable that as a comparative newcomer to the scene I could contribute much that would be of interest to members of the Society. My doubts were strengthened when I looked back through numbers of the Journal to see who had spoken to you in previous years and about what. I found that twelve distinguished authorities in the biological and physical sciences, as well as experts in cosmetics, had pretty well covered the field in a series of lectures of outstanding quality and breadth of learning. Contributions by Bullough on the rejuvenation of the skin, Polano on the effects of detergents, your Patron Lord Todd on the interface between organic chemistry and cosmetic science, Wilkinson on cosmetic function and public expectation and Ebling on sex hormones, to name only some, seemed to have left little for me to say.

However, your President is very persuasive, and when after a short discussion we parted, I found that I had in fact somehow agreed to undertake what was clearly a rather formidable task. It seemed to me on reflection that I ought to try to turn to advantage my limited direct experience with cosmetics, and put to you for consideration some points that, as a relative outsider, seemed to me to be worth discussing in relation to cosmetics in, say, the remaining quarter of this century.

The first difficulty I encountered was to define my subject. What are cosmetics? The very word itself is hedged with ambiguity. To the layman, it often seems to mean mainly decorative products such as lipsticks and mascara (from the Greek *kosmein,* adorn) but for cosmetic chemists the term embraces toiletries, and this wider definition now has a firm legal basis through the Cosmetic Products Directive (1) soon to be incorporated into United Kingdom law. However, that is not all because the definition in the Directive extends to products on the borderline with medicines. Lastly, it must be admitted that the very word 'cosmetic' in popular use can have a pejorative connotation, as when we speak of 'cosmetic changes' as merely patching up and calculated to deceive, although I am not for a moment suggesting that this applies to the description 'cosmetic chemist'! I hope you won't think me impertinent if I say that perhaps an effort should be made even at this late date to find a word that would define

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more clearly, and without ambiguity and possibly misleading overtones, the true nature and scope of your discipline. If none of the 163,000 words in the Shorter Oxford Dictionary are suitable perhaps the so-called dead languages could help out once again? In 1834 Faraday sought the help of Whewell, the Master of Trinity and a scientist and philologist of European reputation, in coining logically impecable names for the phenomena of electrochemistry which he had elucidated (2), and electrolysis, cathode, anion etc. still serve us well a century and a half later. You may think I am making too much of this, but words are powerful things and in my experience apparently trivial problems of nomenclature often reflect more substantial uncertainties and unresolved tensions lying beneath the surface. Perhaps at the same time, incidentally, you could think about 'chemist' in your title. I do not think it adequately defines responsibilities that now extend far into the fields of biology and physics.

What is the general outlook for the cosmetics industry, particularly in this country, in the next 25 years? In broad terms the prospects would appear to be reasonably good. The industry has not so far attracted the suspicious dislike that certain politicians show for the pharmaceutical industry. Cosmetics are not at present used as a major instrument of tax manipulation to anything like the same extent as are alcohol and tobacco. So far as I know, there are not even any proposals to nationalise the industry. But there is no lack of problems that will have to be identified, tackled and solved if the industry is to survive in the form we know.

The only way I know of forecasting the future is by extrapolating the past. Tonight, I want to suggest perhaps paradoxically that what we should try to extrapolate is the past not of this industry but of the food and pharmaceutical industries. As a matter of fact, I made a rather similar suggestion in this very room on 5 January, 1967, when you were discussing currents trends in toiletries legislation but as no one took much notice of what I said at the time I have no scruples in making my point again a decade later!

In a very short time by historical standards the cosmetics industry has been transformed by a rapid growth in the role that science plays in its affairs. It is bad luck, in a way, that this critical change in the internal environment of the industry has coincided in time with a quite remarkable growth in the amount of intervention—Newspeak (3) for interference—in the affairs of the industry by governments. Ten years ago the United Kingdom cosmetics industry operated in a singularly relaxed regulatory climate. There were the general provisions of the law but only a minimum of specific legislation. That era has gone. Consumer protection is bi-partisan policy and the excellent—indeed outstanding—safety record of the industry has in no way inhibited the politicians from moving towards the imposition of detailed regulation. It is no longer a question of whether the industry is going to be closely regulated, but how.

I believe, therefore, that there is something to be learned from the experience of the United Kingdom food and pharmaceutical industries, which have themselves in the last 25 years suffered a vast increase in regulation and control from outside. In fact, to someone like me who has worked in these industries it is really quite fascinating how history is repeating itself. It is hard to realise the formal control of the safety of pharmaceuticals was minimal before 1 January, 1964 when the Committee on Safety of Medicines was set up with Sir Derrick Dunlop, your 1971 Medallist, as chairman. This admirable and effective system, which depended entirely on the voluntary compliance and co-operation of the pharmaceutical industry, was swept away with the passing of Medicines Act 1968. The small, expert and highly regarded staff of the Committee have been replaced by a vast and growing bureaucracy. These developments have had an

immediate impact on an important class of cosmetic products as defined by the Cosmetic Products Directive that are also 'medicinal products' as defined by the Medicines Act. The trend is to judge and treat them more as medicinal products than as cosmetics in regard to safety, efficacy, quality and good manufacturing practice as well as labelling and advertising. I foresee, moreover, an increasing tendency to bring the generality of cosmetics within the same kind of regulatory framework, and here I think that it is extremely important for you all to be very much on the alert in the years ahead.

We live at a time when safety evaluation is a major growth industry worldwide. Large organisations have been established in order to carry out tests prescribed by an army of functionaries and their advisers. A comment by Dr Yale Gressel at the 1976 Cosmetic, Toiletry & Fragrance Association Scientific Conference seemed to me very much to the point: once there was only one kind of toxicology—the science of that name—but now we have several. *Consumer toxicology* is the art and science of maximising the impact of possibly adverse findings in the supposed interest of the general public and so ensuring an effective ban on any questioned compound or product on minimum or no evidence. The leaders in *media toxicology* are expert in generating headlines from a minimum of data. The successful *grant toxicologist* makes sure of a steady flow of funds to his laboratory from a grateful public by following a policy of positive results at all cost. *Political toxicologists* see 'safety' as a stepping stone to high office. *Legal toxicologists* thrive on the impossibility of proving a negative. It is not surprising that an increasing number of useful compounds have been banned or made politically unusable on grounds that owe more to emotion than science. I believe that it is the duty of the scientific community to stand up and be counted on this issue when a ban is threatened that is based on inadequate evidence, or on data obtained by inappropriate test procedures unrelated to ordinary conditions of use. The US National Cancer Institute has several hundred compounds on test for what is called their 'carcinogenic potential'. The extremely high levels of exposure used in this programme are based on the maximum tolerated dose of the compound being investigated, and are calculated to cause so much tissue damage at the cellular and sub-cellular levels that carcinogenic effects are elicited that might never occur in real life. There are scientists in industry as well qualified to generate, handle and interpret toxicological data as any in academic and official life, but all too often in the past they have seemed reluctant to express their doubts and criticisms in public. Last year, with some colleagues, I tried to interest the Society of Toxicology in initiating some public debate on what was going on: I failed. Your Society in particular has a special duty in regard to the relationship between risk and benefit. I urge you all to resist at every opportunity the allegation that there is no 'benefit' from the use of cosmetics. This is how the argument runs: some risk must remain even after the most exhaustive testing; benefit by definition = 0; therefore risk/benefit = infinity. You can put it another way: if the social acceptability of the products of an industry is defined as safety × benefit then if benefit = 0 the future of the industry is to say the least somewhat doubtful.

Don't be persuaded, either, that the products of the consumer protection industry are beyond question or reproach and not themselves in need of safety evaluation. In August 1973 an Oklahoma paediatrician reported to the newly established Consumer Products Safety Commission in Washington that there was a higher incidence of damaged chromosomes in ten persons who had used a spray adhesive than in twelve who hadn't. He had also seen two deformed children born to parents who had used the sprays during or shortly before the pregnancies. The Commission acted in a matter of days in a blaze

of nationwide publicity to 'persuade' manufacturers to stop production and then formally to ban these products. Later it was found that the original allegations were wholly without foundation and that these adhesive products were completely harmless and the ban was quietly withdrawn in January 1974. No publicity has been given by professional consumerists to the results of an enquiry conducted the following May by Hook and Healy of the New York State Department of Health and the Department of Paediatrics, Albany Medical College among medical genetic centres throughout the US (4). They found that the centres had received no less than 1100 enquiries as a result of widespread publicity in the media and that nine women had actually procured abortions, so terrified were they of giving birth to malformed babies. It is easy for us, as scientists, to underestimate the effect on the ordinary man or woman of scare headlines that can arise from the false identification of an environmental agent as toxic, whether these relate to cyclamates, aspirin, amaranth, hairdyes, saccharin or whatever. Perhaps the nine unfortunate women in Oklahoma were only the tip of an iceberg?

The efficacy—or rather the lack of it—of cosmetics is another favourite consumerist theme. As I have said, with products at the borderline between cosmetics and medicines we are moving towards a requirement to demonstrate efficacy by double blind clinical trials just as rigorous in design and meticulous in execution as with a potent therapeutic agent. There are already problems with trials that require the use of human volunteers, and these will increase. Prior demonstration of safety is tending to become more rigorous, and the withholding of therapy in a placebo group may conflict with the code of ethics for human experimentation enunciated in the Declaration of Helsinki (5). With the great majority of cosmetics, however, efficacy must lie in the eyes of the user and the beholder, but this will not prevent increasing demands by regulatory authorities for objective and statistically valid evidence in support of claims made for product classes traditionally promoted by harmless puffery alone. In this situation, it will be particularly important to insist on an interpretation of efficacy wide enough to take account of the imponderable product characteristics that determine consumer satisfaction or otherwise.

When the Directive was going through the Economic & Social Committee, suggestions were made that the interests of the consumer could only be adequately assured by a fully fledged system of product licensing. The French system of dossiers available for government inspection might be regarded as a step in that direction. I have described how product licensing has developed for pharmaceuticals. I do not see how the cosmetics industry as we know it could survive in that kind of strait-jacket, so be on your guard!

The first effective Act to regulate the food industry (Sale of Food & Drugs Act, now Food & Drugs Act) was passed as long ago as 1875 but reinforcement of the general provisions of the Act by compositional standards and lists of approved food additives did not start in earnest until the 1940s. It has taken half a century to establish a system of permitted lists for some 300 food additives and even now flavourings (the analogues of fragrances) have yet to be tackled. There are said to be 13 000 compounds in use in cosmetics (6). How long will it take to marshal these in the positive lists to which the authorities are apparently committed? The course of events in the food industry shows how limited, in reality, is the scope for speedy action. We must continuously remind Government of the facts of the situation, and especially perhaps the consumerists, of the stifling effect on initiative of a rigid system of permitted ingredients in an industry which lives by rapid change. I have discussed elsewhere (7) the minimum safeguards that the industry must seek to have built into the system. The record of the consumer representatives in debate on the Directive in the Economic & Social Committee and the

European Parliament, with their facile demands for instant positive lists, is unimpressive. Experience in the food industry in this regard is dispiriting. It is only too easy for an additive to be struck off the list on real or supposed grounds of danger. To get a new additive included in a permitted list is something else again. The time from first application to the coming into effect of regulations enabling a new compound actually to be used in manufacturing is usually to be measured in years rather than months. Somehow, some better system has got to be found for cosmetics ingredients. There is also the question of cost. I have had something to do recently with the funding of toxicological studies on six well-known food colourings in order to establish their safety in use by developing new, additional data demanded by the EEC Scientific Committee for Food. The cost of this work will be about £700 000 at 1976 prices and will take 5 years. What would the cost be of establishing the safety in use to modern toxicological standards of the 400 + colourings now used in cosmetics in the EEC? It is estimated that it will cost £2·5m to generate the extra toxicological data required for the 215 substances that have been proposed for positive listing as food flavourings. Who can guess what it would cost fully to evaluate the 13 000 cosmetic ingredients to which I have just referred? The CTFA have tackled the problem in a forthright way with their Cosmetic Ingredient Review programme in which independent experts will assess the safety in use of all the compounds (except fragrances) used in the industry and indicate where further toxicological data are required. I very much hope that some means will be found for the European industry to co-operate in this exercise, because otherwise we are going to dissipate money and scarce resources in duplicating their efforts when preparing our own positive lists.

A more encouraging lesson from the food industry is to be found in the field of government–industry relations. Over the years a system of informal and formal consultation at every stage of the legislative process has been built up. I hope that this tradition of collaboration rather than confrontation will prevail in the new field of cosmetics regulations. The signs so far are good. The Government sought the views of industry in the discussions in Brussels on the Directive, and industry is currently being consulted in the drafting of the necessary implementing legislation. Thus it has been possible at an early stage to suggest the inclusion of legislative features that the food industry have found by long experience to be valuable, for example enforcement through local authorities rather than by an FDA-like monolithic machine.

Should the industry go further and seek the establishment of an independent advisory body like the Food Standards Committee (a 'Cosmetic Standards Committee')? This Committee comprises three persons from the scientific field, three from the food industry and three generally representative of the public interest under an independent chairman (8). Together with the similarly structured Food Additives & Contaminants Committee it advises Ministers in the exercising of their regulation making powers under the Food & Drugs Act. You may think that a more formal but also more 'open' system incorporating an advisory committee of this kind could provide some protection should the industry ever have to negotiate in regulatory affairs in a more hostile political environment than we have at present. Our present good but informal relations with the authorities might not necessarily survive the coming to power of elements already active in politics in this country.

We can reasonably expect that non-tariff trade barriers will wither away within the Community but there is not much sign of this happening in the wider world scene. In 1962 a few major firms in the food industry got together to provide money to launch the

Codex Alimentarius Commission under the joint sponsorship of the World Health Organisation and the Food & Agriculture Organisation of the United Nations. The aim was the removal of non-tariff trade barriers by harmonisation of food standards worldwide. Fifteen years later many 'recommended international standards' have been elaborated, but I cannot say that the results in terms of freeing international trade have been commensurate with the time, money and effort expended. On the whole, I would advise the international cosmetics industry to seek some other procedure, perhaps with a much stronger industrial orientation, to solve their problems.

A word of warning from food industry experience relating to food additives may be timely. The Food & Drugs Act requires the technological *need* for an additive as well as its *safety* to be demonstrated. In addition, there is constant pressure to keep the permitted lists as short as possible and so restrict the actual number of colourings, for example, that are available for use. I hope that no one is going to try to apply these principles to positive lists of cosmetics ingredients, because I believe that this would not only discourage innovation but would in addition be inappropriate and perhaps harmful. Need should be left to market forces and, by spreading the total toxicological load, having more rather than fewer compounds could be advantageous in terms of safety rather than the reverse.

The only aspect of *quality* I want to discuss is product stability in relation to label expiry dating. Regulations under the Medicines Act require an expiry date to be shown when the shelf life is less than 3 years. Voluntary marking with a 'sell by' or 'use by' date is now quite common with perishable foods, and a 'best before' date will become mandatory under the draft EEC Food Labelling Directive. The requirement under the Cosmetic Products Directive for an expiry date on products with a stability of less than three years is thus nothing new, and should not cause too much trouble so long as it is reasonably interpreted in the UK counterpart regulations.

In the field of *labelling* mandatory declaration of ingredients of cosmetics is, I know, an issue that raises strong feelings. Ingredient declaration was violently opposed by the UK proprietary medicines industry in 1941 and by the UK food industry from 1945 onwards, but both industries have learned to live with it. With these precedents, and consumerist pressure, perhaps it will come here one day as it has in the US. I personally doubt whether it would prove any more disastrous for the cosmetics industry than it has for pharmaceuticals and food. I would myself trade mandatory compositional standards for ingredient labelling any day.

As for *advertising*, I want only to mention that for 40 years the Proprietary Association of Great Britain has been vetting members' advertisements for proprietary medicines. The strength and reputation of this voluntary system has stood the industry in good stead and it looks as if it will gain official recognition by formal association with the regulations on advertising under the Medicines Act that are now being drafted. Thus the industry will retain a substantial measure of independence in this important matter. I am not necessarily advocating a system of this kind for operation by the Toilet Preparations Federation: I just draw attention to its success in a related sector of industry.

My last problem is animal experimentation. Criticism of the use of animals in safety and efficacy studies has swung away from pharmaceuticals and towards allegedly non-essential items, including food additives and especially cosmetics, which we must admit has become an emotive word in this context. Whatever one's personal feelings are about the use of animals for any experimental purpose, I see no way in which a manufacturer

can fulfil his legal obligation to market safe products without some recourse to animal testing. I do, however, strongly advocate that alternative *in vitro* methods should be actively sought, that the industry should be seen to be interested in moving in this direction and that *Homo sapiens* should be the test species wherever possible. Much, too, can be done by modified test procedures to minimise the discomfort felt by the test animals (9). There is pressure from Continental sources, for example in the draft Dangerous Substances Directive, to impose mandatory test protocols that would include the toxicologically questionable but bureaucratically popular LD50. This trend must be firmly resisted. I think that the industry will have to be ready, more than in the past, to justify its record in regard to animal experimentation to public opinion.

In summary, I see an increasingly important role for the cosmetic scientist in the remaining quarter of this century, and no less for your Society as the guardian of scholarly standards and professional excellence within the industry. All the trends I have been talking about can only mean more scientific activity. Some of this activity—perhaps too much—will be unproductive and defensive. Demands for higher standards of safety and efficacy have already added a new dimension to the responsibilities of the scientist in the industry, and much creative work will be undertaken in dealing with the problems associated with these concepts. On the commercial side, I think that the industry as a whole has adapted successfully to externally imposed change. There are still a few dinosaurs around who are unwilling to admit that the Cretaceous epoch came to an end some time ago, but the recently strengthened Toilet Preparations Federation is doing a splendid job in spreading enlightenment. (Are there any other trade associations where 80% of the senior staff are scientists?) It is essential that the management of member companies should be, and remain, active and fully involved in the affairs of the Federation, and that they should allow—and indeed insist—that their scientists also contribute their skills. A strong trade association working with the wholehearted support of its members will continue to be a pre-requisite for survival. The dialogue that has been established with government at the national and Community levels will prosper only if the industry representatives have the right status, and the high levels of professional attainment, that will enable them to negotiate as equals. It is up to the industry to show self-confidence in its relations with government and with the consumer protection industry. Provided that we all respond adequately to the challenges of the time that I have touched on, and are ready to learn from the experience of other industries which have already passed through the fires of change, I am reasonably confident that although the cosmetics industry will certainly itself have undergone great changes, it will still in the year 2000 be recognisably the same kind of animal as we now know and, one would hope, still progressive, innovative, varied and profitable.

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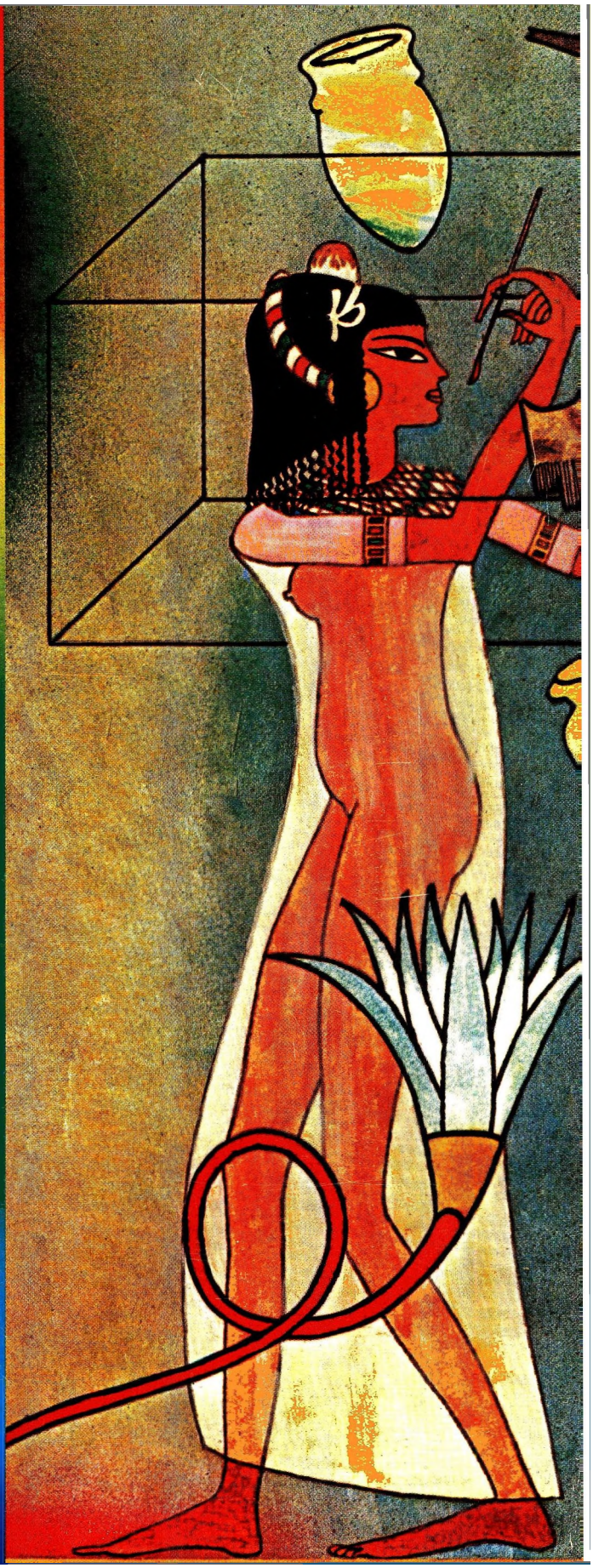
Published on behalf of the Society of Cosmetic Chemists of Great Britain by Blackwell Scientific Publications Ltd, Osney Mead, Oxford OX2 0EL. Printed in Great Britain by Burgess & Son (Abingdon) Ltd, Station Road, Abingdon, Oxfordshire.

Cosmetic Colorants



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