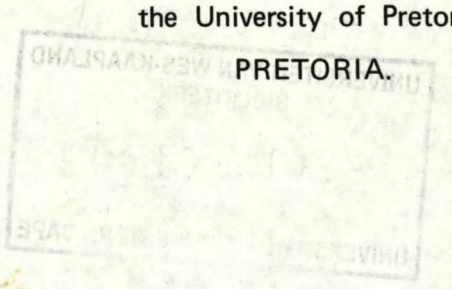
MANDIBULO-FACIAL DYSOSTOSIS – AN INVESTIGATION OF THE CRANIO-FACIAL AND ORAL MANIFESTATIONS IN SOUTH AFRICAN BANTU.

by

JOACHIM ERNST SEELIGER

BSc (UOFS) BDS (RAND)

Thesis presented to comply with
the requirements for the Degree of
MDent
in the Faculty of Dentistry of
the University of Pretoria,
PRETORIA.



1975

SUMMARY

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by

JOACHIM ERNST SEELIGER

Department of Maxillo-Facial and Oral Surgery,
University of Pretoria.

Promotor: Professor D.P. Knobel
Head: Department of Anatomy,
University of Pretoria.
Degree: MDent

PART ONE

The subject, an adult bantu male with most of the features of the classical syndrome, is subjected to a physical investigation with the emphasis on the cranio-facial and oral manifestations. The clinical appearance of the facies and head is discussed and the findings correlated with those of the accepted syndrome. Special attention is paid to the oral and dental manifestations and measurements are recorded and compared. A röntgenographic examination is performed on the cranium, facial bones and the jaws. Utilising the lateral skull radiograph (cephalogram), a cephalometric analysis is done of the skull and jaws to determine the development that has occurred.

PART TWO

The syndrome, known as Mandibulo-Facial Dysostosis (or as the Berry-Treacher Collins of Franceschetti-Zwahlen-Klein Syndrome), is described and discussed in detail under following headings:

- historical background
- etiology
- pathogenesis
- clinical features
- differential diagnosis and
- classification.

The relevant theories are critically examined and compared. Certain deductions are made and some questions raised by the writer.

A table has been prepared, listing most of the features found in the various syndromes which should be considered in the differential diagnosis.

PART THREE

Finally, the most important clinical and radiographical findings of the investigation are compared to those of the three other cases of the syndrome reported as occurring in South African bantu and the significant differences discussed. A new approach to the CLASSIFICATION is suggested.

SAMEVATTING

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deur

JOACHIM ERNST SEELIGER

Departement Kaak-, Gesigs- en Mondchirurgie,
Universiteit van Pretoria.

Promotor: Professor D.P. Knobel
Hoof: Departement Anatomie,
Universiteit van Pretoria.
Graad: MDent

DEEL EEN

Die pasiënt, 'n volwasse Bantoeman wat meeste van die tipiese tekens van die sindroom toon, word aan 'n fisiese ondersoek blootgestel. Die kranio-fasiale manifestasies, asook die mondverskynsels, geniet spesiale aandag. Die kliniese voorkoms van die kop en die gesig word bespreek en die bevindinge met die tipiese tekens van die sindroom gekorreleer. Spesiale aandag word aan die tand- en mondverskynsels bestee en die bevindinge word aangeteken en met ander vergelyk. 'n Röntgenografiese ondersoek word op die kranium, gesigsbene en die kake uitgevoer. Die laterale-skedelopname (kefalogram) word gebruik om 'n kefalometriese ontleding van die skedel en kake te doen om die graad van ontwikkeling van die kake te bepaal.

DEEL TWEE

Die sindroom, bekend as Mandibulo-fasiale disostose (of as die Berry-Treacher Collins – of Franceschetti-Zwahlen-Klein-sindroom) word beskryf en bespreek onder die volgende hoofde:

- geskiedkundige agtergrond
- etiologie
- patogenese
- kliniese beeld
- differensiële diagnose en
- klassifikasie.

Die betrokke teorieë word krities ondersoek en vergelyk. Sekere gevolgtrekkings word gemaak en vrae word deur die outeur gestel. Meeste van die kenmerke wat in aanmerking moet kom by die maak van die differensiële diagnose, word in tabel-vorm uiteengesit.

DEEL DRIE

Ten slotte, word die belangrikste kliniese en röntgenologiese bevindinge met dié van die ander gevalle van die sindroom, wat onder Suid-Afrikaanse Bantoes voorgekom het, vergelyk en die betekenisvolle verskille bespreek.

'n Nuwe benadering tot die KLASSIFIKASIE van die sindroom word voorgestel.

This work is dedicated to

PROFESSOR P.C. SNIJMAN

Director of the Oral and Dental Hospital and Dean of the Faculty of Dentistry of the University of Pretoria, in appreciation of the advice and encouragement afforded to me.

It is also dedicated to my wife and family for their sacrifices, patience and love during the writing of this thesis.

ACKNOWLEDGEMENTS

SINCERE GRATITUDE IS DUE TO:

The Creator, who is all things to all men.

My parents, for their loving guidance.

My wife, Peggy, and my children, for their love and patience.

My promotor, Professor D.P. Knobel, Head of the Department of Anatomy, Faculty of Medicine of the University of Pretoria, for his invaluable advice and encouragement. Although under great pressure of work at all times, he never hesitated to make himself available for consultation. His enthusiasm and wisdom were inexhaustible sources of inspiration.

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Drs. C. Masureik and H. Vogel for referring the patient to me.

Miss H.E. Solz, for typing the original manuscript so patiently and efficiently.

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Hennie's Secretarial Services for printing and binding the final manuscript.

All those who inadvertently have been omitted from this list.

PRETORIA,
SOUTH AFRICA.
JUNE 1975.

J.E. SEELIGER.

TABLE OF CONTENTS

"BUT FOR THE GRACE OF GOD THERE GO I"

— Adapted from an exclamation by
John Bradford (1510—1555)

PREFACE

On the 24th April 1974, an adult Bantu male patient was referred to the Oral and Dental Hospital of the Faculty of Dentistry of the University of Pretoria from the Pietersburg (Tvl.) Hospital for treatment in the department of Maxillo-Facial and Oral Surgery.

As a result of his being assaulted, he had sustained bilateral fractures of the mandible.

On examination, it was noticed at once that he had an abnormal "fish-like" facial form which was unrelated to his injuries.

He was referred for röntgenological examination at which time he was first seen by the writer.

The facial appearance was unmistakably that of a TREACHER COLLINS SYNDROME, also known as the BERRY-TREACHER COLLINS SYNDROME or FRANCESCHETTI-ZWAHLEN-KLEIN SYNDROME or, more simply as MANDIBULO-FACIAL DYSOSTOSIS (MFD).

A thorough search of the literature available through the Merensky Library of the University of Pretoria revealed that, although approximately 300 cases of the syndrome had been reported on over the previous 100 years by authors around the world, *very few* had been described in the Negroid races.

Further investigation revealed that, apart from LEOPOLD, MAHONEY AND PRICE[3] (1945) and FERNANDEZ AND RONIS[1] (1964) who reported on American negroes, ONLY WAYBURNE[5] (1953) AND GLYN JONES[2] (1968) had reported on the syndrome in Southern African Bantu.

Both WAYBURNE and GLYN JONES described the syndrome in infants which did not survive for more than a few weeks.

As far as can be ascertained, the case to be presented (along with those of WAYBURNE and GLYN JONES) is the *only* one featuring an adult Southern African Bantu with the "full-blown" (or "complete") syndrome to be recorded to date.

The incidence of the syndrome amongst the Bantu of Southern Africa is almost impossible to ascertain but it is certain to be extremely low.

In an attempt to establish the existence of further cases of the syndrome in the Bantu, a letter of enquiry, along with a photostat copy of a full-frontal photograph of the subject, was sent to 74 Mission hospitals scattered throughout the provinces and homelands of the Republic.

NOT ONE additional case has been discovered at the time of writing!

From the replies received from the superintendents of the hospitals, it would appear that the majority have *some* knowledge of the syndrome. It is obvious that they have not however, recognised any of these patients at their hospitals.

It is therefore safe to conclude that, amongst the Southern African Bantu, the incidence is extremely low.

It is also very apparent from the literature available, that little attention has been paid to the oral and dental manifestations of the syndrome. This is not surprising when it is realised that the majority of articles have come from the pens of plastic surgeons, radiologists, paediatricians, oto-laryngologists and ophthalmic surgeons.
Very few have been written by oral surgeons, orthodontists or dentists.

The literature abounds with hypotheses as to the etiology and pathogenesis of the syndrome in addition to greatly conflicting views as to the classification of the signs and symptoms, differential diagnosis and final diagnosis.

Articles have been published under the heading of MFD when the syndrome described has not borne a remote resemblance to the true syndrome! (4)

The OBJECT of this thesis is, therefore, two-fold, viz.-

1. to describe, in detail, the cranio-facial and oral manifestations as observed in the subject and as reported in the other cases of syndrome in Southern African Bantu.

AND

2. to attempt to correlate and, possibly, elucidate the facts concerning the etiology, pathogeneses and differential diagnosis of Mandibulo-Facial Dysostosis.

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2. GLYN JONES, R. (1968). The Central Afr. J. of Med. 14, 193–200.

3. LEOPOLD, I.H. et al. (1945). Arch. Ophthal. 34, 210–214.

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PART ONE

THE SUBJECT

Name	:	J.S.
Home	:	c/o RIPAVI, LETABA, EASTERN TRANSVAAL
Sex	:	Male
Age	:	34 years
Tribe	:	SHANGAAN
Marital state	:	Unmarried
Occupation	:	labourer
Family history	:	not available
Intelligence	:	normal

EXAMINATION

General Physical

Build	:	aesthetic type, slim, "wiry"
Condition	:	well-nourished
Height	:	1,72 metres
Mass	:	62,7 kg
Blood pressure (O.E.)	:	$\frac{128}{82}$ mm Hg
Pulse	:	88/minute
Respiration rate	:	$\pm$ 20/minute
Thorax	:	well-developed, muscular
Arms	:	well-developed
Legs	:	muscular, but thin
Hair distribution	:	pronounced hairiness of legs, otherwise normal
Fingers and toes	:	normal in all respects
Face	:	"fish-like", with typical features of the syndrome
Skin of face	:	fine texture, normal
Hair distribution on face and head	:	sparse: the hair in the "sideburn" area was very fine. There was no obvious linguiform extension of the hairline, but hair follicles were undoubtedly present. Apart from a thin moustache and a scanty beard, the hair appeared to have been shaved from the head shortly before the patient was examined, (probably by the hospital staff).

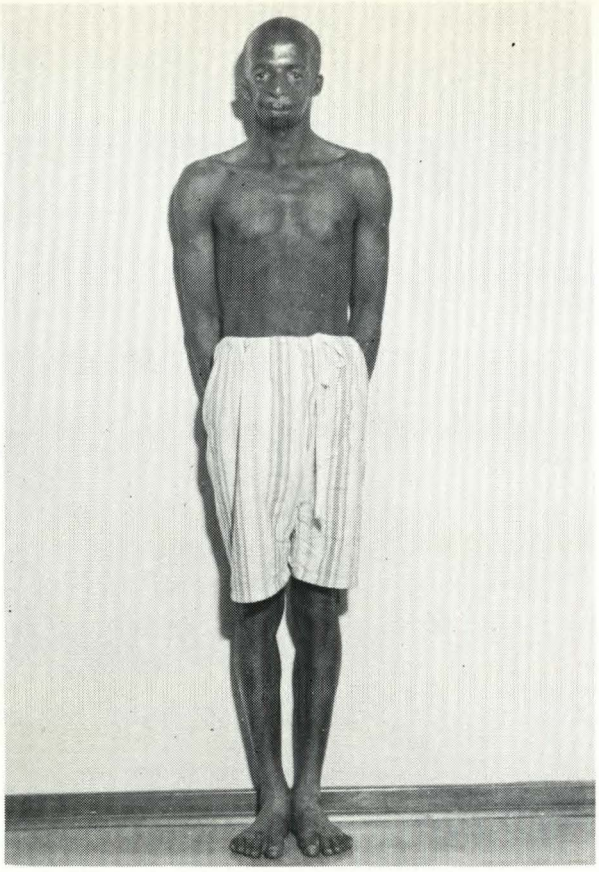

FIG 1 Full-length view of the subject

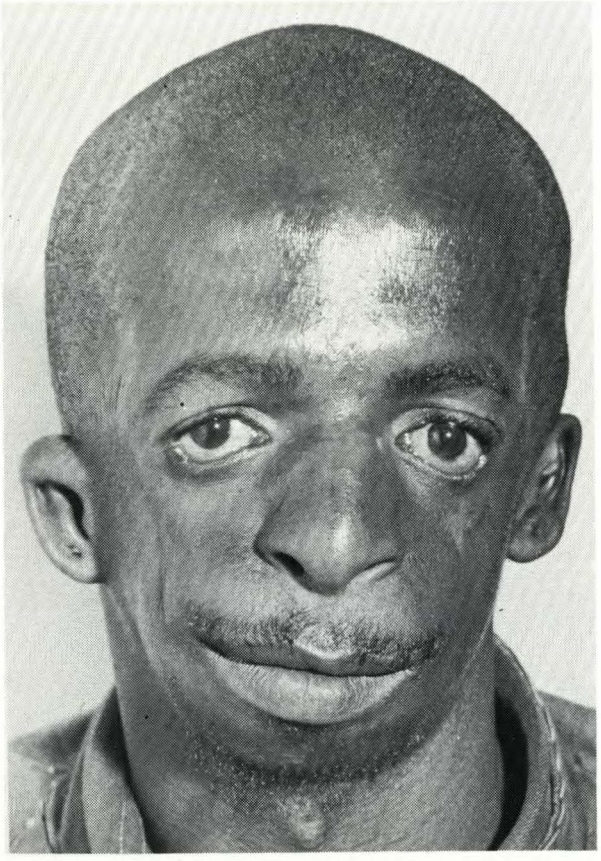

FIG 2 Frontal view of the face

EYES

The eyes exhibited the following features of the syndrome:

1. **Antimongoloid obliquity**

   This was pronounced, as can be seen on the frontal view of the face. (Fig. 2)

2. **Hypertelorism**

   At first glance, this appears to be present, but it is only a pseudo-hypertelorism as the measurements show – distance from inner canthus

to inner canthus	=	3,5 cm
distance from outer canthus to outer canthus	=	9,0 cm
inter-pupillary distance	=	7,0 cm

   The *normal* superior limits in adults are: (Jöhr[2] 1953)

distance between inner angles (canthus) of eye	=	3,7 cm
distance between outer angles	=	9,0 cm

3. **Size of eyeball**

   Clinically, the size of the eye appears to be normal. The small face accentuates the size of the eye and gives the impression of macrophthalmos.

   There is certainly no microphthalmos present.

4. **Coloboma**

   There is a typical coloboma, i.e. notching of the outer portions of the lid, forming a rounded lateral depression ending in a sharp notch, present on both *upper* eyelids.

   The colobomas bear fine hairs, similar to eyelashes. There is no lower lid coloboma. (Figs. 5 and 6)

5. **Eyelashes**

On the upper lids, a *double* row of eyelashes are seen, whilst on the lower lids, the lashes are *absent* on the medial 2/3.

On the outer 1/3, where the lashes are present, they comprise a single, sparse row of hairs.

6. **Lacrimal Canal**

No punctum lacrymalia could be seen in either upper or lower lids.

It is possible, then, that the lacrimal canal exhibits atresia.

7. **Musculis Orbicularis Oculi**

This muscle was found on palpation to be bilaterally hypoplastic in the lower half.

8. **Infra-orbital Bony Margin**

This margin was elongated and thin in a lateral and inferior direction, (probably due to malar bone hypoplasia).

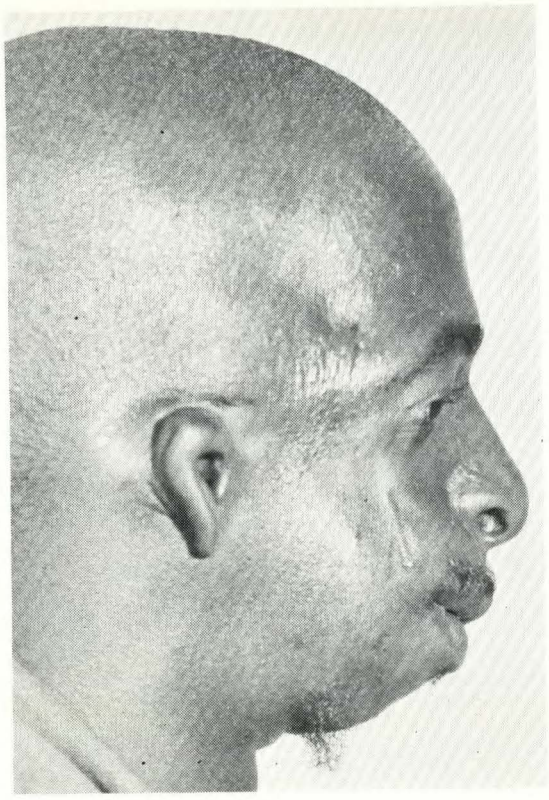

FIG 3 Right profile view

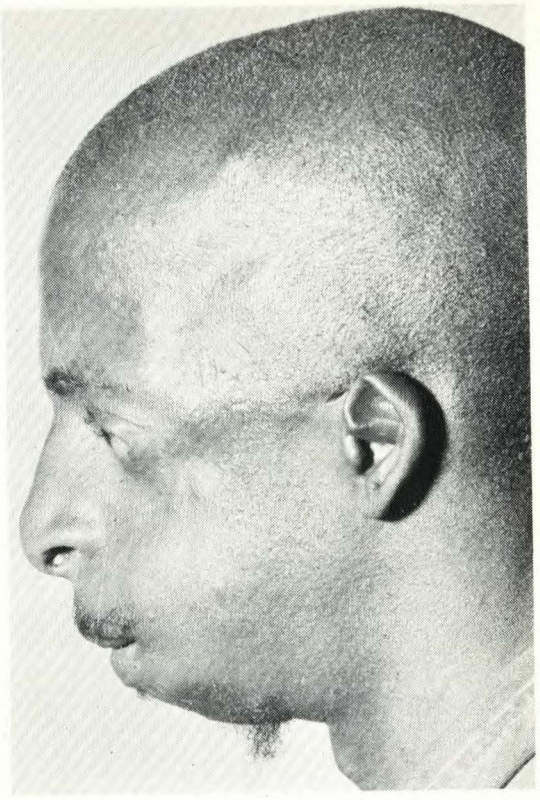

FIG 4 Left profile view

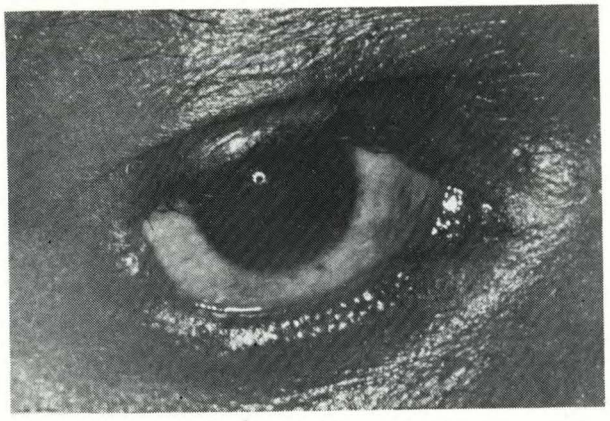

FIG 5 Right eye

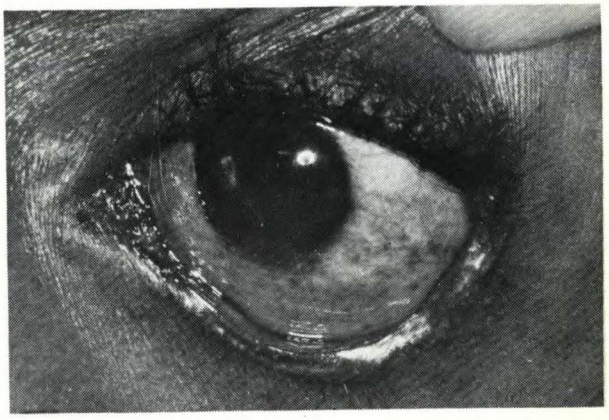

FIG 6 Left eye

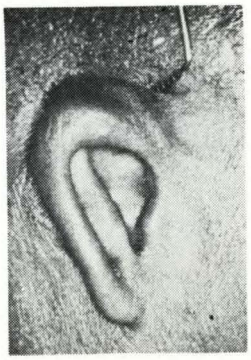

FIG 7 Right ear

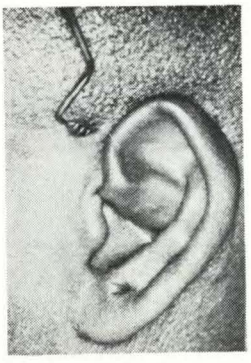

FIG 8 Left ear

EARS

1. EXTERNAL EAR MALFORMATIONS

(a) Both external ears are abnormal, but the right ear is more deformed than the left. It is low-set and angulated down, while the left ear is almost normal in position and form. (Fig. 8)

NORMAL ADULT EAR

(After STREETER[3] (1953)

Unshaded parts are derived from the *mandibular* side of the First Branchial Cleft

Shaded parts are derived from the hyoid side of the cleft.

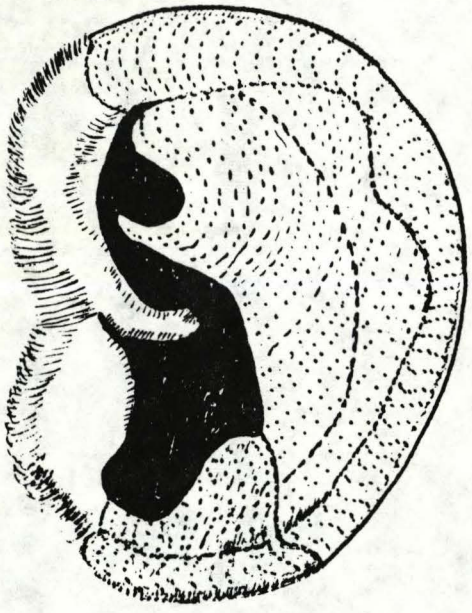

FIG 9

The deficiencies in the right ear correspond to those parts normally derived from the mandibular side of the First Branchial Cleft i.e. the anterior crus of the helix margin and the tragus. (Fig. 7)

Those parts which are *not* quite so deficient, the parts contributed by the hyoid arch viz the helix, anti-helix, scapha, the antitragus and the lobule, are more or less in evidence.

(b) the External Auditory Canal is narrowed bilaterally, but more so on the right side.

(c) there are no preauricular tissue tags, or appendages to be seen.

(d) Bilateral blind fistulae (or sinuses); 1 cm deep, are present just anterior and inferior to the *helix rim.* (Figs 7 and 8)

2. MIDDLE EAR

As there is a bilateral mixed hearing loss (combined 85% – see Audiogram) of which the conductive component is much larger than the sensory-neural component, it may be assumed that middle ear deficiencies are present.

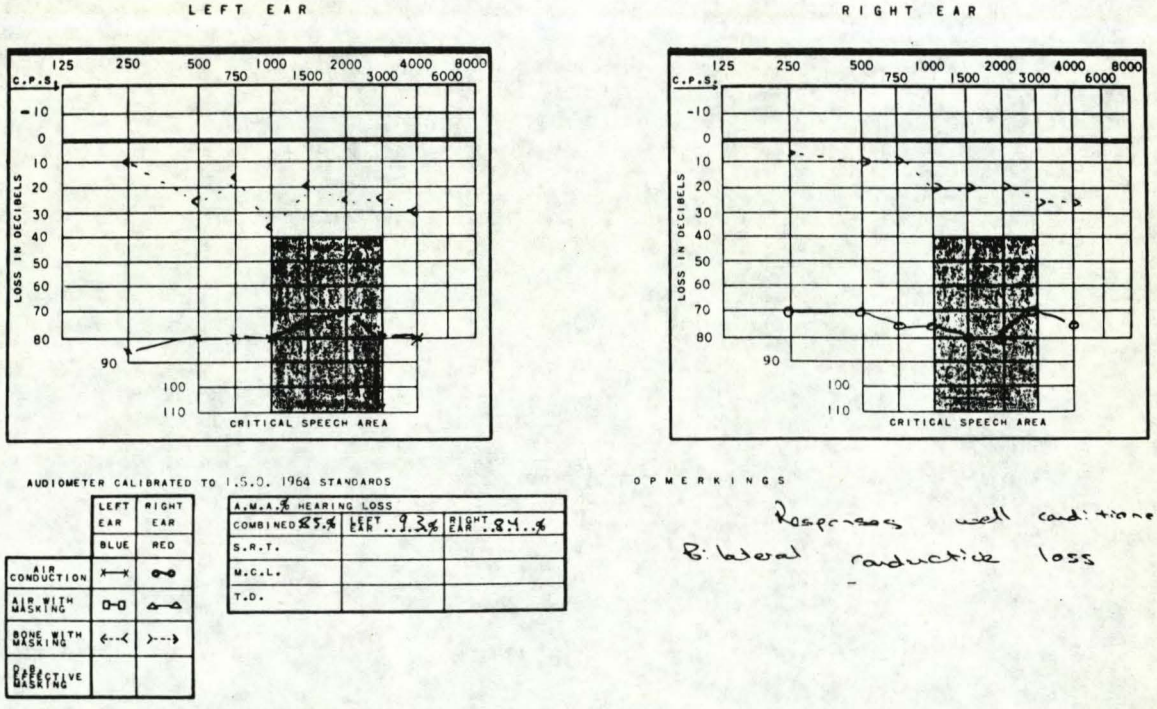

FIG 10 The Audiogram

NOSE

The nose appears *large* (due to hypoplasia of the malar bones and mandibula). (Fig. 2)

There is a distinct deviation to the right.

The nostrils are large and there is no partial atresia of the nares.

The fronto-nasal angle is not pronounced.

On radiological examination, a metallic foreign body was seen anterior to the nasal bones (? a buried pin, folk-medicine or trauma). (Fig. 24)

THE MOUTH AND LIPS

Macrostomia is present; the distance from the angle to angle, with mouth closed, is *6,0 cm.*

Fusion of the lips is bilaterally complete.

Facial clefts, in a very incomplete form, are present. Two very shallow grooves run on the right side of the face, diagonally and inferiorly.

Both start from points approximately 3 cm from the outer canthus of the eye and run for a distance of 2 cm and 4 cm respectively.

The inferior groove ends approximately 1,5 cm from the angle of the mouth, while the superior one peters out on the cheek.

THE ORAL CAVITY

THE TONGUE

The shape is normal; the size is large; the mobility is good, and the motor nerve supply is normal.

THE PALATE

The mucosa has a coarse texture with black pigmentation present in the attached gingiva. This pigmentation is common in the negroid races.

The rugae are coarse, with two enlarged rugae, situated on either side of the midline of the palate and 1,5 cm from the palatal surface of the central incisor teeth.

There is *NO* sign of clefts of the bony or soft palate.

THE UVULA

There is a well-demonstrated median groove which has resulted in a BIFID uvula. (Fig. 15)

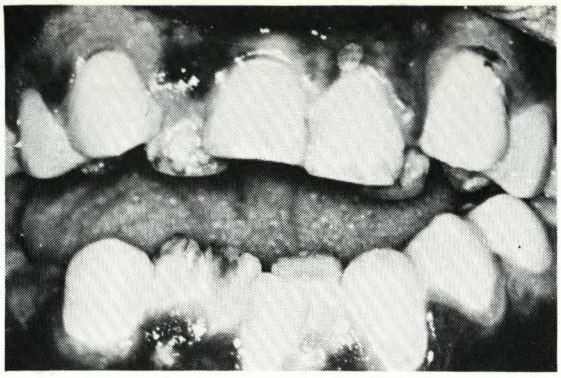

FIG 11 View of anterior teeth showing the open bite

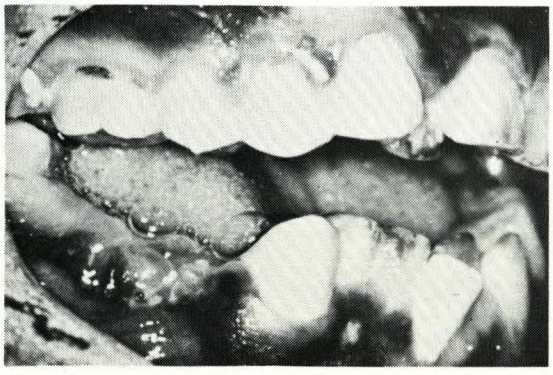

FIG 12 The bite on the right side

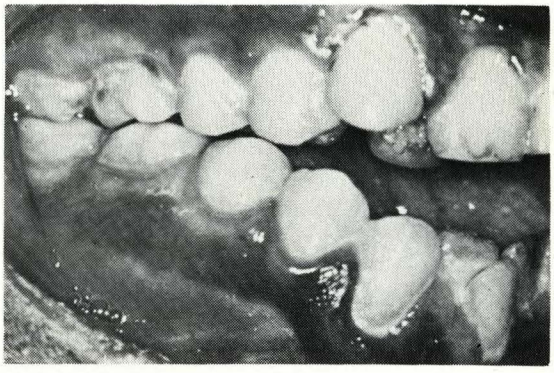

FIG 13 The bite on the left side

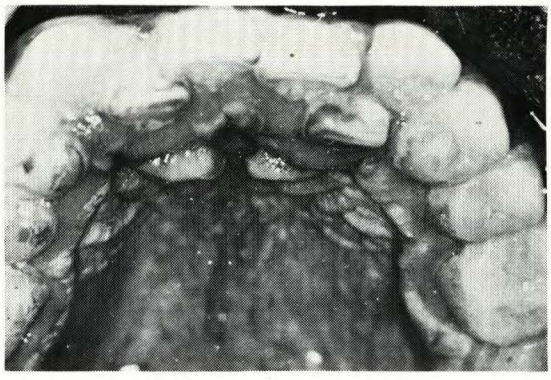

FIG 14 The palatal rugae

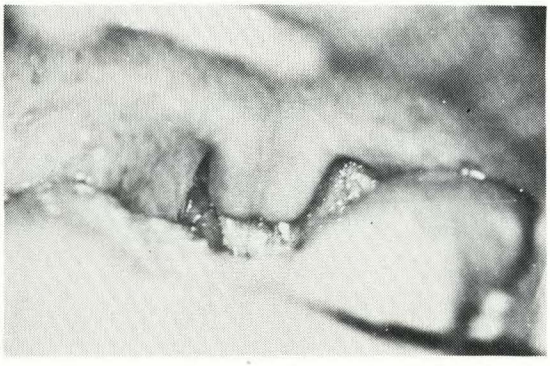

FIG 15 The uvula

THE TEETH

The teeth present on clinical examination are:-

87654321	12345678
87 321	1234567

The teeth extracted (as part of the treatment in the Department of Oral Surgery) are:-

654 | 6 is to be extracted later)

ENAMEL

The colour of the enamel is yellow, the texture is smooth and there is no sign of hypoplasia.

SHAPE AND ANATOMY OF TEETH

Normal in all respects.

OCCLUSION

An anterior open bite is present with an average intercuspal measurement of *7,0 mm.*

ANGLE CLASSIFICATION

Left side: Class I with a slight cross-bite. The 36 lies in slight linguoversion and does not articulate with the 25 or the mesial fossa of the 26.

Right side: There is almost a Class I present with a slight distal "drift" of the 47 (probably due to the fracture of the mandible).

OCCLUSAL CONTACTS

Left side

There are "normal" contacts between the 26 and the 36 as well as between the 27 and 37. There is an over eruption of the 28 due, probably, to there being no opposing 38.

There is contact between the 28 and the lower gingiva.

The palatal cusp of the 25 contacts the medial aspect of the buccal cusp of the 35.

There are no other tooth contacts on the left side.

Right side

There are "normal" contacts between the 17 and the 47, as well as the 18 and 48.

There are no other contacts due to the extraction of the 44, 45 and 46.

THE DENTAL ARCHES

SHAPE

Both the upper and lower arches appear squarish in shape.

INTERDENTAL MEASUREMENTS

In the *upper* arch, the minimum distance between the palatal surfaces of

the first premolars	is 2,8 cm
the second premolars	is 3,4 cm
the first molars	is 3,6 cm
the second molars	is 4,2 cm
the third molars	is 4,7 cm

In the lower arch, the minimum distance between the lingual surfaces of the second molars is 4,5 cm.

(Because the 44,45 and 46 have been extracted, it is not possible to measure the other interdental distances).

DEPTH OF THE PALATAL VAULT

A ruler was laid across the occlusal surfaces of the upper two first and then the two third molar teeth and the distance measured from the lower edge of the ruler to the deepest part of the bony palate.

The measurement recorded was 2,0 cm in both instances.

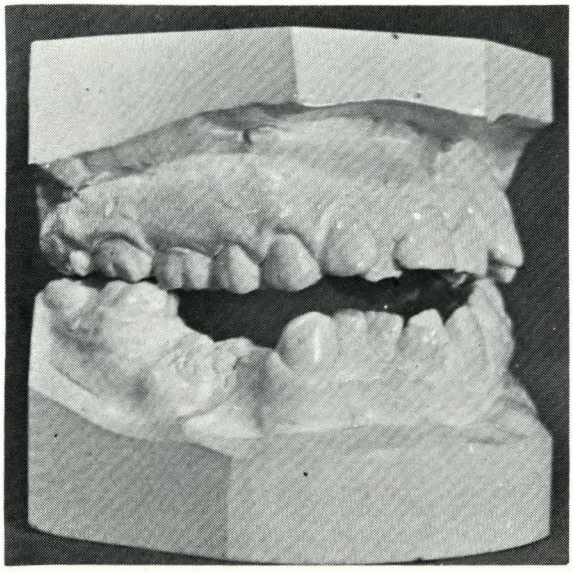

FIG 16 The Occlusion on the Right
Note the Anterior Open bite

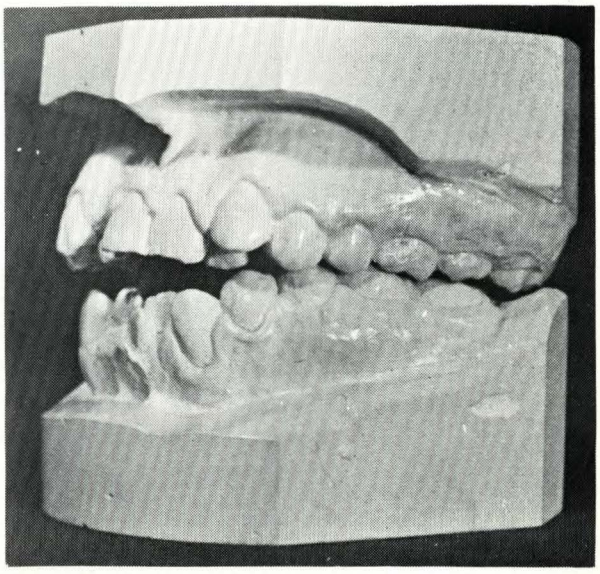

FIG 17 The Occlusion on the Left

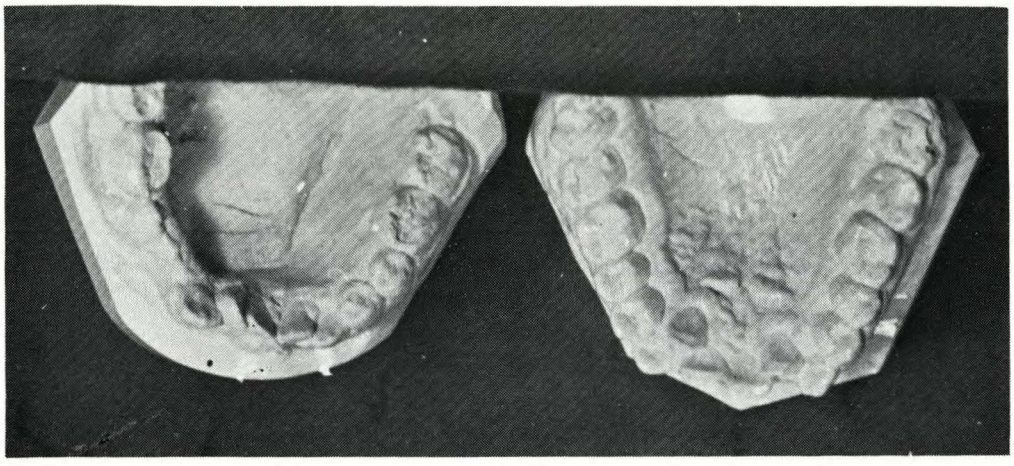

FIG 18 The Palate and the Floor of the Mouth

PATHOLOGY

PULPAL PATHOLOGY

There is evidence of pulpal calcifications in the pulp chambers of 26, 27 and 36.

The pulp chambers of the maxillary molar teeth in particular, and some mandibular molar teeth in general, exhibit smaller-than-normal pulp chambers and secondary dentine formation.

Abnormally large pulp chambers are observed in the crowns of the maxillary incisors and canines.

ROOT PATHOLOGY

Evidence of hypercementosis is seen about the roots of the 14, 15, 25, 33, 34, 35, 36, 43, 47 and 48.

The 14, 15, 24 and 25 have two roots and two root canals each.

CARIES

The incidence of caries is relatively *LOW*. Apart from occlusal caries of the 36, there is only distal interproximal caries of 43.

There is no sign of other interproximal caries.

ATTRITION

The maxillary central incisor teeth exhibit (rather unexpectedly, in view of the anterior open bite which precludes intercuspal contact) flattened incisal edges and facets, indicating that abrasion has taken place at some time or another. There is *NO* attrition of the lower anterior teeth, due to the anterior open bite.

PERSONAL NOTE

It is possible that, at some time or other, the subject had a habit of biting on or chewing a hard object (such as a stick).

The upper lateral incisor teeth show no such abrasion, possibly because, being in palatoversion, they are protected from contacts with abrasive objects.

The maxillary molars exhibit a general rounding-off of the palatal edge of the occlusal surface, which is not so marked in the premolars.

Facets and areas of abrasion can be seen on the buccal edges of the occlusal surfaces of the mandibular molars. They are not noticeable on the premolars or anterior teeth.

The attrition is most probably due to the diet which usually consists of mealie-meal (maizemeal), often with grit from the stone grinding pots, or even sand, which is added to "improve" the consistency!

THE TEMPORO-MANDIBULAR JOINT

CLINICAL FINDINGS

There are *NO* signs of either acute or chronic dislocation on either side. There are, however, definite signs of excessive mobility on both sides. Although the condyle heads cannot be palpated via the external auditory canals, they can be seen moving under the soft tissues during mastication. They are especially noticeable during lateral excursions of the mandible.

There is no "clicking" upon movement in either joint, but there is a slight "grating" feeling, on palpation, in the right joint.

There is a slight deviation of the centre-line of the mandible. On opening the jaws, it is to the right and, on closing, to the left.

There is *NO* anterior displacement of the joint in the closed position. (Fig. 29)

CONCLUSION

In contradistinction to the cases of GLYN JONES[1] (1968) (D.N. and E.D.) where there was a marked limitation of movement of both joints, the case J.S. exhibits a pronounced *MOBILITY.*

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ODONTOMETRY

OBJECT

The object of this procedure was to establish, by measurement of the tooth images on the radiograph and comparison of the findings with those of other investigators, whether or not the teeth of the subject are normal or abnormal as regards crown size and height, tooth length and root length.

Should the findings fall within the bounds of normality, then one should be able to eliminate from the differential diagnosis such conditions as

OCULODENTODIGITAL DYSPLASIA (WEYERS' SYNDROME),
OCULOMANDIBULO DYSCEPHALY (HALLERMANN-STREIFF SYNDROME),
CONGENITAL MANDIBULAR DYSOSTOSIS WITH PEROMELIA
AND THE
"BIRD-HEADED" DWARF SYNDROME

in which dental anomalies frequently occur.

MATERIALS AND METHODS

Alginate impressions were taken of both jaws and stone-plaster models cast for study purposes.

The teeth on the model were measured with sharply-pointed dividers and the measurements recorded in millimetres.

Both the mesio-distal lengths (M-D) and the bucco-lingual widths (B-L) were obtained in this way.

A full-mouth intra-oral radiographic examination was performed, utilising the Parallel (or Long-cone) technique.

The 18 radiographs were mounted on the usual mounting card.

Using the same pointed dividers, the tooth length (TH), the crown height (CH) and the root length (RL) were measured and recorded in millimetres.

With the Parallel technique, the error due to distortion and enlargement (or magnification) of the image was kept to a minimum.

(The writer carried out a simple experiment to compare the accuracy of measuring the anatomical size of extracted teeth and their radiographic images, using the Parallel technique, and could find *no* measurable variation).

RESULTS

The results obtained were tabulated and the mean values compared to the findings of some investigators to determine whether or not the subject's teeth were normal within reasonable limits. (SEE TABLES)

TABLE 1

ANTERIOR TEETH OF SUBJECT

MAXILLARY TEETH					MANDIBULAR TEETH				
Tooth		21	11	Mean	Tooth		31	41	Mean
	Measure-ment	mm	mm	mm		Measure-ment	mm	mm	mm
	M-D	9,0	10,0	9,5		M-D	6,0	6,0	6,0
	B-L	6,0	6,5	6,25		B-L	–	7,0	7,0
	CH	9,0	9,0	9,0		CH	7,0	7,0	7,0
	TH	26,0	26,0	26,0		TH	21,5	21,0	21,25
	RL	17,0	17,0	17,0		RL	14,5	14,0	14,25
		22	12				32	42	
	M-D	7,0	8,0	7,5		M-D	7,0	7,0	7,0
	B-L	8,0	8,0	8,0		B-L	6,0	6,5	6,25
	CH	9,0	9,0	9,0		CH	7,0	7,0	7,0
	TH	26,0	26,0	26,0		TH	22,0	22,0	22,0
	RL	17,0	17,0	17,0		RL	15,0	15,0	15,0
		23	13				33	43	
	M-D	9,0	9,0	9,0		M-D	8,0	8,0	8,0
	B-L	8,0	8,0	8,0		B-L	8,0	9,0	8,5
	CH	10,0	10,0	10,0		CH	10,0	10,0	10,0
	TH	30,0	29,5	29,75		TH	27,5	28,0	27,75
	RL	20,0	19,5	19,75		RL	17,5	18,0	17,75

TABLE 2

COMPARISON OF DIMENSIONS OF ANTERIOR TEETH OF SUBJECT WITH FINDINGS OF OTHER INVESTIGATORS

	MAXILLARY TEETH				MANDIBULAR TEETH			
First Incisor	Dimension in mm	Bjorndal[2] 1974	Subject 1974	G V Black[3] 1902	Dimension in mm	Bjorndal[2] 1974	Subject 1974	G V Black[3] 1902
	M-D	9,0	9,5	9,0	M-D	5,7	6,0	5,4
	B-L	7,4	6,5	7,0	B-L	5,9	7,0	6,0
	CH	11,2	9,0	10,0	CH	9,7	9,0	8,8
	TH	23,7	26,0	22,5	TH	21,8	21,0	20,7
	RL	12,5	17,0	12,0	RL	12,8	12,0	11,8
Second Incisor								
	M-D	6,9	7,8	6,4	M-D	6,0	7,0	5,9
	B-L	6,6	8,0	6,0	B-L	6,2	6,5	6,4
	CH	9,9	9,0	8,8	CH	10,4	7,5	9,6
	TH	23,1	24,5	22,0	TH	23,3	22,5	21,1
	RL	13,0	15,5	13,0	RL	13,5	15,0	12,7
Canine								
	M-D	7,7	9,0	7,6	M-D	6,7	8,0	6,9
	B-L	8,4	8,0	8,0	B-L	7,8	8,5	7,9
	CH	11,0	9,5	9,5	CH	11,6	10,5	10,3
	TH	27,3	29,0	26,5	TH	26,0	27,5	25,6
	RL	16,3	20,5	17,3	RL	15,7	17,5	15,3

CONCLUSIONS

MAXILLARY INCISOR TEETH AND CANINE

The central incisor has a broader crown (M-D) but is narrower in bucco-lingual section in comparison to other findings. (It should be noted, however, that the measurements with which the subject's are compared, were derived from caucasoid teeth, and not negroid teeth. Statistics pertaining to the anterior teeth of the negro races were not available at the time of writing).

Crown height of the central incisor (CH) is reduced but the total length (TH) is considerably increased.

The root length (RL) is proportionately greater.

The lateral incisor is broader in the crown width as well as in bucco-lingual section. Crown height is close to the average, but total tooth length is greater than the average. The root is proportionately longer.

The canine tooth is considerably broader but slightly smaller in bucco-lingual section. Crown height is average, but root and tooth length are greater than the average.

MANDIBULAR INCISOR TEETH AND CANINE

The central incisor has a broader crown and it is considerably thicker in bucco-lingual section. Crown height is average as is tooth and root length.

The lateral incisor also has a broader crown but is average in bucco-lingual section. Surprisingly, the crown height is considerably *less* than the average.

Tooth length is average but root length is considerably greater than the average.

The canine tooth has a much broader crown which is thicker, too, than average. Crown height is average while tooth-length is only slightly greater than normal.

Root length is considerably greater.

TABLE 3

MAXILLARY PREMOLAR AND MOLAR TEETH

Tooth	Measure-ment in mm	Subject			SA Negro(1)	SA Negro(1)	American Negro(1)	Bjorndal(2) Caucasoid
		Left	Right	Mean	Abel 1933	Shaw 1931	1968	1974
4	M-D	9,0	9,0	9,0	7,3	7,2	7,6	7,0
	B-L	11,0	11,5	11,25	9,7	9,0	10,1	9,5
	CH	8,0	8,0	8,0	–	7,9	8,7	9,1
	TH	23,0	23,0	23,0	23,3	21,8	21,4	22,3
	RL	15,0	15,0	15,0	–	13,9	–	13,7
5	M-D	8,0	8,0	8,0	7,3	7,0	7,8	7,2
	B-L	11,0	11,5	11,25	9,6	9,1	9,8	9,4
	CH	7,5	7,5	7,5	–	7,7	8,4	8,5
	TH	23,5	23,0	23,25	23,8	22,3	22,6	22,3
	RL	15,5	16,0	15,75	–	14,6	–	14,4
6	M-D	12,0	11,5	11,75	11,3	10,3	10,5	10,9
	B-L	13,0	13,0	13,0	11,7	11,0	12,1	11,8
	CH	6,0	6,0	6,0	–	6,5	8,0	8,4
	TH	21,0	20,5	20,75	–	20,0	20,5	22,3
	RL	15,0	14,5	14,75	–	13,5	–	13,1
7	M-D	10,0	9,5	9,75	11,1	10,0	11,0	10,2
	B-L	13,0	14,0	13,5	11,9	11,5	12,2	11,8
	CH	6,0	5,0	5,5	–	6,5	8,2	8,4
	TH	20,0	19,0	19,5	–	19,0	21,6	22,2
	RL	14,0	14,0	14,0	–	12,5	–	13,3
8	M-D	10,5	10,5	10,5	9,7	9,5	9,8	–
	B-L	13,0	14,5	13,75	12,3	11,0	11,5	–
	CH	5,0	5,0	5,0	–	6,0	8,1	–
	TH	18,0	18,0	18,0	19,2	17,5	20,0	–
	RL	13,0	13,0	13,0	–	11,5	–	–

MAXILLARY PREMOLAR AND MOLAR TEETH

The first premolar has a much broader crown which is proportionally larger in bucco-lingual section. Crown height is average and so is tooth length, but root length is greater than average.

The second premolar has a slightly broader crown which is similarly larger in bucco-lingual section. Again, crown height is average along with tooth length. Root length is slightly greater than average.

The first molar has a crown which is only slightly broader in mesio-distal section. Bucco-lingually it is thicker than average. Crown height is almost smaller than average, while tooth length is average. Root length is slightly greater than average.

The second molar. Here the crown is average in mesio-distal section but greater in bucco-li..gual section, than the average. Crown height is considerably *less* than average.

Tooth height is slightly less than average, but root length is slightly greater.

The third molar has a crown which is larger in both sections, but which is less in height than the average. Tooth length is less but root length is greater than the average.

MANDIBULAR PREMOLAR AND MOLAR TEETH

The first premolar has a crown larger in all sections, to a small degree, than the average. Both tooth length and root length are considerably greater.

The second premolar. Except for crown height, the crown is larger than average. Both tooth and root length are very much *larger* than average.

The first molar – the crown, except again for crown height, is slightly larger than the average. Both tooth length and root length are nearly average.

The second molar – The size of the crown, in both mesio-distal and bucco-lingual section, is larger than average. Crown height is slightly less than average. Tooth length is average but root length is decidedly greater.

The third molar – This tooth is almost entirely within the bounds of normality in all measurements.

TABEL 4

MANDIBULAR PREMOLAR AND MOLAR TEETH

Tooth	Measurement in mm	Subject			(1) S A Negro	(1) S A Negro	(1) American Negro	(2) Bjorndal Caucasoid
		Left	Right	Mean	Abel 1933	Shaw 1931	1968	1974
4	M-D	8,5	–	–	7,6	7,1	7,8	7,2
	B-L	10,5	–	–	9,0	8,2	8,5	7,9
	CH	8,5	–	–	–	7,7	8,3	8,9
	TH	25,5	–	–	23,8	22,7	20,9	22,9
	RL	17,0	–	–	–	15,0	–	15,6
5	M-D	9,0	–	–	8,0	7,2	7,7	7,4
	B-L	10,0	–	–	9,3	8,1	8,9	8,6
	CH	8,0	–	–	–	9,2	8,0	8,6
	TH	27,0	–	–	23,7	24,4	21,9	22,3
	RL	19,0	–	–	–	15,2	–	14,4
6	M-D	12,5	–	–	12,0	11,0	11,9	11,8
	B-L	12,0	–	–	11,3	10,5	10,8	10,8
	CH	6,0	–	–	–	7,0	7,7	8,3
	TH	21,0	–	–	20,3	20,5	22,0	22,0
	RL	15,0	–	–	–	13,5	–	14,35
7	M-D	13,0	13,0	13,0	12,0	11,0	12,0	11,4
	B-L	12,0	12,0	12,0	11,3	10,3	10,9	10,3
	CH	6,0	6,0	6,0	–	6,5	7,8	8,7
	TH	20,0	21,0	20,5	21,9	20,0	22,3	21,7
	RL	14,0	15,0	14,5	–	13,5	–	13,6
8	M-D	–	12,0	–	11,9	11,1	12,0	–
	B-L	–	11,0	–	11,2	10,4	10,8	–
	CH	–	6,0	–	–	6,5	7,7	–
	TH	–	18,0	–	18,2	18,5	20,1	–
	RL	—	12,5	–	–	12,0	–	–

SUMMARY

From the foregoing, it is apparent that the subject's teeth, in comparison, are

(i) broader in the mesio-distal section and, with a few exceptions, also in the bucco-lingual section.

(ii) average, or slightly *smaller* with regard to crown height.

(iii) greater, or considerably greater as regards the root length.

As the crown height is average or below, the greater than average tooth length measurement obtained *must* be due to the increase in *root length*.

The overall impression thus gained would be that, although the subject's teeth are larger than the average, they are *not* abnormally large.

They are definitely not hypotrophic and can safely be considered to have escaped the effects of the pathogenic factors which has led to the syndrome.

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CEPHALOMETRIC ANALYSIS
(STEINER) [2]

A cephalogram is a standardised radiograph of the head and face which is accomplished by means of a cephalostat (or head holder).

The patient's head is held in a fixed relationship to the central ray of the X-ray source so that the rays coincide with the transmeatal axis.

Because of the method's reliability, subjects can be examined repeatedly, permitting comparisons of cephalograms. Serial cephalometric growth studies of both humans and animals have been a major factor in broadening our knowledge of cranio-facial growth.

Various "cephalometric analyses" have been devised for identifying gross variations in the cranio-facial pattern. They provide the most precise method available today for the diagnosis of cranio-facial deformity, for they reveal the relationships of the various parts of the face and their contributions to the deformity.[2]

For this reason, the subject was submitted to cephalometric analysis (after Steiner) and the results compared to the statistics pertaining to black American subjects as established by KOWALSKI[1] et al. (October 1974)

FINDINGS

SNA

The angle in the subject measured 85° compared to the reference norm of 86,10°.

This means that Point A on the basal bone of the maxilla is very slightly more forward than normal, but it is still well within normal limits. Therefore, it is an indication that the relationship of the maxilla to the cranial base is normal.

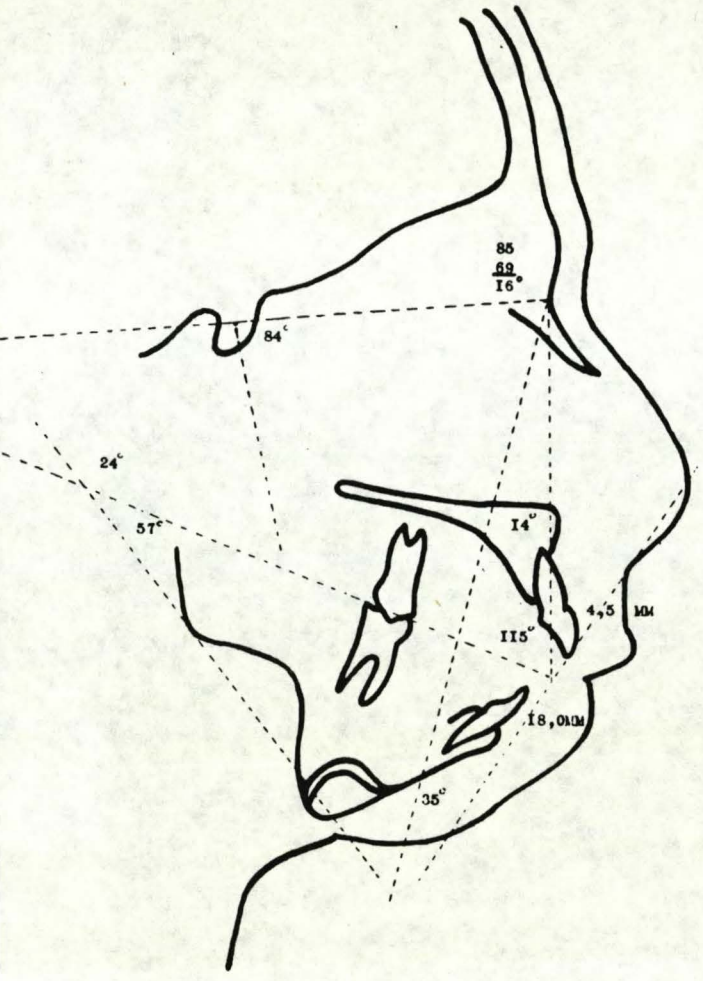

FIG 19 The Points of Reference

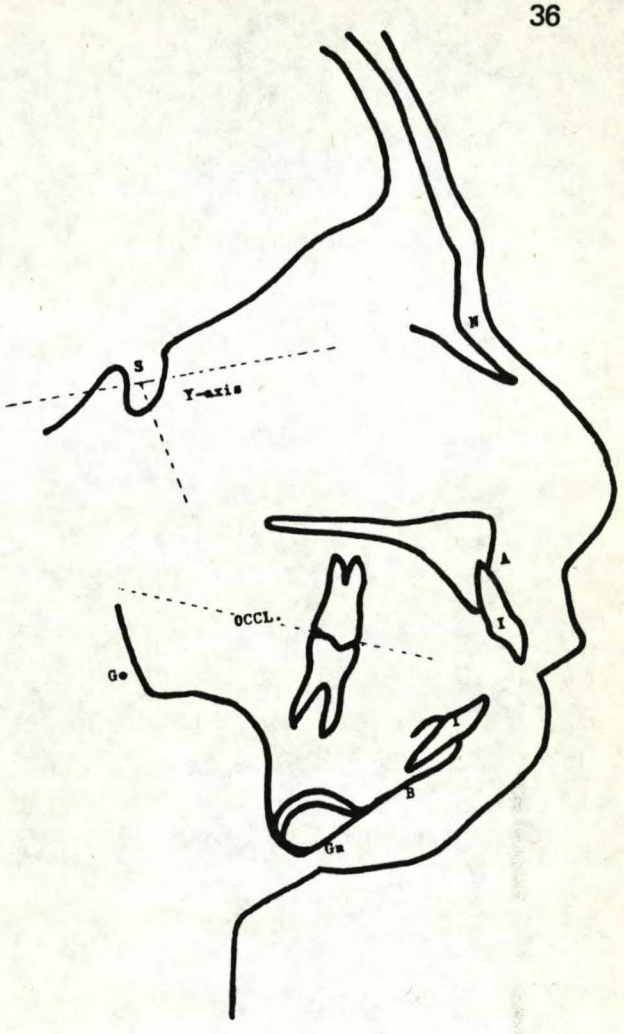

FIG 20 The Cephalometry

TABLE 5

Name: J.S. No. Age: Sex:

CEPHALOMETRIC ANALYSIS
STEINER

		Ref. Norm.	NEGRO	J.S.			
SNA	(angle)	82°	86,10°	85°			
SNB	(angle)	80°	81,22°	69°			
ANB	(angle)	2°	4,88°	16°			
Y-axis	(angle)	67°	–	84°			
$\underline{1}$ to NA	(mm)	4	4,83	4,5			
$\underline{1}$ to NA	(angle)	22°	32,20°	14°			
$\overline{\underline{1}}$ to NB	(mm)	4	9,15	18			
$\overline{1}$ to NB	(angle)	25°	30,14°	35°			
Po to NB	(mm)	Not Established					
Po & $\overline{\underline{1}}$ to NB	(Difference)	Varies					
$\underline{1}$ to $\overline{\underline{1}}$	(angle)	131°	126,31°	115°			
Occl to SN	(angle)	14°	15,48°	24°			
GoGn to SN	(angle)	32°	34,31°	57°			
SL	(mm)	51					
SE	(mm)	22					
Soft tissue line	( )						
$\overline{3}\,\vert\,\overline{3}$ width	(mm)						
$\overline{4}\,\vert\,\overline{4}$ width	(mm)						
$\overline{6}\,\vert\,\overline{6}$ width	(mm)						
$\overline{E}\,\vert\,\overline{E}$ present							
Tooth size Relationship	(Bolton Index)	6=77% 12=91%	6 = % 12= %				
Arch length Discrepancy							
OM	(angle)						

SNB

The angle in the subject measured 69° compared to 81,22° (average). This indicates that Point B on the basal bone of the mandible is very much retruded.

ANB

This is the difference between SNA and SNB and is normally 4,88°. In the present case, it is 16° which indicates a very RETRUSIVE mandible.

THE Y-AXIS

The measured Y-axis is 84°. This reading can only be compared to the norm for caucasoids, (67°) as that for negroes is not available to the writer.

It does indicate, however, that the growth of the subject's face was in a more inferior (downward) direction rather than forward.

$\underline{1}$ to NA (mm)

The distance from the labial surface of the maxillary central incisor to the NA Line was found to be 4,5 mm as against 4,83 mm (average) in negroes.

This is absolutely within the confines of normality.

Angle $\underline{1}$ to NA

The angle between the long axis of the maxillary central incisor and NA is 14°, while the norm is 32,20°.
(There is a decided "blocking out" of the maxillary lateral incisors and "flattening" of the anterior part of the maxillary arch which could be compensatory to the lip action during swallowing).

This lip action could also be the cause of the vertical inclination of the maxillary central incisors.

$\overline{1}$ to NB (mm)

This measured 18,0 mm and, in comparison to the norm of 9,15 mm, is very high.

It is an indication that the tongue has caused the forward inclination of the mandibular central incisors. Although the tongue is "normal" in size, the very small mandible causes it to be *relatively* too large and the result is an anterior open bite with forward inclining incisors.

Angle $\overline{1}$ to $\underline{1}$

This measured 115° against a norm of 126,31°.

It merely means that the maxillary central incisor is more upright than normal, but the mandibular central incisor is *relatively* more upright, and thus the angle is smaller.

OCCLUSAL PLANE TO SN LINE ANGLE

While this angle should be 15,48°, it is in fact 24°.

The larger angle is due to the open bite. Had the bite *NOT* been open, then the angle would have been smaller.
This indicates, once again, that the maxilla is *normal.*

GoGn to SN angle

The norm for this angle is 34,31°.

In the subject, it measured 57°, which is exceptionally high.

This shows the characteristic "notching" of the inferior border of the mandible.

CONCLUSIONS

Apart from the vertical inclination of the maxillary central incisor teeth, which is due to a *dental* rather than a *skeletal* set of circumstances, the maxilla falls comfortably within accepted limits of normality, and its development can therefore be regarded as *NORMAL.*

The growth of the mandible, however, has largely been in a downward direction, with very little forward growth as indicated by the very high Y-axis angulation, (84° as compared to 67°).

The *low* SNB angle (69° as against 81,22°) coupled with the large difference between the A and B angles (16°) would again indicate the gross *UNDERDEVELOPMENT* of the mandible.

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RÖNTGENOLOGICAL FINDINGS

THE CRANIUM

The skull is symmetrical.

The thickness and density of the cranial vault and base are normal.

The maximum thickness of the calvarium is 0,8 cm between outer and inner tables. (The thickest part of a normal vault should not exceed 1 cm. If it measures more, some degree of cerebral underdevelopment or a systemic disease should be suspected.) – ETHIER[2] (1971)

The greatest distance horizontally, between the inner tables of the skull, is 19,6 cm.

The greatest distance vertically, between the tables, is 15,0 cm.

In cases of mandibulo-facial dysostosis, the size of the calvarium is usually normal – STOVIN[4] (1960). The head of the subject *appears* abnormally lage due to the smallness of the facial bones and the mandible. – PAVSEK[3] (1958).

The inner, middle (diploe) and outer tables appear normal in general texture as well as in thickness. There is no evidence of any associated bone changes, such as osteolysis or osteoblastic activity.

The usual, normal-looking vascular grooves (such as the venous meningeal grooves) can clearly be seen. There are digital markings present but these are not accentuated. (Fig. 22).

There is no persistent frontal suture.

There is no evidence of calcification of the falx cerebri.

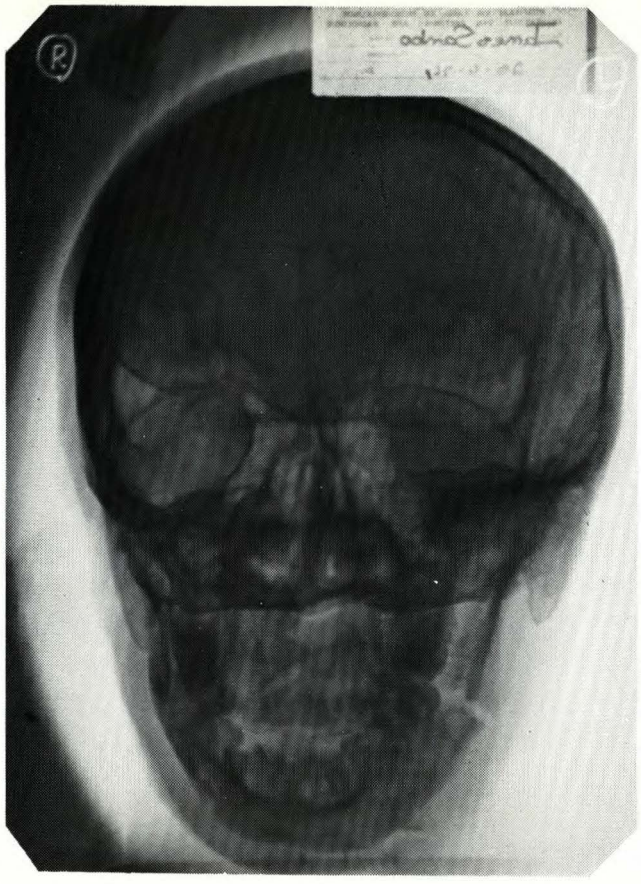

FIG 22 A-P view of skull

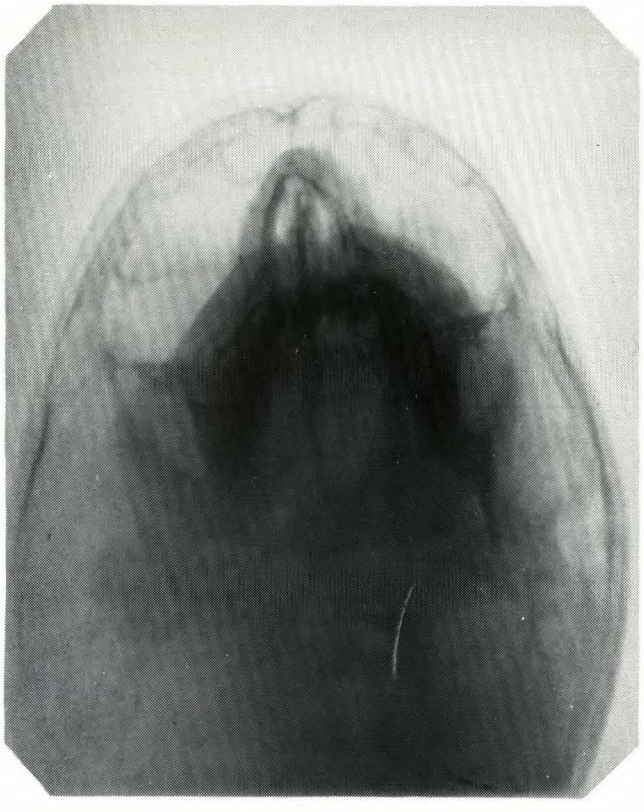

FIG 23 Basal view of skull

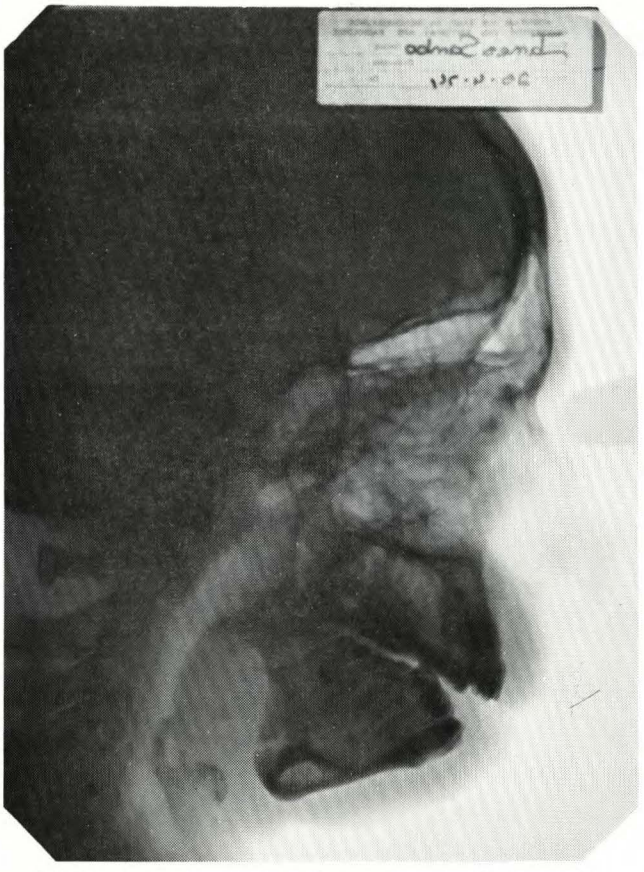

FIG 24 Lateral view (cephalogram) of skull

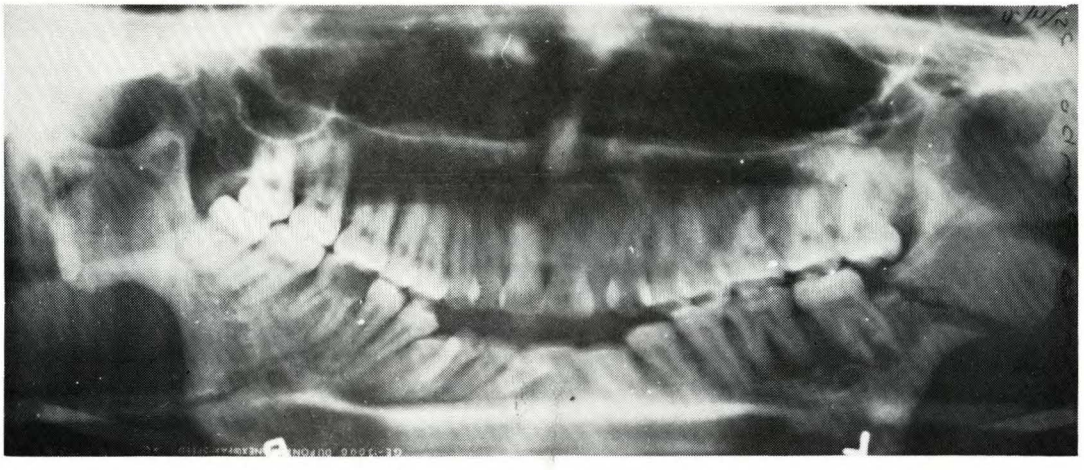

FIG 25 Panoramic view of jaws

THE SELLA TURCICA

SIZE:

CAMP[1] (1924), as reported by PRIBRAM (1971), has stated that a distance of *16,0 mm* or more, between the tuberculum sellae and the dorsum sellae probably indicates an *enlarged* sella. (CAMP used a 40 inch anode to film distance in making his radiographs).

The distance (measured on a radiograph made with a 60 inch anode to film distance to further decrease magnification of the film-image) between the points mentioned above, is *9,0 mm* in the case of the subject.

The greatest antero-postero measurement of the sella turcica, measured on the same radiograph, is *13,0 mm.*

According to TAVERAS and WOOD[5] (1964), 17 mm is the upper limit of normality for this measurement. They employed a 40 inch anode/film distance.

In the case of the subject, the greatest depth of the sella measured *11,0 mm.* The normal depth is anything up to *14,0 mm.*

The conclusion arrived at, therefore, is that the sella turcica is *NORMAL* in all respects.

THE SINUSES

The sphenoid sinuses, as seen on lateral view (cephalogram) appear to be slightly more well-developed than normal.

The ethmoidal and frontal sinuses are EXCEPTIONALLY well-developed and extensive, especially on the left side. (Fig. 22).

The maxillary sinuses are bilaterally under-developed. On the right side there is a larger extension of the antrum into the third molar and tuberosity area; whilst on the left side only a rudimentary antrum can be seen.

STOVIN[4] (1960) states that, in a survey of 24 reported classes of röntgenologically-examined persons with MFD, most exhibited small or normal ethmoidal and frontal sinuses. In the case under discussion, we see exceptionally *LARGE* ethmoidal and frontal sinuses.

THE MAXILLA

This appears normal röntgenologically and shows no signs of hypoplasia. (The lack of hypoplasia is confirmed by the cephalometric analysis).

The bone density and trabecular pattern are both normal.

The nasal septum shows a distinct deviation to the right.

The turbinates are normal.

THE ZYGOMATIC (MALAR) BONES

The zygomatic bones are almost totally ABSENT. There is slightly more bone on the right side.

THE ORBITS

The inter-orbital distance *appears* to be large, but it has been confirmed that there is no hypertelorism present.

The shortest distance between the inner bony margins of the orbits (measured on the Antero-Posterior radiograph) is *3,0 cm.*

The orbits are oval in shape and are ANGULATED in an infero-lateral direction. (This gives rise to the antimongoloid obliquity). (Fig. 22)

THE INFRAORBITAL RIDGES

There are signs that these ridges are INCOMPLETE. (Clinical examination revealed that there is the possibility of a wide bony defect being present).

THE SUPRAORBITAL RIDGES

These are underdeveloped.

THE ZYGOMATIC ARCHES

On the radiograph, the arches could not be distinguished easily and are very hypoplastic clinically.

THE MASTOID PROCESSES

Both mastoid processes appear LARGER than normal.

The right process is LONGER than the left and its tip is also situated closer to the midline. It gives the appearance of having been "bent" inwards.

Both mastoid processes are SCLEROTIC and show very few air-cells.

The absence of air-cells and the sclerosis is in agreement with the findings of STOVIN (1960).
(The sterno-mastoid muscles are both normal in development).

The stylohyoid ligament shows evidence of calcification for a distance of approximately 4,0 cm. It is thin and fragile-looking on both sides.

THE MANDIBLE

Symmetry

The mandible is asymmetrical, with the right side less developed than the left. Both the ramus and the body (corpus) are affected. (Fig. 25)

Shape

The shape is decidedly abnormal. There is a marked "notching" of the inferior border, causing an upward CONVEXITY of the corpus.

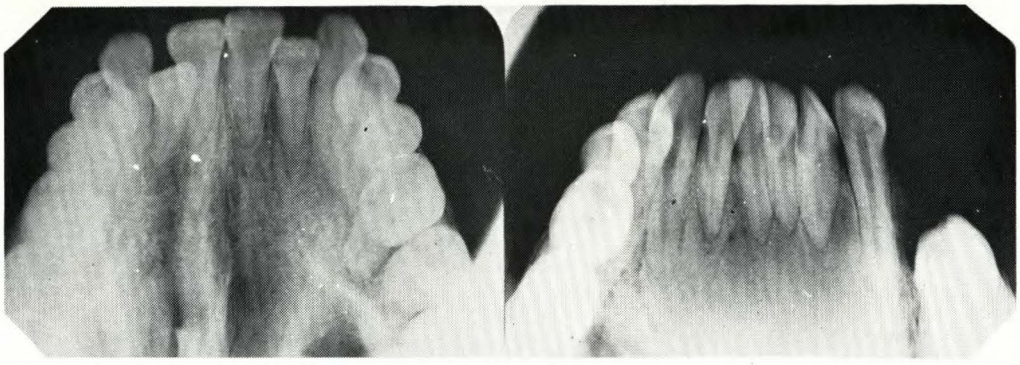

FIG 26 Maxillary occlusal view

FIG 27 Mandibular occlusal view

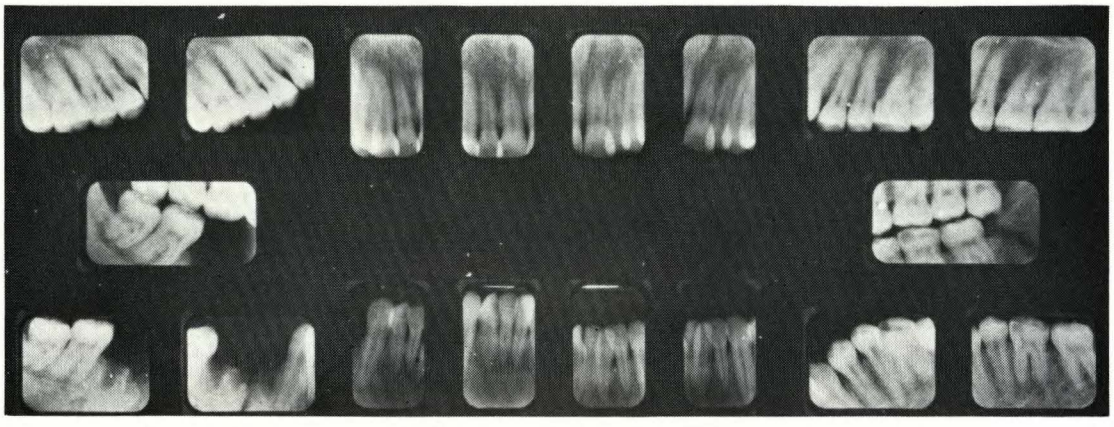

FIG 28 Full-mouth radiographs

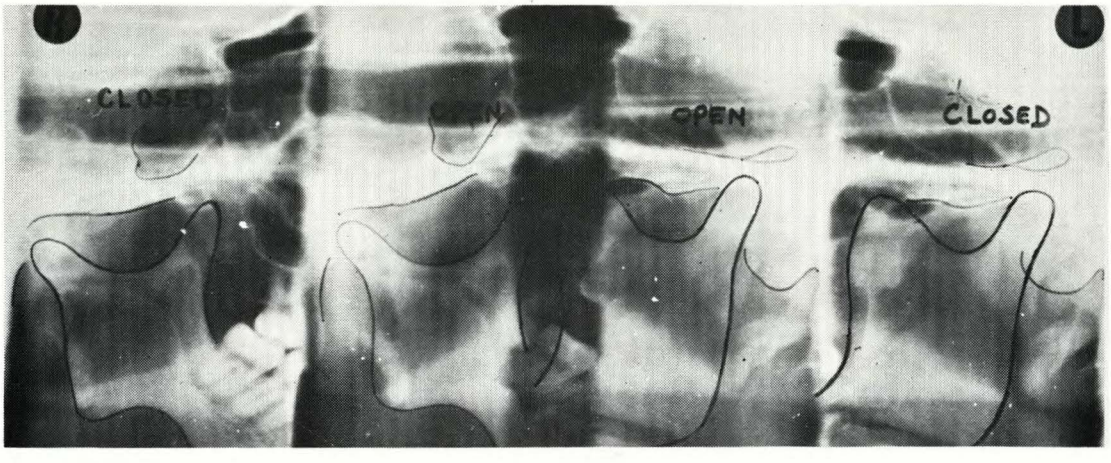

FIG 29 Temporo-mandibular joint radiographs

On the right side, the shortest distance (measured on the radiograph) between the superior and inferior borders is 19,0 mm.

On the left side, it is 27,0 mm.

Anteriorly, the maximum distance is 50,0 mm.

The "notching" of the inferior border is more pronounced on the right side.

The mandibular plane angle is very steep.

There is NO mental process. (Nutrient canals are very clearly seen in the anterior region, due to the thinness of the bone).

Size

The mandible shows distinct signs of a *severe* hypoplasia, a fact which is confirmed by the cephalometric analysis.

This hypoplasia has resulted in an anterior "open" bite (opisthodontia).

Landmarks

The mental foramen can be seen on each side apical, and slightly distal, to the root of the second premolar. The usual position of the foramen is further forward, almost between the roots of the two premolars.

The mandibular foramen is very abnormal in position. On the right side, it is situated in the *neck* of the condyle, whilst on the left side it is more normally placed though at a much higher level than usual. It lies approximately 1,5 cm below the lowest part of the sigmoid notch, in the midline of the ramus.

The mandibular canal runs at a much higher level on the left side, but is otherwise normal.

On the right side, however, it pursues a most peculiar course. It undulates from the foramen, first horizontally and then inferiorly before it "straightens" out to end at the mental foramen. It never strays far from the roots of the molar and premolar teeth.

The left condyle head is normal in size and configuration.

The left condyle neck is normal.

The right condyle head is smaller than the left and less rounded.

The neck is narrower and appears "bent" distally.

The sigmoid (mandibular) notch is, on the left, of average depth and relatively narrow. On the right, it is broad and shallow.

The left coronoid process is triangular in shape, well-formed and bulky in appearance.

The right process is sharper, pointed and narrow.

The glenoid fossa is bilaterally more shallow than normal and the outline cannot easily be seen on the radiograph. (Fig. 29)

The eminentia articularis is practically non-existant.

NOTE:

The shape and size of the condyle heads, along with the relatively underdeveloped glenoid fossae, would explain the reason for the clinical finding of EXCESS MOBILITY of both temporo-mandibular joints.

There is, however, no forward displacement of the joints.

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PART TWO

HISTORICAL

Congenital deformities have been viewed with disapproval through the ages.

In many parts of the world, prehistoric men practised their own eugenics by the elimination of defective children shortly after birth.(19)

The Spartans cast their weak into the sea.

For thousands of years the African tribes set their deformed babies out into the jungle to die.

Among the Pre-Columbian Indians in Mexico, however, there was the feeling that these children, born with cranio-facial defects, had been specially "touched" by the gods, and so were nurtured and preserved. Legend reports that some of these children became chieftains. Many of these defectives are found preserved in the pottery of the period, examples of which may be seen in the Anthropological Museum in Mexico City.(19)

The earliest recording of cranio-facial malformations was found in the teratological tablets written about 2000 B.C. by the Chaldeans of Mesopotamia.(11)

Translation of these cuneiform writings revealed a complete list of deformities of the ear (as well as other parts of the body) and their alleged prophetic significance.

The records are then silent until BARTHOLINUS'(1) account in 1654 of a child with an absent auditory canal orifice and LACHMUNDS'(17) brief description (in 1688) of a girl with a small auricle and absence of the external auditory canal orifice.

However, it was not until 1846 that the first 3 definite reports of MFD appeared, when THOMSON(27) published a paper entitled "Notice of several cases of Malformations of the External ear, together with experiments on the status of hearing in such persons".

In 1860 CANTON[4] described early clinical cases of the 1st and 2nd Branchial Arch syndrome, with the emphasis on the arrest of development of the lower jaw and malformation of the external ears. (It should be pointed out, however, that the Branchial Arch syndromes are not synonymous with MFD, according to modern thinking).

In 1888, G.A. BERRY[2], an Edinburgh ophthalmologist first described the characteristic deformity of the lower lid which, in more or less pronounced form, is now a virtually necessary symptom of MFD. He described 3 cases in 2 generations, thereby paving the way for the theory of heredity in the syndrome which is now universally accepted as fact. Berry called the eye-lid deformity COLOBOMA and stated that the patient's mother had identical symmetrical defects in both lower lids. He was thus the first to mention that the defect was congenital.

E. TREACHER COLLINS[6], also a British ophthalmologist, in 1900 presented two sporadic cases of symmetrical "notching" of the lower lids associated with clinical evidence of faulty development of the malar bones. The syndrome has since carried his name.

KIRMISSON [16] (1902) and TYRRELL[28] (1903) each reported on a similar sporadic case.

In 1923, PIRES DE LIMA and MONTEIRA[21] described the *first* complete form of the syndrome with its 7 characteristics, in 2 brothers.

ISAKOWITZ [14] (1927) described a case of COLOBOMA in a patient whose father and sister also possessed similar defects. He noted a depression in the orbital rim and suggested a defect in the zygomatic bone.

In 1929, LOCKHART[18] first demonstrated a defect of the maxillary artery in this condition and also reported on a skull with bilateral absence of the malar bones and other cranial osseous defects. He found the temporalis and masseteric muscles to be fused and both middle ears defective.

SANVANERO–ROSELLI,[24] in 1940, described several typical cases of the syndrome and, in 1943, MANN and KILNER[20] reported on 2 cases in which they discussed the embryological aspect, and suggested that the maxillary mesoderm was the defective element.

In 1944 FRANCESCHETTI and ZWAHLEN[8] added a further 2 cases, one "complete" and the other "incomplete" or "atypical" and called the defects "dystose-mandibulo-faciale".

STRAITH and LEWIS[26] (1949) described a family in which all 5 members revealed the entire syndrome (as we know it today) and thus confirmed the *familial* pattern.

In 1949 FRANCESCHETTI and KLEIN[9] reported on 3 new cases in an article entitled "MANDIBULOFACIAL DYSOSTOSIS – A NEW HEREDITARY SYNDROME".

HÖRSTADIUS[13] (1950) suggested a NEURAL CREST deficiency as an etiological factor.

HARRISON[12] (1950–51) recorded three cases of facial malformations, two with the typical appearance of the syndrome and a third which was a unilateral intra-uterine facial necrosis. He drew a comparison between the Treacher Collins syndrome and unilateral facial agenesis and referred to the *differences.*

DUKE-ELDER[7] (1952) emphasised that coloboma is almost always a constant feature of the syndrome, is usually symmetrical, found in the lower eyelids and more rarely found in the upper eyelids.

Also in 1952, WAYBURNE[29] described the first case of the fully-developed syndrome to be found in an *African* infant. Unfortunately, the infant did not survive more than a few weeks.

One of the first roentgenologic reports was that of CAMPBELL[3] in 1954. KIBEL[15] (1960) described the syndrome in a White Rhodesian infant of European descent.

In 1962, STARK and SAUNDERS[25] attempted to differentiate the congenital defects according to embryonic derivation. They concluded that the various facial defects could be grouped into 3 categories, viz:

(1) The Treacher-Collins syndrome

(2) The oral-mandibular-auricular triad

(3) The first and second branchial arch syndrome.

The combination of the above deformities was termed (by them) "Mandibulofacial dysostosis".

ROGERS[23] (1963) wrote an excellent review of 200 cases from literature.

GLYN JONES[10] (1968) described the typical syndrome in two Rhodesian African infants. These, too, survived only a matter of a few weeks.

CARONNI[5] (1971) coined the term "auriculo-branchiogenic dysplasia" which referred to the First and Second Branchial Arch Syndrome and differentiated it from MFD.

In 1974, POSWILLO[22] created animal models of the MFD syndrome by injecting pregnant Wistar rats with high dosages of Vitamin A at day 8,5 of development. The results seemed to indicate that early destruction of the neural crest cells was the main pathogenic factor in MFD, whereby a shortage of mesenchyme-derived "bulk" in the bones of the facial skeleton is caused artificially. He clearly differentiated between MFD and Hemifacial microsomia.

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THE ETIOLOGY

INTRODUCTION

COHLAN[2] (1963)

Until 30 years ago, human malformations (except fetal irradiation) were considered to be almost entirely GENETICALLY determined. It was believed that the maternal placenta served as an effective defensive barrier against teratogenic insult to the fetus.

HALE[8] (1933) – in swine, and WARKANY[24] (1944) in rats, proved that fetal malformations could be experimentally produced by maternal *nutritional* deficiencies.

It is now almost universally accepted that most congenital malformations of the cranio-facial area cannot be explained by a simple genetic or hereditary mechanism nor can they be attributed solely to non-hereditary influences (CAMPBELL[1] 1971).

The majority of congenital malformations are most likely to be the result of a COMPLEX combination of exogenous factors *and* a GENE pattern predisposing to malformations (FOGH–ANDERSEN[5] 1968).

FRAZER, WARKANY[6] and KALTER[9] all consider that the majority of congenital malformations result from a combination of genetic predispositions and adverse ENVIRONMENTAL factors operating in early fetal life.

However, SORSBY[18] (1965) has stated quite correctly that malformations can be identical in appearance whether they arise as hereditary (genetic) disturbances or as anomalies-in-development caused by environmental factors.

Studies of causes must therefore be based on circumstantial evidence from patients and their families and must take account of hereditary predispositions, maternal factors and extraneous events occurring during early pregnancy.

THE ROLE OF GENES IN THE PRODUCTION OF CRANIO-FACIAL ANOMALIES

In some instances, a SINGLE dominant autosomal mutant gene may be shown to predispose to a specific malformation in a kindred.

It then produces many different phenotypes as expressions of its varying PENETRANCE and the interaction of the modifying gene on similar chromosomes or other chromosomes of each individual involved (COTTER[3] 1968).

Thus the genetic result is complicated by the prevalence of TRANSITIONAL and MIXED forms.

Genetic influences probably govern the epigenetic pathway of a developing organ through EVERY step of its formation. The opposing gene activities may be so finely balanced that a path is EASILY influenced by exogenous factors. For example, opposing gene activities and associated factors of nutrition may dictate the course of the eventual abnormality. (CAMPBELL[1] – 1971).

GRANRUD[7] (1953) first drew attention, on the basis of 4 cases, to the possibility that MFD may occasionally be due to an EXOGENOUS factor e.g. influenza, rubella, diphtheria or an attempt to interrupt pregnancy by injection of chemical substances into the uterine cavity.

WALLACE[23] (1971) however, stated emphatically that, in contradistinction to the CONGENITALLY-determined disabilities resulting from severe complications in late pregnancy and at delivery, the PRIMARY lesion in all developmental malformations *must* result from a gene-controlled process.

WADDINGTON[22] (1964) has stressed that the primary lesion must always be an effect that occurs at the cell-level of organisation. The progression of a developing structure through a series of stages must ultimately be brought about by the synthesis within the cell of particular components.

The newly-appearing substances will be formed under the influence of the nuclear genes of the cell. The primary lesion which leads to a congenital malformation must always be the result of some abnormal functioning of one or more of these basic "gene-ribosome" action systems.

In order to fully understand how disturbances in genetic function can lead to altered development and growth (in other words, a cranio-facial anomaly), it is necessary to review and discuss the NORMAL genetic course of events as well as the ways in which this course can be altered by various endogenous and exogenous influences.

THE GENETIC DETERMINANTS

(SLAVKIN[17] – 1974)

Nucleic acids are macro-molecules resulting from the linear polymerisation of smaller molecules called nucleotides or bases.

DNA (Deoxyribonucleic acid) contains the entire history of the organism.

In DNA are found four nucleotides that differ from one another. These 4 bases viz ADENOSINE, GUANOSINE, CYTOSINE and THYMIDINE are the nuclear "letters" of the genetic alphabet.

The variations in the sequences in which these bases can occur, are the genetic determinants.

DNA is formed from 2 polynucleotide strands that are joined by means of specific non-covalent bonds. The 2 strands are complementary.

For a parent cell to divide to form 2 identical daughter cells, the DNA must undergo REPLICATION. The replication of DNA proceeds by the separation of the duplex strand followed by the formation, nucleotide by nucleotide, of the new components. The reconstituted DNA molecules each contain one strand of the parent molecule and one newly-formed strand. Thus, each progeny molecule is identical to that of the parent cell.

MUTATIONS result from various pertubations or "accidents" during this replication mechanism. The accidents may take the form of :

1. An alteration or reversal of the normal *sequence* of the nucleotides.
2. Substitution or modification of a specific nucleotide into a sequence in which it previously did not belong i.e., illicit base pairing due to "mutagens".
3. A chemical agent may substitute for the normal base.

4. An illicit molecule or a DNA-virus can wedge itself within the nucleotide sequence, thereby inserting an aberrant sequence of genetic information for development.

5. Substitution, addition or deletion of one or more nucleotides have demonstrable developmental repercussions during the embryonic process.

The structure and properties of a protein are defined by the sequence (i.e. the absolute linear order) of the amino-acids that polymerise to form the primary structure of the protein viz. the polypeptide. This sequence of aminoacid residues is determined by the sequence of nucleotides in a specific segment of a DNA strand.

The genetic code is, therefore, the information prescribed within the unique sequence of nucleotides that make up the DNA strands. This information specifies the sequence in which each of the 20 amino acids will be in the synthesis of the protein.

The genetic code is stored within long sequences of polynucleotides and is "read" in triplets.

Each of the 20 amino acids is specified by a sequence of 3 nucleotides (a CODON).

Following TRANSLATION, i.e. the assembly of amino acids into a unique protein on the polyribosomes in the cytoplasm of the cell, proteins are further modified and are used within the cells as structural components, enzymes, or are packaged in secretory vesicles in the Golgi region of the cell and secreted for extracellular functions (e.g. elastin, collagen, glycoproteins and albumen). EACH of these processes requires exquisite regulation and is a critical site for developmental aberrations.

Experiments on frogs, in which diploid nuclei from differentiated cells were transplanted into unfertilised eggs from which the haploid nucleus had been removed,

have proved that the somatic cell nucleus contained ALL the genetic history of the frog. It was able to instruct the selective expression of gene influences at the right time, in the right order and place – leading to the formation of specific molecules essential to carry the fertilised egg through the appropriate cell divisions (timed in a most exquisite manner) to lead to the blastula and the following stages of embryogenesis.

REVERSE TRANSCRIPTION – THE ROLE OF VIRUSES IN CARCINOGENESIS[17]

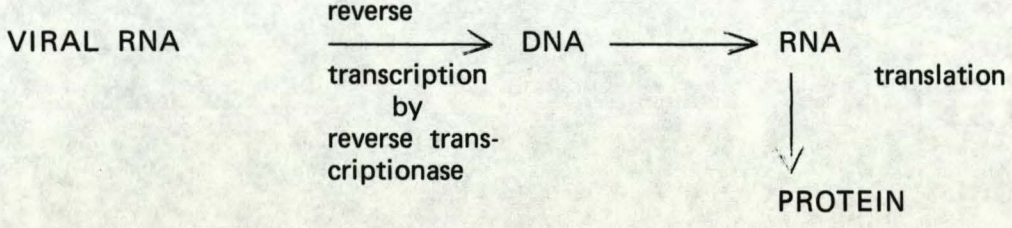
During the past 2 decades, much research has been performed on the etiology of carcinogenesis with the result that viruses are today considered to be dominant factors in cancer.

RNA-containing tumour viruses are large viruses. The nucleoid of the virus contains a single-stranded RNA.

RNA viruses differ from DNA-viruses in that the RNA-virus can cause TUMOURS in the host-tissues while DNA-viruses cannot. (Avian and Mammalian vertebrates contain 2 types of RNA-viruses viz. the C-type causing leukemia and sarcoma and the B-type causing tumours of the breast and perhaps other carcinomas).

In experiments, RNA-viruses were incubated with a variety of different vertebrate somatic cells. The RNA-viruses were then incorporated by pinocytosis, the RNA of the virus was transported to the nucleus and the viral RNA then directed NEW DNA-synthesis that was complementary to the nucleotide-sequence found in the RNA of the virus.

This interpretation and the complementary observations indicated that there was an RNA-directed DNA-synthesis or a REVERSE TRANSCRIPTION mechanism at work.



When a RNA-virus transformed a cell, it would become a *permanent* transformation in that a new sequence of DNA would be added to the normal, endogenous INHERITED DNA of the somatic cell.

Recent advances have shown that there is an ENZYME activity called "reverse transcriptionase" which catalyses the reaction.

This transformation can affect the outer surface properties of a cell or *function* within a variety of processes including those associated with *cell-division.*

THE SIGNIFICANCE OF REVERSE TRANSCRIPTION IN DEVELOPMENTAL ABERRATIONS[17]

The central dogma of genetic expression is DNA→ RNA → PROTEIN and must be modified to include RNA-directed, DNA-synthesis (by RNA-containing-viruses) to lead to tumour-formation in vertebrate somatic cells.

Identification of RNA-containing Viruses is done by:

1. detection and identification of viral reverse transcriptionase
2. detection of interspecies as antigen and elimination of a known species of origin as a contaminant.
3. the use of a DNA-product-of-reaction as a probe to search for viral-specific RNA in tumour cells.

C-type RNA-containing viruses (leukemia and sarcomas) have *repeatedly* been identified in avian, murine, feline, rat and primate and human tumours.

In 1969[17], it was proposed that the cells of most vertebrates contain genomes which contain C-type viral-RNA-directed DNA-sequences that are vertically transmitted from parent to offspring.

Depending on the organisms' genotype (DNA) and a variety of environmental factors which could modify the expression of the genotype into various PHENOTYPIC

characteristics, *EITHER* virus production or tumour formation (or both) may develop at some time during:

embryogenesis
growth
maturation or
senescence.

The so-called viral oncogene hypothesis (of TODARO and HUEBNER[20] 1972) states that vertebrates contain the genetic information for producing a C-type RNA containing virus in an UNEXPRESSED form within ALL somatic and germ cells. This information for gene expression is assumed to have been vertically transmitted throughout Evolution.

It is assumed that the endogenous virogenes (the genes for production of the C-type viruses) and the oncogenes (that portion of the virogene responsible for transforming a normal cell into a tumour cell) are maintained in UNEXPRESSED form by REPRESSORS in *normal* cells.

Innumerable environmental influences such as:

1. Ionising irradiation – Röentgenrays
2. Chemical carcinogens – tars etc.
3. Teratogens – drugs, Thalidomide etc. and
4. Exogenously-added viruses, serve to transform cells by "switching-on" the endogenous oncogenic developmental information.

The presence of reverse transcriptionase, one of the criteria (see above) required to demonstrate the presence of RNA-containing viruses, IS detectable in *normal* embryonic *primate* cells (as well as in avian, feline and murine cells).

"MASKED" INFECTION

(SOUTHAM[19] – 1963)

The term "masking" was introduced to designate the phenomenon whereby an oncogenic virus disappears, or at least becomes undetectable, after a period of infection which produced a tumour. The explanation of this phenomenon is unknown, but an intriguing possibility is that the virus has truly disappeared after producing a PERMANENT and transmissible change in the affected cells or that the virus nucleic acid has been INTEGRATED into the genetic material of the cell.

Development ABERRATIONS, for example the expression of cancer in adult tissues, may result from destruction of the normal REPRESSOR systems required to INHIBIT the expression of both the oncogenic and the virogenic information.

Further extrapolations regarding CRANIOFACIAL anomalies and other congenital defects can be made from this evidence.

TOOLAN[21] (1960) demonstrated an agent in several human tumours grown in conditioned rats and hamsters which caused a GROWTH defect described as "MONGOLISM" when innoculated into new-born hamsters. The agent has *NO KNOWN* capacity to produce tumours.

The effect was caused by VIRUSES of at least 2 serological types.

The GROWTH defect is the result of SELECTED damage to OSTEOBLASTIC tissue.

Blastocyst-transplantation, in which a mouse embryo can be "manufactured" to contain an assortment of genetic characteristics adopted from 2 different strains, has produced a "Pandora's Box" regarding genetic "engineering" of reproduction.

More than 20 years ago, it was shown that cortisone could be used as a teratogen to produce cleft palates and lips in a variety of mouse strains.

Experimentally[10], it has been shown that:

a) when cortisone was given to A/J strains, *at a specific stage* in histo-differentiation, cleft lips and palates resulted in 100% of animals. This strain (A/J) was highly *susceptible* to this environmental influence, viz. the teratogen.

b) when cortisone was given to C 57 BL 10 mice, there was a drastic *reduction* in the % that developed clefts.

Therefore we can deduce that:

Specific strains of mice have varying degrees of resistance to both birth-defect-producing influences during embryogenesis *and* tumour-forming influences during maturation and senescence.

There is an INTRINSIC property in the genetics of defined mice strains which somehow provides the animals with either a low or high RESISTANCE to a variety of factors which produce diseases.

Susceptibility to teratogen-induced or spontaneous development of cranio-facial anomalies and tumours is evidently STRAIN-dependant in mice. Genetic factors are undoubtedly involved.

The myriad of individual cell types composing an individual organism *all* result from successive divisions of ONE ORIGINAL CELL – viz. the fertilised OVUM.

All somatic cells within an organism contain the same content of DNA.[17] This uniform content of each cell, nevertheless, results in a dramatic disparity in the transcription of unique sequences of DNA, resulting translation of m RNA (messenger RNA) into specific proteins (enzymes) and the synthesis of species-specific and cell-specific antigens.

If ALL somatic cells contain the SAME content of DNA within their nuclei, how then can cell-diversity arise? In other words, how can the *diversity* of the adult animal be derived from the unity of the fertilised ovum?

Through the process of DNA-replication, we know that DNA is partitioned *equally* to each daughter cell after each cell-division. ALL somatic cells have the same genotype (as demonstrated by the nuclear transplantation experiments with frogs described previously). In other words, the somatic cell nucleus contains ALL of the genetic history of the organism.

Therefore:- to obtain differentiated gene-expression, and subsequent cell and tissue diversity, one must consider that such a mechanism would be mediated by factors involving NON-DNA molecules, i.e. *EPIGENETIC* factors.

Factors local to the particular micro-environments presumably facilitate differential, highly selective gene-expression or gene-repression.

Therefore:- by *changing* the micro-environment of a diploid cell that is capable of subsequent cell-division, one should be able to REGULATE gene-expression.

Indeed, this IS the case.

DNA does *not* regulate DNA-activity.

ANY ONE of the Non-DNA-molecules such as

- histones
- non-chromosomal acidic proteins
- chromosomal RNA
- cytoplasmic molecules
- membrane-bond cell-surface or
- extracellular molecules

could serve as epigenetic factors or influences on cell-differentiation, histogenesis, morphogenesis, organogenesis and the integration of organ systems leading to the formation of the animal.

Most genetic diseases are *not* monogenetic (i.e. they are not caused by a single defective gene) but are polygenetic in that they are caused by a *series* of genes either in a unique sequence or by a combination of unique gene sequences.

GENES AND TERATOGENIC AGENTS

(SLAVKIN[17] – 1974)

Factors other than purely genetic aberrations appear to be responsible for developmental anomalies, viz the so-called teratogenic agents or teratogens.

Some well-known teratogenic agents are:[26]

Viruses – Rubella, Toxoplasmosis, Salivary gland virus disease (cytomegalic inclusion body), cortico-steroids, metal-ions, anti-metabolites, salicylates, Röntgen-irradiation (WILSON AND KAN – 1951), Vitamin A avitaminosis, Vitamin A in very large quantities (hypervitaminosis), Thalidomide, certain hormones, Aminopterin (cytotoxic agent) and Tolbutamide (oral hypoglycaemic agent). Riboflavin deficiency (GILMAN, PERRY AND HILL – 1952) (and NELSON et al. 1956), folic acid deficiency (THIERSCH – 1952) and Pantothenic acid deficiency (GIROND et al. 1955).

PRINCIPLES OF TERATOLOGY[2]

1. The effect of a teratogenic agent depends on the developmental stage at which it is applied. An example is Thalidomide-induced malformation for which the critical period of gestation is from the 27th to the 40th day.

   (LENZ AND KNAPP[13] – 86 cases, found it to be between the 27th and 33rd days).

   The susceptibility of embryonic structures to environmental insult is most acute during the phase of most active *differentiation*.[2] Prior to embryonic differentiation, teratogens are unable to produce or induce malformations and, when organogenesis is complete, teratogenic potential diminishes rapidly (as proved by maternal rubella and its timing).

2. KALTER, WILSON[10]

   The susceptibility of the embryo to one teratogen in a particular species does NOT necessarily carry over to others. In other words, the effect of a single teratogen may *vary* in different species and in different genetic strains of the SAME species, (e.g. cortisone produces cleft palate in mice and rabbits, but not in rats, and in certain strains of mice (the susceptible type) and not others.

   It has also been proved that susceptibility to cortisone is a MULTIFACTORIAL GENETIC situation. Not only the embryonic but also the maternal genotype is involved in the response to the teratogen. (KALTER)[10]

This multigenetic trait is found to be influenced by NON-GENETIC conditions such as:[10]

1. **Parity** – repeated breeding of a group of female mice revealed that the frequency of cleft palate consistantly declined with advancing pregnancy order.

2. **Maternal weight** – heavier mice had fewer malformed offspring than the lighter ones.

3. **Fetal weight** – malformed fetuses weighed significantly *less* than the normal ones.

4. Amount and type of food fed to pregnant females.

5. Uterine position of fetus.

6. Time of year when teratogenic agent was given e.g. cortisone given during the *colder* months led to a higher frequency of clefts.

The genetic component of mother *and* embryo ultimately determines why one fetus is susceptible to a teratogenic influence (e.g. rubella) while another is not.[2]

"PENETRATION" OF GENES

REFSUM[16] (1963) has stated that:

a number of genes exist which the usual environment is NOT able to influence greatly in their mode of action. In some cases, once the gene is present in the zygote a SPECIFIC trait will invariably develop. This does not mean that the environment is irrelevant. The conclusion is based only on what is called the "usual" environment.

Genes of this type are called highly PENETRANT.

From this type there is a gradual transition to those genes of very *low* penetrance, meaning that variations in the usual environment ("external milieu") are able, in a particular individual, to *alter* the course of development started by a gene.

Laboratory findings support the hypothesis that ENVIRONMENTAL malformations are a subtle product of the EFFECT of a potential teratogen exerting its influence in the developmental milieu of variable genetic susceptibility.

A teratogenic agent may produce NO apparent material disturbance (e.g. in some cases of rubella and Thalidomide) and, according to WILSON[25] (1959) – there is apparently *NO* standard relationship between the reaction of the embryo and the reaction of the mother to extrinsic agents. (? genes of high penetrance).

D. KLEIN[11] (1968) – "from the genetic point of view, MFD is transmitted as a dominant and reveals a great variability in PENETRANCE and EXPRESSIVITY."

The high infant mortality noted amongst siblings and close relatives of the patients *may* be a manifestation of the occasional LETHAL effect of the gene.

COTTER[3] (1968) – was able to examine 19 members of one 5-generation kindred where the grandmother was a typical case of MFD. Here, he had one mutant gene within the one large family.

His findings were that there was a *broad* spectrum of phenotypic manifestations of the single genetic defect, indicating the presence and importance, of MODIFYING genes on the *same* chromosome or on some other chromosomes in the genome. There was regular, autosomal dominant gene transmission, but the affected females appeared to produce a greater number of affected than of normal offspring. (About 35% of all affected individuals demonstrated some anomalous development of the palatal shelves).

MUCOPOLYSACCHARIDE SYNTHESIS

The etiology of cranio-facial anomalies MAY be related to mucopolysaccharide synthesis.[4] The ground substance of bone, fibrous tissue and cartilage has a high content of acid mucopolysaccharides in such components as:

- chondroitin sulphate
- terato sulphate
- heparitin sulphate
- heparin and
- hyaluronic acid

These components are metabolically active with constant new formation, break-down and resynthesis occuring.

The presence, or absence, of these compounds influences the core-pattern of certain anomalies.

DE MEYER and DE PLAEN[4] have stated that congenital malformations can occur when the carbohydrate metabolism is disturbed in the mother.

The incidence of congenital malformations is *significantly* higher in infants of diabetic mothers – 8% as against 2%. In rat embryos, it has been shown that:[4]

1. Co_2 production and glycogen incorporation have been established in *normal* embryos as early as 13 days. At this stage, teratogenesis *does* occur.

2. Teratogenic agents produce measurable disturbances in metabolic pathways both in vitro and in vivo.

3. Close correlation was observed between the teratogenic potency of the drug in question and the % of metabolic inhibition.

The total quantity of sulfo-mucopolysaccharides is REDUCED in embryos from cortisone-treated mother mice.[4] This conclusion is based on the fact that chemical and histo-chemical studies of other tissues have shown such a *reduced synthesis* of acid mucopolysaccharides.

This change in the sulfo-mucopolysaccharides of the groundsubstance (which fills in the space between cells and fibrous structures in the connective tissue of the palatal shelves) may be envisaged to result in INSUFFICIENT development of INTERNAL FORCE in the palatine shelves.

This, in turn, would delay the wave-like movement of the shelves from the vertical to the horizontal plane.

In view of the continued growth of the rest of the face, the palatine shelves are deprived of the possibility of reaching each other, with a cleft palate as the result.

Thus experimental evidence *does* exist in favour of the view that a decrease in the sulfo-mucopolysaccharide synthesis is one of the mechanisms by which cortisone is teratogenic.

Other factors which cause a decreased synthesis are:

1. administration of hydro-cortisone and salicylates.
2. AVITAMINOSIS and HYPERVITAMINOSIS of Vitamin A.
3. Röntgen irradiation LARSSON[12] – (1962).

A reduced synthesis of sulfo-mucopolysachharides can be surmised to depend on either:

1. damage to the cells that produce these substances.
2. interference with some of the enzyme-systems that regulate the synthesis.

It may therefore be presumed that such a decreased synthesis is caused by a number of apparently *widely divergent* factors.

The possibility of the appearance of fetal damage as a result of reduction in sulfomucopolysaccharide synthesis must be evaluated on the basis of the *degree* of disturbance and the *stage* at which it occurs.

CHROMOSOMAL CHANGES

(LUSTENBERGER and SHAPIRO)[14] (JULY–SEPTEMBER 1974)

Over 1800 inherited diseases have been described and one in every 150 live births has a chromosomal abnormality.

MECHANISMS OF PRODUCTION OF CHROMOSOMAL ABNORMALITY

1. MEIOTIC NON-DISJUNCTION

One of the most common, especially in mothers older than 35 years, is meiotic non-disjunction where the chromosome *fail* to separate during meiosis.

The result is a fertilised ovum (zygote) having one chromosome *pair* from the mother and a *single* chromosome from the father.

The anomaly is called ATRISOMY (DOWNS – 21) – MONGOLISM.

2. TRANSLOCATION

A break occurs in each of 2 separate chromosomes with the two broken ends sticking together in the healing process. This individual has a normal phenotype because there is NO SIGNIFICANT LOSS in genetic material. Albeit "re-arranged", it is said to be "balanced".

Some of the gametes (sex cells) produced by this individual *may* result in an unbalanced zygote when fertilised by a normal gamete from the other parent.

3. "FRACTURE" OF CHROMOSOMES – NICHOLS, et al.[15] (1962)

A recent observation of chromosomal changes induced in man during measles is the "fracturing" of the chromosome by the virus.

This could mean that an unidentified viral illness could be the ultimate offender rather than the agent employed for its treatment, for example Tetracycline.

We are able to define many chromosomal abnormalities by the newer techniques but we[14] still (July–Sept 1974) cannot detect changes in the gene. In many cases, we see the *effect* of a change in the gene by the change in the ENZYME for which it codes.

There is a growing list of diseases caused by the absence or change of an enzyme.

The diagnosis of a disease can be made by biochemical assay.

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PATHOGENESIS

INTRODUCTION

Whilst there would appear to be a general agreement on the role played by the heredity - genetic - exogenous-factor triad in the etiology of MFD, the same can, unfortunately, not be said for the pathogenesis of the syndrome.

Over the past 7 or 8 decades, a number of widely-differing hypotheses have been advanced by various workers, ranging from a genetically-controlled interference in the vascular supply to a specific embryonic area to a defect in the normal migration of neural crest cells which control mesodermal production.

Before commencing with a discussion of the merits or otherwise of the theories, it would seem to be advisable to revise briefly certain aspects of the normal course of events in the embryological evolution of the fetus if we are to understand the abnormalities to be recounted (STARK).[16]

At the third week of intra-uterine life, the 3 millimetre-long embryo develops a head and tail FOLD.

Below the bulging fore-brain is an invagination or a dimpling of the ORAL PIT at the bottom of which is the STOMODEUM.

Because of this invagination the region of the upperlip forms a bilamellar membrane, consisting of an outer and an inner layer of EPIDERMAL CELLS.

Into this epithelial branchial membrane, NEUROECTODERM, in the form of MESODERM migrates to form three masses, one medial and two lateral.

If any of these masses are in short supply, or absent, the epithelial wall will pull apart and a cleft will develop.

The deficiency of mesoderm that is present may be great or small; if small, an INCOMPLETE CLEFT will result, and, if large, the cleft will be total or complete.

Between the Stomodeum and the heart are the BRANCHIAL ARCHES.

Once the Stomodeum ruptures and the oral pit joins the primitive gut, in the mento-cervical region, the embryo has an outer layer of ectoderm and an inner layer of endoderm. The bilamellar membranes are called BRANCHIAL MEMBRANES.

Into this branchial membrane, as in the upper lip, NEUROECTODERM will migrate from the dorsum as MESODERM.

In the area of the mandible and neck there is migration into several areas forming surface elevations, or BRANCHIAL ARCHES. These areas are mesoderm, surfaced on either side by epithelium.

Between the arches are the branchial membranes (bilammelar structures) which, if not adequately supported above or below, will PULL APART, forming clefts or cervical fistulae.

Behind the convex arches are concavities or pouches that will give rise to well-known adult structures.

There is MESODERMAL MIGRATION (normally) into the maxillary region, forming the ZYGOMATICO-MAXILLARY COMPLEX.

Similarly, there is mesodermal penetration into the mandibular region, forming the FIRST BRANCHIAL ARCH, of which Meckel's cartilage makes up the major part.

This arch will form the malleus, incus and part of the stapes as well as the muscles of mastication, the MANDIBLE and the TRIGEMINAL NERVE.

The branchial cleft between Arches One and Two, forms the EXTERNAL AUDITORY CANAL.

The bilamellar membrane persists as the TYMPANIC MEMBRANE.

The First Pouch forms the EUSTACHIAN TUBE.

The Second Branchial (or Hyoid Arch) depends on migration of mesoderm to form the remainder of the external ear as well as portions of the hyoid arch. The Second Arch gives rise to the muscles of facial expression and the FACIAL NERVE.

MESODERMAL DEFICIENCY AS A PATHOGENIC FACTOR

(RICHARD B. STARK)[1]

If the relative or total absence of mesoderm occurs in the zygomatic region, a Treacher Collins Syndrome will result.

If the First Arch be deficient, there will be a distortion of the helical crus, and in addition, pre-auricular tabs, hemignathia and macrostomia.

(*Relative* hypoplasia of the First Branchial Arch will produce a Pierre Robin Syndrome).

Absence of the Second Branchial Arch will result in distortion of the lower part of the auricle and facial paralysis.

If the mesodermal deficiency is in the First *and* Second Arch regions, the patient will exhibit hemignathia and microtia.

FERNANDEZ AND RONIS[2] (1964)

Consider that the Treacher Collins Syndrome results from a retardation or failure of differentiation of maxillary-mesoderm at or after the 50 millimetre stage of the embryo. The fact that the *teeth* of the upper jaw are usually unaffected and ordinarily are present by the sixth week, is further evidence of retardation or arrest of differentiation AT or AFTER the SECOND MONTH of fetal life.

The FIRST BRANCHIAL ARCH of the Visceral Mesoderm also advances secondarily to form the mandible and again retardation occurs on the same basis.

DEFICIENCY IN THE VASCULAR SUPPLY AS A PATHOGENIC FACTOR

The first implication that an ARTERIAL MALFORMATION might be the causative mechanism for congenital anomalies was made by TANDLER of VIENNA in 1902.[18]

VOGEL[19] (1952) – pointed out that cerebral vascular anomalies occurred regularly in the region normally supplied by the INTERNAL CAROTID ARTERY.

STARK[16] performed experiments on chick embryos in which certain arteries and veins were destroyed by an electric current.

20% of the treated chicks developed anomalies while none of the untreated control group were so affected.

J. McKENZIE[12] (1958) WROTE:

In the interval, (3rd–5th week), between the disappearance of the 1st Aortic Arch and the full development of the EXTERNAL CAROTID ARTERY, the 1st Branchial Arch has a hazardous existence, dependant during that time on a relay of THREE successive vessels.

These are –

the remains of the 1st Aortic Arch
the STAPEDIAL artery with its branches

and

the External Carotid artery.

The existance of the 1st Branchial Arch is also dependant upon some split-second timing on the part of these vessels as one relinquishes and the next adopts the supply of that region.

At this stage, it is as well to recall the effect of any obliteration of any large artery during adult life.

Providing that the patient is young and healthy, arterial ANASTOMOSES with adjacent vessels can compensate for the injured artery.

Compensatory anastomoses will be *as* active during embryonic life and survival of the tissues supplied will be as easily assured.

These tissues, however, are seething with an activity, viz. growth and differentiation, which is known to have a high utilisation of oxygen and other nutriments.

All these compensatory anastomoses may develop in response to such a defect (a poorly-developed STAPEDIAL ARTERY) and, consequently, NO abnormality need ensue.

On the other hand, a SLOWER response by one of the neighbouring vessels may result in a relatively short but nevertheless crucial period of malnutrition in a region normally supplied by the Stapedial artery.

HALE[4] (1935) showed that anophthalmos and cleft palate occurred in pig embryos when the sows were fed on a Vitamin A – deficient diet.

As a result of experiments carried out on the production of deformed limbs by deficiencies of nutrition on pregnant animals by GIROUD, LEFEBRES, PROST and DUPUIS[3] (1955) – they reported that "arrest of blood circulation" in the dilated marginal veins (of the limbs) had occurred.

The vascular endothelium had disappeared and the coagulated blood had come into direct contact with the tissues.

Not only is it possible to produce a condition like the 1st Arch Syndrome, but it also appears, from experimental procedures as well as anatomical findings, that teratogenic effects are mediated THROUGH the vessels of the part concerned, and, since the bloodvessels of the 1st Arch normally provide it with a rather hazardous existence at one period, it is not surprising that this region is among the most vulnerable.

It is not suggested from such findings that the 1st Arch Syndrome is caused by DIETARY deficiencies or conditions akin to experimental procedures for these are extreme and unlikely to occur naturally.

It is, however, ENOUGH to postulate a GENE or GENES as the INITIAL FACTOR *inhibiting* or even preventing the development of the Stapedial artery.

The compensatory anastomoses of the surrounding vessels in such an emergency call for unusually *large* supplies of nourishment. The normal or minimal amount for normal development is unlikely to allow for compensatory reactions.

The RESULT, then, will be INHIBITION of growth in the area supplied by the faculty Stapedial artery and its branches and, therefore, a congenital anomaly such as MFD.

The PENETRANCE of the gene responsible for the 1st Arch Syndrome therefore depends on the NUTRITIONAL STATE and DIET of the mother during the first few weeks of pregnancy.

> Even if the diet is minimal or "adequate", the child may be abnormal because only an excellent nutritional state can successfully prevent the appearance of the anomaly.

The EXPRESSIVITY and SPECIFICITY of the gene depend on the details and TIMING of the maladjustments occurring among the vessels concerned.

McKENZIE (1968)[13] –

The degree of failure of the development of standard vascularisation may determine the SEVERITY of the anomaly. Such failure might even determine, *despite* abnormal genes, whether or not the anomaly would eventually occur.

MECHANISM OF THE VASCULAR DEFICIENCY

(McKENZIE)[11] – writes:

According to KEIBEL and MALL[8] (1910–12) the normal development of the 1st Aortic Arch is as follows:-

Three arteries are produced from the 1st Aortic Arch. They are:-

i) the Supra-orbital artery (later to become the Middle Meningeal artery)
ii) the Infra-orbital artery (representing the Maxillary artery) and
iii) the Mandibular artery (or Inferior Dental Artery)

With the disappearance of the 1st Aortic Arch, these 3 vessels are all maintained by the Stapedial Artery, a short-lived vessel in the human embryo, passing through the Stapes, and supplying the structures derived from the posterior end of the 2nd Branchial Arch.

It affixes itself to the stem of the Supra-orbital artery.

When the External Carotid artery develops, it takes over these 3 vessels again and the Stapedial artery disappears.

McKENZIE[11] –

The two vessels whose absence is involved in the production of the Treacher Collins Syndrome are the Stapedial and Infra-orbital arteries.

YET, according to the foregoing description, there is no more reason for the Infra-orbital vessel being associated with the absence of the Stapedial artery than for either of the *other* two 1st Aortic vessels.

Could the *actual* development not be as follows?

Instead of the Supra-orbital, Infra-orbital and Mandibular arteries, arising fanwise from a single point, as proposed by KEIBEL and MALL,[8] let them arise SEPARATELY.

Let the Infra-orbital artery, since it originally runs deep to the Mandibular nerve, be the vessel which receives the Stapedial artery and which depends upon it to a greater extent than do the others for survival.

Without the help of the Stapedial artery, the Middle Meningeal artery could still continue to function by retaining its connection with the Dorsal Aorta.

This is SIGNIFICANT when it is remembered that the specimen described (A.R. 456/1954) *had* an aberrant vessel from the Middle Meningeal artery which *could* have

anastomosed with the Internal Carotid artery at one time around the back of the Mandibular nerve.

The Mandibular artery could, likewise, have survived from its connection with the Ventral Aorta or the developing EXTERNAL CAROTID ARTERY.

In addition to describing what is the more probable sequence of events in the development of the vessels in this region we can SHOW that there is still, in the adult, a remnant of the First Aortic Arch, viz. that part of the Middle Meningeal Artery between its origin from the Maxillary Artery and a point near its bifurcation.

That small piece of 1st Aortic Arch, between the Infra-orbital Artery and Mandibular Artery is TRANSFERRED to the Middle Meningeal Artery as well, when the Infra-orbital artery forms its anastomotic loop around the Mandibular nerve to lie superficial to it in the adult.

It seems then, that the ORIGINAL LESION in the Treacher Collins Syndrome lies with the Stapedial artery.

Its ABSENCE will give rise to defects of the Stapes and Incus as well as to maldevelopment of the 1st Aortic Arch vessels, usually involving, but not necessarily restricted to, the Maxillary artery.

Failure of the Inferior Dental artery to retain or find an auxillary source of supply, will give concomittant abnormalities of the mandible.

The possibility of a NORMAL Stapedial artery capable of supplying the posterior end of the 2nd Branchial Arch and no more, will account for the defects of bones and soft tissues being confined to the FACE.

We can in this way account for ALL the recorded anomalies constituting the Treacher Collins Syndrome, however severe, however variable and, furthermore, we can point to the 6th week of intra-uterine life as being the age for INCEPTION of the abnormality, i.e. immediately AFTER formation of the primitive face.

(The recent finding of a decreased heat pattern over the region of the external maxillary artery is also suggestive of a circulatory disturbance – IDE, MILLER AND WOLLSCHLAEGER [7] (1970).

THE ROLE OF GENES IN THE PATHOGENESIS OF THE SYNDROME

McKENZIE[13] (1968). has already stated that mutant genes have expressivity and penetrance and that the epigenetic pathway of a developing organ (in this case, the Stapedial artery) is governed by genetic influences at *every* step with such a fine balance between opposing genes, that the path is easily influenced by EXTRANEOUS or minor factors, the result varying from no visible abnormality to a gross defect.

He believes, further, that opposing gene activities and associated factors such as NUTRITION (c.f. Vitamin A, and Muco-polysaccharides) are eventually responsible for what we see in the child.

In Man, the Stapedial artery disappears after the External Carotid system has taken over. In rats, it *persists* into adult life and, in view of this phylogenetic variation, its "coming and going" behaviour MUST be regarded as gene-controlled.

The Stapedial artery with its genetic misbehaviour may be compensated for by the establishment of anastomoses (as described above) and expressivity and penetrance may therefore be a measure of the degree of compensatory vascular anastomoses, instead of or as well as, the balance of gene activity in an epigenetic pathway.

ARYA[1] (1973)

There is evidence, from cephalometric analysis of twins, that development of the skull, face and dentition is dependant upon an INHERITED GROWTH PATTERN, the genetic factors involved acting *separately* on different components of the cranio-facial complex.

The identity of these components and their specific modes of genetic control remain largely obscure, one of the major problems being the complexity of multifactorial inheritance.

It is generally accepted, however, that virtually all the dento-facial characteristics are POLYGENETIC and continuously variable.(10)

A small area of the skull may be under pure genetic or pure environmental control, or a combination of the two, but, unless a small area is considered, MULTIPLE and, possibly, independant mechanisms may be operating which may nullify each other.

KRAUS, WISE AND FREI(9) (1959) suggested that the contour of a bone segment is an expression of the "Total Morphologic Configuration" of that bone and thus may reflect the GENETIC control of that bone.

NEURAL CREST CELL MIGRATION AS A PATHOGENETIC FACTOR

HÖVELS[6] (1953) –

Based his attempts at finding the cause of the anomaly on the work of HÖRSTADIUS[5] (1950) who found that the Branchial (Visceral) Arches were derived in their entirety from the rostral end of the NEURAL CREST, where areas could be mapped out according to these derivatives.

Extirpation of these areas resulted in deficiencies in, or ABSENCE of, the corresponding arches.

HÖVELS maintained that some defect in the Neural Crest area responsible for the 1st Branchial Arch produced the structural anomalies of the Treacher Collins Syndrome.

According to MCKENZIE[11] –

this theory will *not* stand critical examination.

He writes:

"for example, the most frequently affected part of the face is the zygomatic bone which is the proximal part of the maxillary process.

If, as Hövels suggests, it were predetermined within the neural crest that there was to be NO zygomatic bone, then surely, the maxillary processes would not be long enough to meet and fuse with the NASAL processes?

Yet they DO; there is *no* cleft palate, hare-lip or interference with the NASO-LACRIMAL duct".

(Personal note: But there *ARE* cases where these features are most certainly present. Cleft-lip and cleft palate have regularly been reported. Some authorities have placed the incidence of clefts at between 25% and 50%. – STOVIN[17] (et al.) (1960).

Abnormalities of the naso-lacrimal apparatus are *much* more frequent than was previously thought (WHITAKER, KATOWITZ and RANDALL[20] – 1974).

In the light of present knowledge, MCKENZIE's objection to the theory put forward by HÖVELS should not, therefore be taken too seriously.

In fact, some excellent work done by POSWILLO[15] (1974) has done much to support that which was done by HÖVELS over 20 years ago.

PATHOGENESIS – according to POSWILLO[15] (1974)

In an effort to explain the pathogenesis of the syndrome, POSWILLO constructed, and subsequently investigated, ANIMAL MODELS of the malformations.

Study of the serial development of both embryo and fetus affected by a teratogen, leading to a specific type of deformity, has provided important information on the mechanism by which the developing structures are disorganised.

An animal model of the syndrome was constructed by administering 100,000 I.U. of water-soluble Vitamin A to pregnant WISTAR rats at day 8,5 of development. This lead to a 100% incidence in the off-spring of oto-mandibular defects, characteristic of the human syndrome.

Serial stages of the embryological development were observed and the indications were that the mechanism of the malformation was an early DESTRUCTION of the NEURAL CREST CELLS of the facial and auditory primordia which migrate to the 1st and 2nd Branchial Arches.

The destruction of these cells in the vicinity of the neural crest, *before* migration has been well-established, leads to the formation of a "vacuum" in the neighbourhood of the OTIC cup into which the surrounding tissues "flow".

The first consequence is that the developing otic pit which is usually located adjacent to the 2nd Branchial arch, "floats" upwards into 1st Branchial arch territory.

Thus, the future ear becomes re-located over the angle of the mandible rather than further back on the head.

The second consequence of the loss of many of the cells destined to provide the mesenchyme of the 1st and 2nd Branchial arches, is a SYMMETRICAL overall HYPOPLASIA of many of the derivatives of the 1st and 2nd Branchial arch mesenchyme.

In this tissue develops the outer and middle ear, the zygomatic arch and malar bones, as well as the maxilla and the mandible.

From the clinical appearance of both the animal model and the human syndrome, it appears that those neural crest cells which are *most* affected are those which have the *least* distance to travel, i.e. those which contribute to structures close to the primitive otic cup.

It may well be that those neural crest cells which have the greatest distance to travel, begin their migration EARLIER than those destined to play a formative part in the development of the oto-mandibular regions.

Thus, they may be at, or close to, their destination when destruction of the "late-starter" cells takes place.

The details of this selective phenomenon, both in Vitamin A-induced rat models and in genetically-programmed humans with the syndrome, await elucidation. Nonetheless, the OVERALL effect of this abnormal and excessive death of neural crest cells is a symmetrical hypoplasia in those structures affected in the face, jaw and ear.

That these structures are not entirely absent is due, probably to the survival and migration of SOME neural crest cells and also to the contribution made by the lateral plate mesoderm.

McKENZIE[13] (1968)

has written that he considers that the adjoining tissue, for example the FRONTO-NASAL process, has NOT suffered (as a result of an abnormal Stapedial artery) and it can "HELP" a tissue in distress (by sharing its blood-supply with it).

At this stage, the vascular system is a widespread meshwork of capillaries and compensatory anastomoses can readily be developed.

Nature abhors a vacuum and avascular tissues and attempts to contribute to the adjoining blood-supply in this way.

STARK[16] (1968)

believes that vascular hypoplasia may be accompanied by MESODERMAL HYPO-PLASIA and states categorically:-

"The Thesis that mesodermal deficiencies are secondary to vascular hypoplasia, is an ATTRACTIVE ONE"

The work by VOGEL[19] (1952) on vascular anomalies seems to support this view.

PERSONAL NOTE:

Why cannot a mutant or defective gene, responsible for an un-sound, non-functioning Stapedial Artery, be the *direct* cause of a failure of vascularisation of the already-migrated mesoderm and an indirect cause of an "absence" or deficiency of mesoderm required for the development of the 1st Branchial arch?

POSWILLO[15] continues:

Despite the very early deficiency in mesenchyme, the design of the face proceeds according to plan; the end-result of the deficiency of mesenchyme (i.e. the "building

blocks" of human morphology) is a REDUCTION IN SIZE and dimension, but the creation of a facial form recognisable by reference to the original design of facial morphology.

There *IS* a degree of growth of the facial complex during infancy and childhood in the syndrome, which leads to *some* cosmetic improvement.

This capacity for growth and improvement is related to the existance of a functioning periosteal matrix.

While the ramus and condyle of the mandible, and the malar bones, may be hypoplastic, they are STILL influenced by the MUSCLES which display near-normal activity.

Thus, a functional matrix system exists in this syndrome which provides the IMPETUS for symmetrical and progressive growth of the hypoplastic facial skeleton.

MOSS[14] (1968) has shown that skeletal units grow in response to their periosteal matrices.

Although they are entirely separate entities, it is well worth comparing, at this stage, the pathogenesis of the Treacher Collins Syndrome and HEMIFACIAL MICROSOMIA.

POSWILLO[15] – (1974)

In hemifacial microsomia, there is *no* genetic background identifiable. The abnormalities of the ear and jaw are UNILATERAL.

The most common form consists of a reduction in size of the pinna and tragus, hypoplasia of the mandibular condyle and ramus, hypoplasia of the MALAR bone, deficiency of the Masseter, Temporal and Pterygoid muscles and paresis of facial expression.

POSWILLO has demonstrated on an animal model of this anomaly, that the UNSELECTIVE destruction of differentiating tissues in the vicinity of the ear and jaw by an expanding HEMATOMA produced this anomaly.

The causative event took place AT THE TIME OF RAPID DIFFERENTIATION of structures designed to form the functional matrix of the cranio-facial complex.

It is *important* to note that where, in MINOR cases, where the haemorrhage was small and localised close to the original site (AT the anastomosis forming the Stapedial arterial stem), only MINIMAL damage was done to the oto-mandibular structures; minor defects were observed in the outer and middle ear and mandibular condyle, BUT the integrity of the principle growth-determinant viz. the muscle-bone periosteal matrix, was but little impaired.

In severe cases, where the hematoma was extensive, VAST tracts of tissue destined to form the ramus of the mandible and masticatory muscles were obliterated with ensuing severity of the deformity.

STARK[16] (1968)

attempted to simplify the various eponymic facial syndromes that have been described, scrambled and confused in the past. He assigned to them a possible common pathogenesis viz that of a MESODERMAL DEFICIENCY and postulated that:-

most of the elements of such syndromes produce precise patterns and occur in well-defined ZONES of mesodermal penetration.

Thus:-

1) failure of adequate mesoderm migration of the upper lip will lead to formation of cleft-like deformities.

2) in the area of the mandible and the neck, the mesodermal tissues form the Branchial arches.

Normally, mesoderm migrates into the maxillary region and forms the zygomatic-maxillary complex – STARK[16] (1968).

Similarly, mesodermal penetration into the mandibular region forms the 1st Branchial Arch, of which Meckels' cartilage is the greatest part.

A RELATIVE TOTAL ABSENCE of mesoderm in the xygomatic region results in the Treacher Collins Syndrome.

If the 1st Arch is deficient, the HELIX of the ear, and preauricular ear tabs, will be distorted with hemi-gnathia and macrostomia present.

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THE CLINICAL PICTURE

LONGACRE[6] (1965) along with the majority of authorities, reserve the term Treacher Collins Syndrome to signify that group of BILATERAL cases which are definitely HEREDITARY and which present the following characteristics:-

1. Antimongoloid obliquity.
2. Coloboma (notching) of the outer third of the LOWER eyelid.
3. Defects, both variable or extensive, of the EARS.
4. Defective development of the maxillary and mandibular components of the FACIAL-BONE-COMPLEX.
5. Prominent (unaffected) FRONTO-NASAL elements which dominate the face.
6. LINGUIFORM extension of the hair-line into the pre-auricular area.
7. ASSOCIATED MALFORMATIONS such as cleft palate, facial clefts, accessory or pre-auricular tissue tags, micrognathia, macrostomia etc.
8. The NEUROMUSCULATURE is unaffected.

1. THE AXIS OF THE ORBIT – ANTIMONGOLOID OBLIQUITY

The Treacher Collins Syndrome is, of course, not solely responsible for anti-mongoloid obliquity or hypertelorism of the eyes. (It can be racial, a variation within a population-group or the result of some other malformation).
However, should the malar bone be completely *absent* or represented by a mere vestige, then the obliquity is part of the syndrome. The absence of the malar bone is then the cause of the anti-mongoloid obliquity.

In the syndrome, there is only a vestige of the zygomatic arch extending backwards from the maxillary bone and the temporal extension, too, is missing.

The eyeball may protrude or deviate laterally. The absence of the lateral palpebral ligament allows the lower lids to droop downwards.

2. COLOBOMA

A coloboma is always present in the full-blown syndrome and occurs at the junction of the outer 1/3 and inner 2/3 of the lower eyelid.

The inner 2/3 (or 1/5) of the lid is defective: the eyelashes are immature or absent, the Meibomian glands are absent and the inter-marginal strip is missing. Although much more rarely, the coloboma of the upper lid is sometimes present.

(Explanation: it is generally accepted that the inner 2/3 of the lid arises from the maxillary process while the outer 1/3 is paraxial in origin).

The formation of colobomas of the lids and the associated defects of the lashes and the Meibomian glands, and other anomalies of the lid apparatus, must be regarded as secondary effects of the skeletal hypoplasia and consequently malposition of the soft tissues (LONGACRE[7] 1968).

3. DEFECTS OF THE EARS

Malformations of the outer, middle and inner ears are variable, and in most cases, fairly extensive in nature, ranging from "notching" to total microtia.

Cases have been reported with only the merest rudiments present with associated degrees of deafness, as the middle ear is just as vulnerable as the external parts.

Commonly found are:-

1. Absence (Atresia) of external auditory canal and ossicles i.e. sclerosis of inner ear. No middle ear of tympanic space.

2. Deformities of the pinna and hypoplasia of various portions of the auricle (microtia).

3. Ears are set low down, or inclined (i.e. synotia).

4. Small tragus and auricular lobe remnant derived from the 1st Branchial Arch components.

5. Fusion of the malleus and incus and deformity of the ossicles, including the stapes which is occasionally absent.

4. DEFECTIVE DEVELOPMENT OF THE FACIAL BONES

All the bones arising from the maxillary and mandibular processes show some disturbances in growth potential.

The absence of the malar bone does not deter the orbit from becoming encircled by the bone.

The malar bone is the only bone that is ever entirely absent. This leads to the absence of the zygomatic area (or eminence).

The maxilla displays a defective growth pattern and the palate is usually high, narrow and frequently cleft.

The mandible shows changes that range from severe degrees of micrognathism to jaws with a more normal form.

The angle is often more obtuse than normal and the ramus may even be absent.

The condyloid cartilage appears to be the most vulnerable tissue and reduction in length of the mandible depends on the extent to which it has been affected.

The Temporo-mandibular joint may be under-developed or even absent. It is often displaced anteriorly.

The combined effect of failure in development of the maxilla and the mandible often accounts for some form of anterior open bite. It is sometimes argued that this is due to lack of tongue room. There is usually a steep mandibular plane.

5. PROMINENT FRONTO-NASAL ELEMENTS

In many cases, the fronto-nasal elements, which are *unaffected* in the disorder, tend to dominate the face and stand out in contrast to the reduced maxillary process parts. Where the nose happens to be a prominent feature of the individual, it is rendered even more so in the syndrome.

The absence of the fronto-nasal angle leads to the bridge of the nose being raised. The columellae are very short, the lateral cartilages small and the nares narrow.

6. LINGUIFORM (TONGUE-SHAPED) EXTENSION OF HAIR

There is a distinctive extension of hair extending downwards onto the cheek in front of the *defective* ear or ears.

This has consistently been referred to in the literature and is a feature not seen in any other malformation of cranio-facial structures. (See Table 6).

7. ASSOCIATED MALFORMATIONS

The following associated malformations have been reported as occurring with the syndrome.

They are:-

(i) MANN[8] (1943) – deformity of the sternum.

(ii) STRAITH and LEWIS[11] (1949) – enlarged second metatarsal.

(iii) Cleft palate.

(iv) Facial clefts – viz. a transverse cleft which varies from macrostomia to complete oro-tragal fissure, i.e. along the line of the superficial gill clefts.

(v) Accessory ear (or pre-auricular) tissue tags.

(vi) Blind fistulae, or pouches or dimples found between the angle of the mouth and the ears.

(vii) Macrostomia is usually present but microstomia has been known to occur.

(viii) The mastoid bones are usually *not* pneumatised and the tips are hypoplastic.

(ix) The antra and para-nasal sinuses are usually *smaller* than normal.

(x) Rarely, nasal atresia and mouth-breathing.

(xi) Hypotrophy of the lacrimal and Meibomian glands with the absence of the lacrimal punctum.

(xii) Hare-lip, club-foot, synostosis of the joints of the limbs and spine, aplasia of the meta-carpals and phalanges as well as asymmetry of the chest.

(xiii) Cardiac anomalies.

DISCUSSION OF THE CLINICAL PICTURE

FRANCESCHETTI and ZWAHLEN[3] in 1944 reviewed the then known cases of the syndrome and described the spectrum of its manifestations so fully that little subsequent amplification has proved necessary.

Their classification of the syndrome into the five types, however, has been the subject of some criticism. (This will be discussed later).

The classification according to FRANCESCHETTI and ZWAHLEN:-

1. The Complete form
2. The Incomplete form
3. The Abortive form
4. The Unilateral form
5. The Atypical form

1. THE COMPLETE FORM

There is little disagreement on this group. It comprises all, or most of, the following:-

(a) *All* have anti-mongoloid obliquity or slant of the palpebral fissures.

(b) Coloboma of the lower lid (sometimes of the upper) combined with deficient or absent eyelashes of the medial two-thirds or four-fifths of the lower eyelid.

(c) Hypoplasia or underdevelopment of the malar bone and mandible is obligatory. There is often concomittant underdevelopment of the other facial bones.

(d) Malformation of the external ears, and sometimes of the middle and inner ears.

(e) A high palate, abnormal dentition with malocclusion in the form of an anterior open bite.

(Macrostomia is a poor sign as it is difficult to judge by comparison with hypoplastic facial features).

(f) Blind fistulae or dimples between the ears and the angles of the mouth.

(g) Atypical lingui-form or tongue-shaped projections of the hair-line (side-burns) towards or onto the cheeks.

(h) Associated anomalies such as skeletal deformities and facial clefts may be present.

2. THE INCOMPLETE FORM (SYMMETRICAL)

Here the deformity is less marked and less extensive. The "minimal criteria" here are:-

(a) Anti-mongoloid obliquity of the palbebral fissures.

(b) Colobomata of the lower eyelids.

(c) Hypoplasia of the malar bone and/or mandible.

(d) The ears may be normal or almost normal as far as the external ear is concerned but deafness is often present.

3. THE ABORTIVE FORM

These cases are very rare in the literature, only three being fully reported viz. by BERRY[1] (1889) ISAKOWITZ[7] (1927) and SCHACHTER[10] (1947).

This classification is based upon the anti-mongoloid obliquity and the eyelid anomalies ALONE.

The value of this classification is thus problematical and has certainly resulted in the reporting of the numbers of doubtful cases as the syndrome.

4. THE UNILATERAL FORM

In this group, the congenital anomalies, *regardless* of number, degree or severity are confined to *one* side of the face. Only a few unilateral cases (which sometimes include hypoplasia of the facial muscles) have been described by FRANCESCHETTI, BROCHER and KLEIN[4] (1949), WEYERS[12] in 1951 and WILSON[13] (1958).

ROGERS[19] (1964) considers that this may be an artificial and inapplicable classification-terminology due to the fact that the so-called "unilateral" and some "atypical" cases reported to date seem to have been loosely assigned to a conglomeration of cases inappropriately designated as some form of "mandibulo facial dysostosis". LONGACRE[6] (1965) and ROGERS[19] (1964) agree that the term MFD or Treacher Collins Syndrome should be applied *only* to BILATERAL cases and that unilateral forms are properly to be regarded as First or Second Branchial Arch syndromes – separate entities *entirely* (see later).

5. THE ATYPICAL FORM

This includes the "incomplete" forms of the syndrome in which one or more of the principal characteristics of the complete, full-blown form are missing, whereas other abnormalities, which do not belong to the complete form (such as microphithalmos) may be present.

This group includes cases showing enough of the typical features to qualify as the syndrome but, with many "atypical" features, has often been "stretched" to include cases merging with other syndromes such as Cruzons' disease, Aperts' syndrome, Turners' syndrome, Oto-mandibular dysostosis and even "bird-headed" dwarfism.

Associated and less salient features include:

(a) Eye region

Microphthalmos
orbital hypoplasia
cataract
lacrimal canal atresia (ROGERS[9] 1964) (CONVERSE[2] 1964)
ectopia of pupils
double-row of lashes on lower eyelids
convergent strabismus

(b) Nasal region

absence of fronto-nasal angle
partial atresia of nasal fossae or nostrils
enlarged frontal sinuses
rudimentary sphenoidal sinuses

(c) Oral region

Macrostomia
cleft lip
cleft palate
prognathism
underdeveloped epiglottis

(d) Aural region

absence of external auditory canal
absence of mastoid air cells

(e) Skull region

Temporo-mandibular joint malarticulation
hypoplasia of petrous bone
narrow and deep Sella Turcica
enlarged sphenoidal and sphenomaxillary fissure

(f) Additional

Agenesis of homo-lateral lung
agenesis of frontalis muscle
club foot
synostosis of joints
mental retardation

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THE DIFFERENTIAL DIAGNOSIS

A large number of malformations of the face and, more particularly in the area of the 1st and 2nd Branchial Arches, have been described in the last two decades.

These observations were reported variously by pediatricians, ophthalmologists, oto-laryngologists, orthodontists, plastic surgeons and others.

Their descriptions reveal a large degree of heterogeneity, because most of these authors considered their cases only in the light of their own speciality.

The classification of the cranial-dysostoses of the 1st Branchial Arch is also complicated by the prevalence of transitional and mixed forms.

Consequently, KLEIN[2] – (1968) feels that under present circumstances (1968), any classification must be considered to be PROVISIONAL only.

CAMPBELL[1] and NEWTON AND POTTS (1971)

– have suggested the following classification of the cranio-facial anomalies:

A. ANOMALIES *PROBABLY* RELATED TO THE 1ST AND 2ND BRANCHIAL ARCH DEFECTS

1. Mandibulo-facial Dysostosis Syndrome.
2. Pierre Robin Syndrome.

B. ANOMALIES *POSSIBLY* RELATED TO THE 1ST AND 2ND BRANCHIAL ARCH DEFECTS

1. Otomandibular dysostosis (Hemifacial Microsomia)
2. Oculoauriculovertebral dysplasia (Goldenhar's Syndrome)
3. Oculodentodigital dysplasia (Weyer's Syndrome)
4. Oculomandibulodyscephaly (Hallermann-Streiff Syndrome)
5. Orodigitofacial Syndrome (Papillon – League Syndrome)
6. Otopalatodigital Syndrome (Langer – Gorlin Syndrome)

A.

1. MANDIBULOFACIAL DYSOSTOSIS
(TREACHER COLLINS SYNDROME)

The ESSENTIAL features are:

- antimongoloid palpebral fissures
- abnormal angulation of the lower eyelids
- colobomas of the outer third of the lower eyelids and, sometimes, of the upper lids.
- occasional microphthalmos

- ears are low-planted
- atresia or deformity of pinna of the ear
- atresia of the external auditory canal (deafness)
- absent ear ossicles (deafness)
- pre-auricular appendages (tissue tags)

- large nose, narrow nares
- obliterated fronto-nasal angle

- linguiform extension of hair onto cheek

- large, fish-like mouth (macrostomia)
- blind fistulas between angle of mouth and ear

- poorly developed supra- and infraorbital ridges
- absent, or hypoplastic malar bones
- non-fusion and flattening of zygomatic arches
- hypoplasia of mandible (ramus) – receding chin

- malocclusion – anterior open bite
- cleft or high arched palate
- sclerotic mastoids

- no mental retardation
- no dwarfism
- parental cosanguinity 10%

2. THE PIERRE ROBIN SYNDROME

- "bird-like" facies
- microgenia – small receding jaw
- deformed external ears
- occasional microphthalmos
- cleft palate – widely cleft
- glossoptosis
- marked hypoplasia of entire mandible
- agenesis of pterygoid muscles
- congenital heart lesions
- mental retardation 20%
- no dwarfism

B.

1. OTOMANDIBULAR DYSOSTOSIS (MANDIBULAR DYSOSTOSIS–HEMIFACIAL MICROSOMIA)

- macrostomia
- unilateral microtia
- unilateral supernumerary ear tags
- unilateral atresia or deficiency of the external ear canal in 30% of cases
- unilateral deficiency of infraorbital rim
- unilateral hypoplasia of malar bone and mastoid process
- unilateral failure of formation of mandibular ramus and condyle leading to facial asymmetry with eye and ear lower on affected side.
- malformed temporomandibular joint
- normal intelligence
- no dwarfism

2. OCULOAURICULOVERTEBRAL DYSPLASIA (GOLDENHAR'S SYNDROME)

- macrostomia – frequent
- unilateral coloboma of upper eyelids

- epibulbar ocular dermoids or lipo-dermoids
- microtia (occasional)
- preauricular appendages
- pretragal blind fistula
- aplasia or hypoplasia of pinna
- hypoplastic malar bone, flattening of eminence
- unilateral mandibular agenesis or hypoplasia with micrognathia
- hypoplastic facial muscles
- vertebral anomalies such as cervical vertebral fusion, spina bifida block vertebrae, occipitalisation of the atlas, hemivertebrae, supernumerary vertebrae, scoliosis
- anomalies of the fingers
- mental retardation 10%
- no dwarfism

3. OCULODENTODIGITAL DYSPLASIA (WEYERS' SYNDROME)

- microphthalmos
- epicanthic folds and iris anomalies
- micro-cornea
- narrowing of the palpebral fissures
- small orbits (pseudo-hypertelorism)
- thin nose with hypoplasia of the alae nasi and anteversion of nostrils
- dental anomalies with exposed dentine
- wide mandibular ramus and body
- finger and toe anomalies – cutaneous syndactyly, camptodactyly of the 4th and 5th fingers, anomalies of the middle phalanges of fingers and toes
- severe mental retardation 10%
- no dwarfism.

4. OCULOMANDIBULODYSCEPHALY (HALLERMANN – STREIFF SYNDROME)

- small face
- long, tapered, parrot-beak-like nose
- acute fronto-nasal angle
- microphthalmos and small orbits
- bilateral cataracts
- blue sclera
- hypotrichosis of eyebrows, eyelashes and in area of cranial sutures
- delayed sutural closure
- hypoplasia of nasal, maxillary and zygomatic bones
- hypoplasia of mandible – receding chin
- absent mandibular condyles
- anterior displacement of temporomandibular joints
- high arched palate
- dental anomalies, abnormal implantation and natal teeth
- brachycephaly
- vertebral anomalies
- no mental retardation
- proportional dwarfism

5. ORODIGITOFACIAL SYNDROME (PAPILLON – LEAGE SYNDROME)

- females only (disproved!)[3]
- telecanthus with pseudohypertelorism
- aquiline thinning of nose – hypoplasia of the alar cartilages
- alopecia of scalp
- aplasia or hypoplasia of mandible
- pseudo-cleft through midline of upper lip
- clefts of the hard and soft palate
- palate cleft laterally at biscuspid teeth
- malposition of maxillary canines
- cleft of tongue – trifurcation
- duplicated, hyperplastic frenulum
- malformation of digits – brachydactyly of hands, syndactyly, clinodactyly, polydactyly, camptodactyly
- mildly retarded
- no dwarfism

6. OTOPALATODIGITAL SYNDROME (LANGER – GORLIN SYNDROME)

- microstomia – "turned-down" corners of mouth
- anti-mongoloid obliquity
- broad nasal root
- prominent supra-orbital ridges
- low-set, deformed ears
- deafness
- absent frontal sinuses
- decreased pneumatisation of sphenoid and mastoid sinuses
- deformed extremities
- finger anomalies
- cleft palate
- severely retarded
- dwarfism present

In addition to the syndromes as classified by Newton and Potts, KLEIN[2] (1968) has described a number of others which, he feels, should be included in the same group to complete the classification of craniofacial anomalies derived from a perturbation of the First Branchial Arch.

They are:

OTOCEPHALIA (ST HILAIRE SYNDROME)

This represents the extreme and lethal stage among malformations of the First Branchial Arch. The outstanding features are:-

- almost total absence of the mandible
- rudimentary tongue
- ears planted so low that they converge and merge in the median ventral line
- ankylosis of the temporomandibular joint.

The lesion, according to KLEIN[2], may be assumed to be in the cephalic organisor, caused by a genetic or exogenous factor.

MANDIBULO-OCULOFACIAL DYSCEPHALIA

- microphthalmos
- cataract
- hypotrichosis
- hypoplasia of malar bone and maxilla
- high-arched palate
- dental anomalies
- brachycephalia

- prominent parietal and frontal protuberances ("bossing")
- persistent fontanelles.

PERSONAL NOTE:

Although the 7 first listed features are *identical* to those found in Mandibulo-oculo-facial dysmorphia (Hallermann - Streiff) syndrome, KLEIN[2] prefers to classify this syndrome separately. The only difference between the two would seem to revolve around the mandible. In the case of the HALLERMANN - STREIFF, it is very hypoplastic, while in the case of Mandibulo-oculo-facial dyscephalia, it is unaffected.

Would this not be a case of hair-splitting? Could this not be an example of a slightly "atypical" case of the Hallermann - Streiff Syndrome?

OCULOVERTEBRAL DYSPLASIA (WEYERS AND THIER)

- Unilateral deformities
- microphthalmia or anophthalmia
- dysplasia of maxilla
- macrostomia
- alveolar hypertrophy and malocclusion
- vertebral column anomalies, hemi-vertebral and rib anomalies
- *slight* hypoplasia of mandible

OTOVERTEBRAL DYSPLASIA (WEYERS)

- unilateral, low-implanted rudimentary ear (microtia, anotia)
- multiple malformations of the cervical and thoracic vertebral column

CRANIOPALPEBRO-IRIDOCUTANEOUS DYSPLASIA WITH LABYRINTHINE DEAFNESS AND OTHER CONGENITAL ANOMALIES (KLEIN)

- antimongoloid obliquity
- hypertelorism
- partial albinism with blue eyes and deaf-mutism
- widening of nose
- absent fronto-nasal angle
- hypoplasia of ascending rami
- retrognathia
- high-arched palate
- skull deformities
- defective implantation of teeth
- dysplasia of skeletal system
- joint ankylosis of upper limbs
- "webbing" of both axillary folds
- cutaneous syndactyly with "claw" hands
- normal intelligence

CERVICO-OCULOFACIAL DYSMORPHIA WITH DEAFNESS (FRANCESCHETTI AND KLEIN)

AND

CERVICO-OCULOACOUSTIC SYNDROME (WILDERVANCK)

- unilateral hypoplasia of face
- unilateral preauricular appendages
- labyrinthine deafness on affected side
- pneumatisation of mastoid process on the affected side
- linguiform extension of hair on affected side
- irregular implantation of teeth
- cervico-dorsal synostosis
- cranial asymmetry

PARALYSIS OF THE FACIAL NERVE, MIDDLE-EAR DEAFNESS (MALFORMATION OF THE OSSICLES) PRE-AURICULAR APPENDAGES, PRE-AURICULAR APPENDAGES, PRE-AURICULAR AND CERVICAL FISTULAE

- paralysis of the lower parts of Facial nerve
- slight malformation of the auricles and external auditory meatus
- malformations of the ossicles (deafness)
- pre-auricular pits and appendages
- cervical fistulae
- bilateral and symmetrical

PERSONAL NOTE:

KLEIN[2] has presented his classification as pertaining to perturbations of the *First* Branchial Arch.

The *Second* Branchial arch gives rise to the Facial nerve as well as portions of the external ear; therefore, this syndrome, with paralysis of the Facial nerve, must in all probability involve the Second Arch as well as the First.

OCULODENTODIGITAL DYSPLASIA WITH MICROPHTHALMIA

- microphthalmia (or even anophthalmia)
- dental anomalies (hypoplastic enamel)
- hypotrichosis
- epicanthis
- camptodactyly and/or cutaneous syndactyly

PYGO-PHALANGEAL DYSCRANIA WITH MICROPHTHALMIA

- narrow and deep palpebral slits
- microphthalmia
- coloboma of the iris and opacities of the cornea
- prominent forehead
- macrostomia
- hypoplasia of mandible
- malformation of the ears ("cats" ears)
- preauricular appendages
- polydactylia
- spina bifida

CONGENITAL MANDIBULAR DYSOSTOSIS WITH PEROMELIA

- hypoplasia of mandible
- prominent nasal elements ("bird-like" profile)
- hypoplasia of teeth (opisthodontia)
- peromelia (ectromelia, ectrodactylia)
- short stature – dwarfism
- normal intelligence

MAXILLOFACIAL DYSOSTOSIS (PETERS AND HÖVELS)

- hypoplasia of malar bones
- antimongoloid slant (obliquity)
- hypoplasia of maxilla
- mordex apertus
- "parrot-beak"-like nose
- reduced fronto-nasal angle
- *NO* mandibular hypoplasia – therefore a pseudo-lower-prognathism
- small oral cavity

ACROFACIAL DYSOSTOSIS (WYERS)

- hexadactylia
- median mandibular slit
- atrophic central incisor (? mandibular)

CRANIOMANDIBULOFACIAL DYSPLASIA

("BIRD-HEADED" DWARFS – SECKEL)
AND THE
RUBENSTEIN–TAYBI SYNDROME

BIRD-HEADED DWARFS

- dwarfism with "beak-like" nose
- hypoplasia of malar bones
- hypoplasia of mandible
- antimongoloid obliquity
- lobe-less, low-attached pinnae
- generalised hypotrichosis

- hypodontia and enamel hypoplasia
- clinodactyly
- no mental retardation (?)
- high-arched, narrow palate

RUBENSTEIN–TAYBI SYNDROME

- dwarfism with microcephalia
- antimongoloid obliquity
- hypotelorism
- prominent nose
- low implantation of ears
- occasional microstomia
- ocular anomalies
- mental retardation (I.Q. 15–30)

To facilitate the making of a diagnosis, the CHARACTERISTIC signs of eight of the above syndromes are set out hereunder in comparative table form. (Tables 6–9).

TABLE 6

Characteristic Sign of Syndrome	Mandibulo-facial Dysostosis	Pierre Robin Syndrome	Otomandibular Dysostosis	Oculoauriculo-Vertebral Dysplasia	Oculodento-digital Dysplasia	Oculomandibulo Dyscephaly	Orodigitofacial Syndrome	Otopalatodigi-tal Syndrome
Antimongoloid obliquity	++++	+	0 to +	++ to +++	0	++	0	++
Hypotelorism	0	0	0	0	++	0	0	0
Pseudohypertelorism	0	0	0	0	++	0	+++	0
Telecanthus	0	0	0	0	0	0	+++	0
Microphthalmia	+	+	+	+	+++	++++	0	0
Small orbits	0	0	0	0	+	++	0	0
Coloboma of lower lid	++++	0	0	0 to +	0	0	0	0
Coloboma of upper lid	+ (sometimes)	0	0	Unilateral +++	0	0	0	0
Coloboma of Iris and/or choroid	0	0	+	+	+	0	0	0
Epibulbar dermoids (or lipodermoids)	0	0	0	Bilateral ++++	0	0	0	0
Bilateral cataracts	0	0	0	0	0	+++	0	0
Micro cornea	0	0	0	0	+++	0	0	0
Blue sclera	0	0	0	0	0	++	0	0
Epicanthic folds and Iris anomalies	0	0	0	0	++++	0	0	0
Microtia	++++	0	Unilateral +++	++	0	0	0	0
Low-planted ears	+++	0	+ Unilateral	0	0	0	0	++
Deformed external ear (Pinna)	++++	++++	+++	+ to ++	0	0	0	++
Atresia of external auditory canal	+++	++	Unilateral ++	++	0	0	0	+
Absence or fusion of ossicles	+++	+	+ Unilateral		0	0	0	+
Hearing loss and deafness	+++	++	+ Unilateral	++	0	0	+	++
Preauricular appendages (Tags)	++ to +++		Unilateral +++	++++	0	0	0	0
Pretragal pits	+++	0	++	+++	0	0	0	0
Facialclefts or blind fistulae	++++	0	0	++	0	0	0	0
Linguiform extension of hair	+++	0	0	0	0	0	0	0
Aquiline thinning of nose	0	0	0	+	+++	+++	++	0
Nose root broad — thick and large	+++	0	0	0	0	0	+ (pseudo)	++
Nose large — nares narrow	++	0	0	0	0	0	0	0
Obliterated fronto-nasal angle	++	0	0	0	0	0	0	0
Macrostomia	+	0	+++	++++	0	0	0	0
Microstomia	0	0	0	0	0	+	0	++ turned-down corners

TABLE 7

Characteristic Sign of Syndrome	Mandibulo-facial Dysostosis	Pierre Robin Syndrome	Otomandibular Dysostosis	Oculoauriculo-Vertebral Dysplasia	Oculodento-digital Dysplasia	Oculomandibulo Dyscephaly	Orodigitofacial Syndrome	Otopalatodigi-tal Syndrome
Agenesis of mandible	0	0	++++	Unilateral ++	0	++	+	0
Hypoplasia of mandible	++++	++++	+ to ++	+ to ++	0	+++	+ to ++	0
Hypoplasia of ramus	+++	++	Unilateral +++	++	0	++++	+	0
Hypoplasia of condyle	+	0	Unilateral +++	++	0	+++	+	0
Absence of condyles	+	0	0	0	0	++	0	0
Wide mandibular ramus + corpus	0	0	0	0	+++	0	0	0
Anterior displacement of condyles	0 to ++	0	0	0	0	+++	0	0
Receding Chin	++	+++	0	+	0	+++	+	0
Hypoplasia of Malar bones	++++	0	Unilateral ++	++	+	0	0	0
Flattening of eminences (malar)	+++	0	Unilateral +	+	0	0	0	0
Hypoplasia of Maxilla	0	0	0	++	0	++	0	0
Deficient supraorbital ridges	++	0	0	0	0	0	0	0
Deficient infraorbital rims	++	0	0	0	0	0	0	0
High palatal vault	+	+	0	+	0	++	+	0
Cleft of hard palate	++ 40%	+++ (wide)	0	++	0	0	+++	+++
Cleft of hard and soft palate	0	0	0	0 to+	0	0	++	0
Clefts of upper lip (pseudo)	0	+	0	+	0	0	+++	0
Lateral cleft of palate	0	0	0	0	0	0	+++	0
Clefts of tongue	0	0	0	0	0	0	+ trifurcation	0
Glossoptosis	0	++++	0	0	0	0	0	0
Facial hypoplasia	0	0	Unilateral ++++	Unilateral +++	0	+++	0	0
Micrognathia	0	++	0	+++	0	0	0	0
Malocclusion	+++	++	++	++	0	++	Maxillary canines ++ infraocclusion	0
Anterior open bite	+++	0	0	++	0	+	0	0
Abnormal implantation of teeth	0	+	0	0	0	++	+	0
Dental Anomalies	0	+	0	0	+	+	0	+ Absent laterals
Natal teeth	0	0	0	0	0	++	0	0
Supernumerary teeth	0	0	0	0	0	+	0	0
Exposed dentine	0	0	0	0	+++	0	0	0
Hypoplastic enamel	0	0	0	0	++	0	0	+

TABLE 8

Characteristic Sign of Syndrome	Mandibulo-facial Dysostosis	Pierre Robin Syndrome	Otomandibular Dysostosis	Oculoauriculo-Vertebral Dysplasia	Oculodento-digital Dysplasia	Oculomandibulo Dyscephaly	Orodigitofacial Syndrome	Otopalatodigital Syndrome
Sclerotic Mastoid process	+++	0	+ Unilateral	0	0	0	0	+
Paranasal sinuses small/absent	++	0	0	0	0	0	0	0
Frontal Sinuses abn. small/absent	0	0	0	0	0	0	+	++
Decreased Pneumatisation of sphenoid sinus	0	0	0	0	0	0	0	++
Hypoplasia of mastoid process	0	0	Unilateral ++	0	0	0	0	0
Decreased Pneumatisation of mastoid sinus	++	0	Unilateral +	0	0	0	0	++
Frontal bone "Bossing"	0	0	0	+	0	0	++	0
Delayed sutural closure	0	0	0	0	0	++	0	0
Brachycephaly	0	0	0	0	0	++	0	0
Non-fusion + flattening of zygomatic arches	++	0	0	0	0	0	0	0
Small face	0	0	0	0	0	++	0	0
Facial asymmetry	0	0	++++	0	0	0	0	0
"Fish-like" facies	++++	0	0	0	0	0	0	0
"Bird-like" facies	0	++++	0	0	0	++	0	0
Hypotrichosis	0	0	0	0	+++	+++	0	0
Hypotrichosis of eyebrows and lashes	0	0	0	0	+	++	0	0
Skin atrophy — nose and scalp	0	0	0	0	0	+	0	0
Hypotrichosis (Alopecia) Scalp	0	0	0	0	0	0	++	0
Hypoplastic facial muscles	0	0	0	++	0	0	0	0
Agenesis of Pterygoid muscles	0	++++	0	0	0	0	0	0
Hyperplasia (Duplication) of Frenum	0	0	0	0	0	0	+++	0

TABLE 9

Characteristic Sign of Syndrome	Mandibulo-facial Dysos-tosis	Pierre Robin Syndrome	Otomandibular Dysostosis	Oculoauriculo-Vertebral Dysplasia	Oculodento-digital Dysplasia	Oculomandibulo Dyscephaly	Orodigitofacial Syndrome	Otopalatodigi-tal Syndrome
Skeletal Anomalies	0	0	0	++++	0	++	0	+++
Vertebral Anomalies	0	0	0	++++	0	++	0	+++
Occipitalisation of atlas	0	0	0	+++	0	0	0	0
Scoliosis	0	0	0	++	0	0	0	0
Deformed Extremities	0	0	0	0	0	0	0	+++
Finger anomalies	0	0	0	++ thumb hypoplasia	0	0	++	+++
Brachydactyly	0	0	0	0	++	0	++	0
Syndactyly	0	0	0	0	++ (cutaneous)	0	+	0
Clinodactyly	0	0	0	0	0	0	+	++ 5th finger
Polydactyly	0	0	0	0	0	0	+	0
Camptodactyly	0	0	0	0	++ 4th+5th fingers	0	+	0
Toe anomalies	0	0	0	0	++	0	0	+
Pulmonary agenesis	0	0	+++	0	0	0	0	0
Cardiac anomalies	0	+++	0	+	0	0	0	0
Sex Predilection	0	0	♂ 6 : ♀ 4	0	0	0	? ♀ only	Equal
Mental retardation	0	+ 20%	0	+ 10%	+ 10%	0	+ mildly	+++ Severe
Dwarfism	0	0	0	0	0	+ Proportional	0	+++
Inheritance	Irregular	Autosomal dominant	Genetically heterogenous	Sporadic auto-somal recessive	Possible autosomal dominant (or recessive)	Possible auto-somal dominant	X-linked dominant	X-linked reces-sive

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PART THREE

TABLE 10

THE TESTING OF THE SUBJECT – CONFIRMING THE DIAGNOSIS

MANDIBULO-FACIAL DYSOSTOSIS – THE ESSENTIAL FEATURES	PRESENT IN THE SUBJECT
antimongoloid obliquity of eyes	YES
abnormal angulation of the lower eyelids	YES
colobomas of the outer third of lower eyelids	YES
microphthalmos	NO
low-planted ears	YES
atresia or deformity of the pinnae	YES
atresia of the external auditory canals	PARTIAL
absent ear ossicles – (deafness)	POSSIBLY
preauricular appendages (tissue tags)	NO
large nose	YES
obliterated fronto-nasal angle	PARTIAL
linguiform extension of hair onto cheek	POSSIBLY
macrostomia	YES
blind fistulae between angle of mouth and ear	YES
hypoplastic supra- and infra-orbital ridges	YES
hypoplastic or absent malar bones	YES
flattening or non-fusion of zygomatic arches	YES
hypoplasia of mandible	YES
mal - occlusion-anterior open bite	YES
high - arched or cleft palate	NO
sclerotic mastoids	YES
hypoplastic antra (maxillary sinuses)	YES
enlarged frontal sinuses	YES
enlarged ethmoidal sinuses	YES

CONCLUSIONS

According to LONGACRE[5] (1965), and the majority of other authorities, the ESSENTIAL features, which must be present before a positive diagnosis of the syndrome can be made, are the following:-

1. antimongoloid obliquity
2. coloboma of the lower eyelids
3. deformity of the pinnae
4. defective development of the mandible and malar bones
5. prominent fronto-nasal elements
6. linguiform extension of hair onto cheek
7. associated cleft palate, facial clefts, preauricular tissue tags, macrostomia etc.

Examination of the foregoing table will confirm that the subject conforms to the above in practically all respects.

The features of the subject are now compared, in table form, with those of the three other bantu cases of MFD taken from the literature. (Table 11).

TABLE 11

FEATURES	CASE D.N.[2]	CASE E.D.[2]	CASE S.N.[6]	CASE J.S.
Sex	M	M	M	M
Age on Admission	New-born	Two weeks	Five weeks	34 Years
Death	Day 22 after admission	Day 24 after admission	At 3 months	Living
Weight on Admission	5 lb 5 oz	4 lb 6 oz	5 lb 8 oz	Not Applicable
Consanguinity or Family History	None	None	None	Not Established
Facies	Very Abnormal-Fishlike	Very Abnormal-Fishlike	Peculiar-Fishlike	Abnormal-Fishlike
Antimongoloid Obliquity	Yes	Yes	Yes	Yes
Fronto-Nasal Angle	Obliterated			Less acute than Normal but not Obliterated
Coloboma	No	No	Lateral part of each lower lid	Yes — both lower lids
Eyelashes	Absent on Medial Two-thirds both Lower Lids	Present on Medial Two-thirds of Lower Lids — But Sparse		Absent on Medial Two-thirds of lower lids
External Ear	Both Malformed	Both Malformed	Pinnae Deformed	Pinnae Deformed — Especially on Right Side
Internal Ear		No Middle Ear	Tympanic Membranes Normal	Deafness Present
Auditory Canals	Blind Pits	Ended Blindly		Narrowed
Hair Tongue	Yes	Yes	Yes	Possibly
Dimples, Facial Clefts	Bilateral Dimples on Orotragal Lines	Pits on Orotragal Lines	Small Blind Fistulae Anterior to Ears	Blind Fistulae near Ears — Facial Grooves
Malar-Zygomatic Hypoplasia	Yes	Yes	Yes — Depression in Region of Zygoma	Yes
Hypoplasia of Mandible	Yes — Marked	Marked	Yes — Marked	Yes — Marked
Temporomandibular Joint	Limited Movement Both	Limited — Mouth Could not Open Widely		No Limitation — Abnormal Free Movement
Parietal Bossing	No	Yes	No	No
Tongue			Large	Normal
Macrostomia	Yes	Yes	Yes	Yes
Cleft Palate	Yes	Yes	No	No
Toe Anomalies	Second Toes On Both Feet Abnormally Long		None	None
Röntgenological: Facial Bones (Malar)	Hypoplastic	Poorly Formed	—	Only a Vestige of Malar Bone Present
Zygomatic Arches	Interupted	Poorly Visualised		Poorly Visualised
Mandibula	Severely Hypoplastic	Hypoplastic		Hypoplastic
Bones of Base of Skull		Sclerotic		Normal
Petrous Temporal Bones	Sclerotic	Flattened		Sclerotic Mastoids
Spina Bifida	Yes	Yes	No	No
Limb Anomalies	None	Ulnas Angulated Radii Absent	None	None
Finger Abnormalities	Only 4 Digits on Hands — No (L) Thumb Rudimentary Thumb (R)	Only 4 Digits No Thumbs	None	None

AN ANALYSIS OF THE BANTU CASES

1. **ABNORMAL, FISH-LIKE FACIES**

   All four cases show this feature which is common to MFD.

2. **ANTIMONGOLOID OBLIQUITY OF THE PALPEBRAL FISSURES**

   All four cases demonstrate this requirement for the diagnosis of the syndrome of MFD.

3. **THE FRONTO-NASAL ANGLE**

   In case D.N., it is obliterated, whilst in case J.S. it is not. Neither of the other two cases exhibit this feature.

4. **COLOBOMA OF THE LOWER EYELID**

   Cases S.N. and J.S. show this typical sign, but (surprisingly), not the other two.

5. **THE EYELASHES**

   Only case S.N. is not reported as having absence or sparseness of the eyelashes on the medial two-thirds of the lower lid. It may well be that this feature was present but not reported.

6. **THE EXTERNAL EAR (PINNA)**

   All four cases exhibit some deformity of the pinna of either one or both ears.

7. **THE INTERNAL EAR**

   Cases E.D. and J.S. have obvious abnormalities concerning the internal ear while case S.N. exhibits normal tympanic membranes, although no mention is made of an examination of the middle ear. The internal ear in the case D.N. is not reported upon.

8. **THE EXTERNAL AUDITORY CANALS**

   In all the cases except case S.N., the canals are narrowed or end blindly.

9. THE LINGUIFORM EXTENSION OF HAIR ("HAIR TONGUE")

There is evidence that it is present in all cases.

10. DIMPLES AND/OR FACIAL CLEFTS

Present in all cases.

11. HYPOPLASIA OF MALAR AND ZYGOMATIC BONES

A feature of all cases.

12. HYPOPLASIA OF THE MANDIBLE

This is marked in all four cases.

13. MOVEMENT OF THE TEMPORO-MANDIBULAR JOINT

In cases D.N. and E.D. there is a marked limitation of movement in the joint and it is reported that the mouth could not open fully. In case J.S., the *opposite* is true and there is a decided hypermobility.

14. CLEFT PALATE

Cases D.N. and E.D. both have clefts of the palate, whereas cases S.N. and J.S. do not.

15. TOE ANOMALIES

Case D.N. exhibits abnormally-long second toes on both feet.

16. FINGER ANOMALIES

Case D.N. lacks a thumb on the left hand and has only a rudimentary thumb on the right hand.

Case E.D. has only four digits and no thumbs.

Case S.N. and J.S. have NO finger anomalies.

17. LIMB ANOMALIES

Case E.D. has angulated ulnas and absent radii which caused fore-shortening of the limb.

18. VERTEBRAL ANOMALIES – SPINA BIFIDA

Cases E.D. and D.N. both exhibit spina bifida. There are no vertebral anomalies in the other two cases.

DISCUSSION

1. All four bantu cases satisfy the requirements for a diagnosis of the COMPLETE form of Mandibulo-Facial Dysostosis, except for the fact that cases D.N. and E.D. do not have coloboma of the eyelid. However, the absence of coloboma is insufficient reason to exclude them from classification along with cases S.N. and J.S. which fulfil all the requirements – FRANCESCHETTI AND ZWAHLEN[2] (1944).

2. Case D.N. and E.D. differ from case J.S. in that their temporo-mandibular joints possess very limited movement while those of the latter have abnormally free movement.
   Typically, cases of the syndrome display *greater* than average movement (due to the under-development of the joint structures) and there is occasionally a forward displacement (up to 15 mm) of the condylar heads.

3. Cleft palate occurs in cases D.N. and E.D.
   It can also be found in the PIERRE ROBIN SYNDROME
   OCULOAURICULO-VERTEBRAL DYSPLASIA
   OCULOMANDIBULO DYSCEPHALY
   the ORODIGITOFACIAL SYNDROME
   and the OTOPALATODIGITAL SYNDROME.

4. Of *GREATER* significance, however, is the occurrence of finger, toe and skeletal anomalies in the cases D.N. and E.D.
   Although FRANCESCHETTI and ZWAHLEN[2] have stated that skeletal deformities may be present, these are *NOT* part of the true syndrome.
   In fact, the writer cannot recall having encountered a *single* recorded case in which finger and toe anomalies have been present either in conjunction with spina bifida or alone.
   Finger anomalies can occur in OCULOAURICULOVERTEBRAL DYSPLASIA (particularly thumb hypoplasia)
   OTOPALATODIGITAL SYNDROME
   and OCULODENTODIGITAL DYSPLASIA.

Toe anomalies occur in

OCULODENTODIGITAL DYSPLASIA

and the OTOPALATODIGITAL SYNDROME.

Vertebral anomalies, such as spina bifida, occur in

OCULOAURICULOVERTEBRAL DYSPLASIA

OCULOMANDIBULO DYSCEPHALY

and OTOPALATODIGITAL SYNDROME.

From the above, it is apparent that, although we have four cases of the syndrome which, at first glance, are *all* TYPICAL, COMPLETE cases of Mandibulo-Facial Dysostosis, two of them (cases D.N. and E.D.) exhibit certain characteristics "belonging" to at least six other, totally different syndromes!

KLEIN[4] (1968) has stated that, under present circumstances, any classification must be considered to be *PROVISIONAL* only. CAMPBELL[1] (1971) suggested a classification in which the first group (comprising Mandibulo-Facial Dysostosis and the Pierre Robin syndrome) is stated as being *probably* related to the 1st and 2nd BRANCHIAL ARCH defects, whilst the second group of six syndromes is to be regarded as *possibly* related to 1st and 2nd BRANCHIAL ARCH defects.

The second group includes

OCULOAURICULOVERTEBRAL DYSPLASIA

OCULODENTODIGITAL DYSPLASIA

OCULOMANDIBULO DYSCEPHALY

the ORODIGITOFACIAL SYNDROME

and the OTOPALATODIGITAL SYNDROME

All of which share some characteristics with cases D.N. and E.D. which are supposedly "pure" examples of MANDIBULO-FACIAL DYSOSTOSIS! It should be obvious, then, that with the overlapping of characteristics seen in the UNRELATED cases D.N. and E.D. that ANY CLASSIFICATION made in the light of present knowledge, *MUST* be regarded as purely provisional and arbitrary.

In view of the above findings, the writer would like to propose that CAMPBELL'S[1] classification be revised and the two groups included under *one* heading, viz., "Anomalies *PROBABLY* related to the 1st and 2nd Branchial Arch defects".

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120, Vigilans Building,
Pretorius Street,
PRETORIA.
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