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The background of congenital abnormalities in general, and especial consideration of rubella (German Measles), its epidemiology, symptomatology and teratology: A review of the literature

Fasser, E.

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THE BACKGROUND OF CONGENITAL ABNORMALITIES IN GENERAL, AND ESPECIAL CONSIDERATION OF RUBELLA (GERMAN MEASLES), ITS EPIDEMIOLOGY, SYMPTOMATOLOGY AND TERATOLOGY.

A REVIEW OF THE LITERATURE.

THESIS

Presented to

THE FACULTY OF MEDICINE,

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the requirements for the Degree

DOCTOR OF MEDICINE.

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by

Ellis Fasser, M.B., Ch.B., D.C.H.

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P A R T O N E.

THE BACKGROUND

OF

CONGENITAL DEFECTS

IN

GENERAL.

THE BACKGROUND OF CONGENITAL ABNORMALITIES IN GENERAL, AND ESPECIAL CONSIDERATION OF RUBELLA (GERMAN MEASLES), ITS EPIDEMOLOGY, SYMPTOMATOLOGY, DIAGNOSIS AND TERATOLOGY.

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I N T R O D U C T I O N.

Every morbid condition occurring in Medicine is based fundamentally on the genetic constitution of the individual, but only diseases which are significantly related to hereditary factors are regarded as hereditary diseases. In the thesis presented by the writer, an attempt is made to show how the environment affects the development and expression of factors genetical in origin. The first part of this work is really only a sketchy introduction to the genetic processes involved, and is presented as a background on which to paint the picture of certain conditions regarded as significantally environmental in origin. Hence the early chapters cannot be regarded as being very complete or detailed, but an attempt has been made to present the basic genetic laws, and to interpret various morbid processes in the foetus and newborn in the light of these laws. Some of these pathological conditions have only recently been understood, and a few are enumerated in the hope of producing an over-all picture. Some are touched upon as being of some practical importance either at the present date, or possibly in the near future.

This brings us to the conception of "prenatal paediatrics." There is a tendency at the present time for a closer relationship to develop between obstetrician and paediatrician just because of the newer knowledge regarding the reciprocal relationship between maternal and foetal status. Maternal nutri-

importance. Obstetricians, today, in introducing newer and safer procedures, operations, and analgaesic methods for delivering their patients, consider more and more, the management of labour in terms of the effect upon the foetus. Psychological, as well as physiological care of the pregnant woman must be instituted because psychological disturbances may significantly affect the actual physiology of pregnancy and parturition. Paediatric attention, initiated early in pregnancy, is therefore not necessarily an impractical procedure.

As the genetic constitution cannot be varied the aim of "prenatal paediatrics" must be directed towards modification of adverse environmental factors. One of the great aims of Eugenics is to prevent the action of adverse genetic factors, but the scope of eugenics at the present time is limited in its application. There appears to be a tendency, as the centuries roll on, for balanced genetical systems to evolve, which seem to be resistant to change. Whether the future use of atomic radiation, either in Peace or in War, may change this, remains to be seen. The effects of maternal rubella, as described in the second part of this work, appear to be so diverse in different instances, that the operation of co-existent genetical background factors cannot entirely be excluded.

It is essential to obtain better statistical information regarding gene frequencies. Biochemistry, physiology, and Serology should be allied to Clinical and Social Medicine in an attempt to discover

and diabetes, and also various types of defects and malformations, such as congenital morbus cordis, deaf-mutism, mental deficiency, etc. An investigation of the relationship between neonatal status and the development of subsequent disease patterns during later childhood, or even adulthood, will undoubtedly prove to be of the greatest import. In this work reference has been made to the value of epidemiological studies as a means of uncovering mechanisms which produce congenital defects. It should be remembered that, due to differences in diet, medical care, and a thousand other factors of changed environment, maternal status today is different to what it was fifty or one hundred years ago, and any effects for good or ill on the foetal population can be unearthed by careful, prolonged statistical study. It is obvious that the correlated efforts of many branches of Clinical, Experimental and Social Medicine over long periods, are essential to produce useful results. For instance, mongolism occurring in two sibs may not necessarily represent an hereditary condition, as one of the cases may be incidental, or dependant on environmental factors obtaining for both affected sibs. Similarly, many of the less typical congenital defects, which in late years have been described as appearing in children born after maternal rubella may be incidental, and either represent the risk to the foetal population at large, or may yet be the means of uncovering the operation of other environmental factors as well.

Hence we see the need for a closer follow up of all morbid or abnormal conditions during pregnancy,

particularly/....

particularly virus infections, with complete reports on the infants subsequently born, whether normal or otherwise. This need becomes clear, when the latter part of this work is consulted.

The investigations carried out on maternal rubella as an aetiological factor in the production of congenital defects is presented as a most important step in the understanding and prevention of unfortunate accidents of foetal development.

The present thesis is essentially a review of the literature, but several cases are presented on account of the paucity of reports in the world literature. In this connection, the writer would like to acknowledge case histories given by Doctors E.G. Melle, S.N. Javett, M. Chitters, W. Tope, M. Epstein and C. Faerber all of Johannesburg, and Doctors B. Epstein, P. Oosterhagen and J. Rudolph of Pretoria. Valuable assistance and great courtesy has been offered by the Matron, St. Vincent's School for the Deaf, Johannesburg, Mr. Wentworth of the National Council for the Blind, Pretoria, Dr. le Riche of the Union Health Department, Pretoria, Major Dreisenstock at Defence Headquarters, Pretoria and those most efficient librarians, Miss A.C. Dick and Miss Krige of the Witwatersrand Medical Library. My thanks are also due to the doctors at Union Health Department, Pretoria who so graciously placed their excellent library material at my disposal. Last but not least, I am indebted to Mrs. T. Mellet, Miss E. Marcus and my wife for clerical assistance.

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January, 1951.

CHAPTER I.

THE GENETIC BACKGROUND.

(1) GENERAL EMBYOLOGICAL PROCESSES AND MECHANISMS.

Congenital malformations is a subject which has come more to the fore in recent years owing to the growth of the science of genetics. Although at birth, a malformation may be recognisable by the most untutored, nevertheless it may sometimes only be identified by the closest physical examination, sometimes by a microscopic examination; and in some instances only autopsy will disclose internal abnormalities, not obvious, or not even suspected from external examination. We often have to enlist the aid of radiological, histological or even genealogical methods of investigation. By closer examination, what is at first apparently sporadic, turns out to be hereditary or familial. Today, we are closely investigating patterns which may represent alternative expressions of hereditary characters.

Probably the genesis of congenital anomalies occurs in quite a number of cases, during the early weeks of embryonic development, where growth is occurring during this period, false steps in the wrong. directions continue along abnormal pathways, and are often incorrigible.

Now, a zygote consists both of nuclear material and cytoplasm, defects in either of which will give rise to abnormalities. Nuclear defects are often transmissable to the offspring, and possibly

cytoplasmic/....

cytoplasmic defects may act on similar lines. The environment consists of *internal* surroundings, and *external* surroundings which comprise not only the uterus, but also the climate and locality of the mother who carried the uterus, her nutritional state (Cosmosphere), and even more broadly her social and economic and educational status (Biosphere). From the first cell division to the blastula stage, internal environmental factors are more important as regards defects. After this stage, the influence of gene action becomes noticeable; also a close relationship is established with the maternal organism. From then on until birth, growth and development occurs more in accord with genetic constitution. Josef Warkany (1947) says, "Obviously the genes contain the plan of the future organism, but for its growth, huge amounts of building materials must be obtained from the environment".

During cell division, the genetic constitution of *all* the somatic cells is identical with that of the united sexual cells. Hence differentiation does not depend on genes solely, but partly on close interaction between nuclear material and external and internal environment. Development depends on innumerable physico-chemical processes: that is to say, in each cell division, reactions occur between the nuclear substance, (gene), and cytoplasm (which is part of the environment), "a form of 'systole' and 'diastole' in exchange of material."

(2) GENE ACTION.

Genes act apparently as enzymes, or catalysts but for normal action they require normal cytoplasm

and normal environment. Hence a certain type of malformation could be the result of the disturbance of a specific reaction between genes and environment so that the same type of congenital defects may arise from environmental abnormalities as from genetic abnormalities. Where however, as a result of a normal genetic constitution interacting with an abnormal environment, a defect is produced, although the latter may be congenital, it is not hereditary. Such a malformation is designated *phenocopy*, and this type is morphologically indistinguisable from the other, which originates from abnormal genes, and which may only be differentiated by consideration of genealogical records. The morphological type is called phenotype whereas the term *genotype* refers to its genetic constitution. For example, people of different blood groups are phenotypically alike, being only differentiated into their respective groups, (i.e. classed as to genotype) by means of blood agglutination tests.

The duality of environment and gentics can never be separated, although there is accent sometimes on the one, sometimes on the other. The same applies to the expression of disease. Pathological processes are the product of environment plus constitution. To illustrate this point we have only to observe the work of Morgan, who bred the fly, Drosophila, with vestigial wings by exposing the larvae to a low temperature. He also found that vestigial winged flies arose as a hereditary mutation. As the temperature of incubation in the larval stage was increased, so did the length of the wings increase until at 31°C they approached normal size.

The/...

The intra-uterine environment is never constant or homogeneous, hence Mendelian ratios are not exact. Whether an actual gene will ever be seen is problematic, although its location on a particular chromosome may be known from a geographical point of view. Gene action is postulated to be that of a catalyst acting on certain parts of the embryo which are receptive at a particular stage. Such areas called *organizers*, then respond by liberating *evocators*, substances bringing about differentiation of tissues. There are secondary and tertiary organizers which operate at the appropriate bio-chemico-physical levels arrived at by a previous succession of events. Some of these events are constantly repeated (synchronic events) to build up to a stage of organiser action, and the production of a single diachronic event which is essential for a procession of further events. Hence the importance of previous happenings in the life history of a embryo. This is illustrated by the accompanying figure taken from H. Grüneberg. (Fig. 1). Organiser action can be studied by its effect on the developing embryo. The organiser exerts a stimulating effect in a particular direction, sometimes also when the organiser tissue has been destroyed by boiling. Even cell-free extracts exhibiting organiser activity have been prepared: these are really evocator concentrates. (Needham 1942).

Each cell is regarded as having a *competance*, or a potential range of development. The exact outcome of its development depends then on previous events, on the cell's relationship to its neighbouring cells, and hence on the environment, which is the

result/...

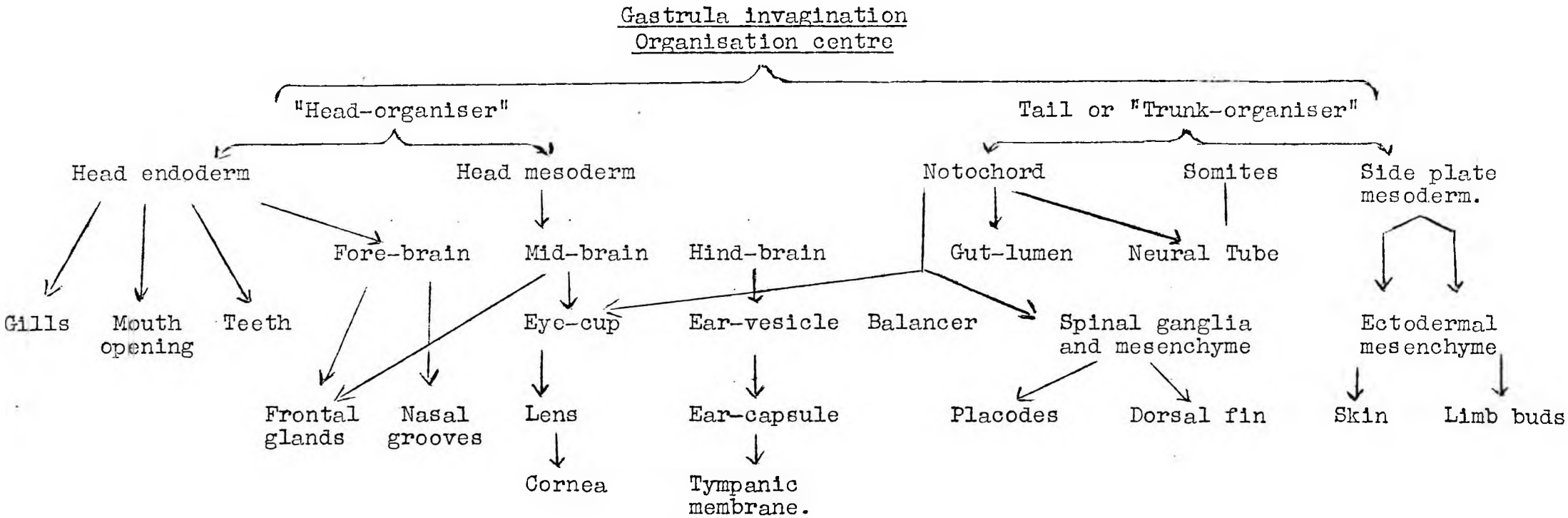

FIGURE 1.

Schematic diagram to illustrate action of primary and subsidiary organisers.
(adapted from Holtfreter, J. and Needham, J. – "Biochemistry & Morphogenesis", (1942) p.290).

result of a passage of events, and in which are concerned the nutrition, and hence the physical basis of the developing organism, its carbohydrates, its fats and its proteins. The proteins from which the cells are constructed may be derived from "food" taken in under adverse environmental conditions, thus becoming in some way modified. The whole molecular structure of rat cells is different from that of the mouse, or cat, or human. However, in the fertilised ovum, there is a limit to the extent of differentiation, "rats remain rats, cats remain cats, even rat protein is different from cat protein." As the environment is constantly changing, so the material substratum, from which the embryo is developing, is also changing. Take the case then, of identical twins, who inherit similar genetic constitutions, i.e. they are genotypically identical. However, because the environment of the one is not precisely the same as the environment of the other, development is not exactly identical in both. This even applies to the Dionne Quintuplets. For instance the one embryo lies on its head, the other on its bottom or side, one may develop from the left half or the other from the right half of the developing zygote. Similarly fraternal twins represent the result in two different individuals of environmental conditions as nearly identical in two cases as it is possible for them to be. And again, it is conceivable that the mother's proteins may be modified by the injection of different antigens. Such antigens, especially if diffusible across the placental barrier may alter intra-uterine environmental conditions. The altered proteins produced

may only be utilised by the embryo with difficulty, if at all.

During this developmental process, the embryo viewed from instant to instant, appears to be static. From instant to instant there may be no chemical bio-chemical or physical differences detectable, but nevertheless *integration* is occurring all the time. Soon the embryo is polarised towards the uterine wall, soon a cranial and a caudal part become indentifiable. Then, the approximate position of the eye or the tail is recognisable; and although as yet there may be no suggestion of eye form, or even tail form, the optic region and caudal region are areas of organiser activity. Before differentiation occurs, at a very early stage one may remove any portion of the embryo but the neighbouring cells replace the loss and apparently normal development proceeds. When differentiation occurs, such interference will lead to abnormalities of development, or even be lethal, because the direction taken in the development of a particular part is dependant upon the extent of development up to date . *(Dependant development).* That is to say, if no limb-bud forms, then the stage is not set for the development of fingers. Each embryonic system seems to have a certain critical period during which rapid growth in the direction of differentiation occurs; and during this period, as we shall see later, that particular system is most vulnerable to interfering factors. (Stockard 1920-1).

On the other hand, transplantation of the presumed optic parts into the caudal section of the

embryo may lead to the development of an eye situated in the tail because organiser activity is now transferred. Such an eye may morphologically resemble a normal eye, but because it has developed independantly of the nervous system, it will be non-seeing. (Needham, 1942). Therefore the intergration of a normal individual depends on the proper sequence of *neighbourwise* development of cells up to a stage where *selfwise* development can proceed in the direction of differentiation. The genetic complex of each cell provides a range of *biological potential*, or range of alternative actions for that organism, and the final determination is influenced by the environmental conditions prevailing.

The level at which normal deviation of the cells into a direction of differentiation, or any deviation from normal, becomes *obvious* to the embryologist with his comparatively crude methods of investigation, does not represent however, the actual level. Divergence must have occurred long previously at some physiological level, later at a physico-chemical level, and very much later at the morphological level, which is the more easily recognisable. Hence our earliest recognition of defects in the embryo implies misdirected processes occuring much further back in the life track of the individual.

In the cases where eye- anlages are tampered with, we find that in some cases, namely in Bombinator Pachypus, the removal of eye-cup will ensure that the lens by dependant development will not develop. On the other hand Spemann found that a highly developed lens developed from a lens disc without an eye-cup in the case of Rana Esculenta.(See figures in

Needham's "Biochemistry and Morphogenesis," page 294). The inference here however, is that the inducing chemical substances for development of lens is not always contained in the eye cup itself but in the surrounding mesoderm, say, as heparin is found in the tissues surrounding the great vessels. The older theory of "double assurance" suggests that to guard the embryo against possible defects in development, more than one factor is necessary to produce a given end result.

Every hereditary trait, in fact is influenced by one or several pairs of genes. This latter fact also explains differences in the expression of abnormalities not quite conforming to type. In general, genes are ranged in pairs. The human being has in his cells 24 pairs of chromosomes (or autosomes), one of each pair being derived from the mother, the other from the father, and each containing one of a pair of genes in series. Each pair of genes govern the expression of a character. Therefore we have in inheriting a character, the possibility of taking a gene from the paternal or maternal side. These alternative genes are known as *allelomorphs*. In general, if two members of a pair tend to produce different results in the expression of a particular character, the zygote is said to be *heterozygous*, that is to say, one of the pair is suppressed by the other *(dominant)*, in the individual and becomes *recessive*, but may yet be transmitted to one of its zygotes, becoming obvious only if paired with a similar recessive gene. Where two such recessives are paired, or where two dominants are paired, the zygote is known as *homozygous* (rr or DD) :/...

DD) : the progeny of all homozygotes when mated to any recessives, will all be phenotypes for the homozygous characteristic, e.g. rhesus factor in human blood.

Heterozygotes as a rule conceal completely the recessive character. The genotype becomes morphologically indistinguishable from the phenotype, and recognition may occur in animals and plants by breeding experiments, and in man by examination of pedigree or blood agglutination tests. The appearance of certain defects in a family does not necessarily indicate a hereditary transmission. These defects may be yet dependant on environmental conditions as for example, rickets and goitre. Even criminality which is observable in some families may be the result of environment and not due to an inherited defect of moral character.

(3) VARIATIONS AND CONCEPT OF "NORMALITY".

There is a protozoön organism *Paramoecium Caudatum*, which can reproduce assexually. Such offspring, all of which are of identical genetic constitution, are called *clones*. Investigating a given number of clones, it was found that there was variation in size, throughout the group. Most of the individual were of the medium size class, slightly smaller of larger individuals being rather less common, very long and very small individuals rare. (Ride, 1938). Plotted on a graph, size classes as against number of individuals, the shape follows that of Galton's distribution, coefficients of the expansion of the binomial (a plus b)^n.

Number of Individuals.



Size, Classes, etc.

Figure 2.

Theoretical Curve : Binomial Distribution.

The larger the number of individuals measured, the smoother the curve and the more closely does it approximate to the theoretical shape. Thus we have an excellent example of variation in individuals of the same genetic constitution, which variation must be due to environmental factors, i.e. the biophysical conditions are not exactly the same during the formation of each individual, and are reflected by differences in constitution. Most of the individuals will find conditions, in general, favourable; these are "normals". Those on either side of normal on the curve represent development under conditions increasingly unfavourable.

Should the small and larger individual be grouped and bred from each clone, generation after generation, we find the identical symmetrical distribution applies to the offspring, and the "normal" remains constant, thereby indicating that difference due to environmental causes are not inherited; they are therefore termed "variations".

On the other hand, if individuals from the general *Paramecium* population, are selected and bred,

into/....

into clones, we find that the average or normal size of different clones varies, though the shape of the curve in each particular case remains the same. Different clone curves may even overlap, but some of the small sized individuals from a genetic strain of large paramoecium may be identical in size and appearance as some large-sized individuals arising from small paramoecium. This means that although the phenotypes are the same, they may be sorted into their respective genetic constitutions by breeding experiments.

In the case of the human population, our concept of "normality" depends for close approximation of the number of individuals examined. Since no two individuals are exactly alike, there can strictly speaking be no single normal individual; and an individual can only be classed as normal in respect of certain characteristics. Every individual is sure to have in one way or another some "abnormal" characteristic as well. J. Bauer (1945), points out that according to the strict text-book criteria, only 9% of individuals examined at random were found to have a "normal" greater splanchnic nerve.

Some characters vary more amongst individuals than do others. If a particular variation of a particular character occurs more often than in 4.5% of the population, it may be regarded arbitrarily, as normal, although still a deviation from the average. Clinical medicine (and teratology) really resolves itself into a determination of, and a proper evaluation of variations existing amongst individuals. In treatment, it resolves itself into an appreciation of individual differences in response

to different therapeutic media; and that is why there can never be any fixed dose of any chemical or physical agent. A normal dose may sometimes even be fatal. Some abnormalities may be carried through life without affecting the health in any way; others are potentially dangerous, e.g. abnormal mesenteric attachment of bowel may never have been harmful and yet one day, when the individual becomes atonic and constipated with age, his bowel may be obstructed by volvulus. A formula was devised by German pathologists to express relationship of disease factors (Bauer, 1945):

$$D = I/R,$$

where D = Disease,
I = Injury in its widest interpretation,
R = Resistance of organ to injury (genetic constitution.)

We see also that milder cases of a particular disease are the most difficult of diagnosis because of the resemblance to many other conditions. In fact there can be no routine diagnosis, and no routine treatment based on a single clinical sign alone or isolated laboratory or radiological data.

(4) THE MENDELIAN LAWS.

At this stage it will be advantageous to briefly review the Mendelian Laws.

First Law: F.1. The first hybrid generation derived from a cross from homozygous parents is uniform (uniformity of F.1). For example, in the garden plant *Mirabilis Jalapa* there are red flowering plants and white flowering plants which breed true red and white respectively, shown diagramatically below. Matings between Red and White turn out as follows/...

follows:-

RR X WW

P : Homozygous red X Homozygous white (P - Parents)

F1 all R W (F1 - First filial generation.)
(all pink)

Note that both *alleles* red and white, are dominants.

Second Law: F.2. The second hybrid generation exhibits segregation of factors in a definite numerical proportion, e.g.

RW X RW

P : Pink X Pink

F2: 1 RR 2 RW 1WW (F2 - 2nd filial generation)

i.e. 25% red 50% pink 25% white

This illustration is from a cross involving characters which are both dominant and hence which both exert equal actions phenotypically. Applying it to a cross between a dominant and a recessive character, as for instance, when tall plants (T), a dominant, are mated with dwarf plants (d) a recessive, the following results occur.

Parents (P) tall X dwarf

T X d

F1. Td

all tall (because T is dominant, expresses itself; d is recessive, therefore concealed).

If members of the first filial generation are crossed, we get

Td X Td

hybrid tall Tall hybrid

F2: 1TT 2Td 1dd

Tall : dwarf as 3 : 1.

25% homozygous tall 50% tall dominants

25% homozygous dwarf.

Third/...

Third Law: If several pairs of characters enter into the same cross, these segregate independently of each other. e.g.

If we mate agouti non-wavy haired mice with non-agouti wavy, the allelomorphs involved are as follows:

w equals wavy, recessive
W " non-wavy, dominant
A " agouti, dominant
a " non-agouti recessive

P Non-agouti wavy X agouti non-wavy
aaww X AAWW
F1 1 aa ww 2 aA wW 1 AA WW

that is : 3 Agouti non-wavy, and 1 non-agouti wavy.

The various unions are shown graphically as follows:-

Eggs / Sperms	A Wv	A wv	a Wv	a wv
A Wv	AA Wv Wv	AA Wv wv	Aa Wv Wv	Aa Wv wv
A wv	AA Wv wv	AA wv wv	Aa Wv wv	Aa wv wv
a Wv	Aa Wv Wv	Aa Wv wv	aa Wv Wv	aa Wv wv
a wv	Aa Wv wv	Aa wv wv	aa Wv wv	aa wv wv

After Mendel had formulated these laws, and after they had been accepted, which was only after a lapse of many years, there followed a period when it was discovered that they did not always apply in the statistically correct proportion, even allowing for the element of chance in sampling errors. It was even found that homozygous dominants had children apparently normal. Eventually the correct explanation was found in the phenomenon of linkage, and other more recently discovered modes of gene action to be dis-

In Medicine, we are confronted with the problem of recognising and isolating Mendelian units, i.e. the genes. As the gene is really a form of potential energy, a force tending to move the development of the organism in a particular direction, it should not be regarded as a particle bearing definite morphological characteristics. When considered in this light, namely, that the gene plays a small part in a complex whole, we realise that a "gene" by itself, and out of relationship to the whole genetic constitution of the individual, means nothing. This concept also serves to emphasise the complex nature of transmission of hereditary characters.

(5) DOMINANT TYPE OF INHERITANCE.

Individuals with dominant hereditary genes are usually heterozygous. If mated with normal individuals they will have 50% of their progeny showing the dominant trait. Children not showing the abnormal trait can therefore expect normal offspring. The following congenital anomalies are believed to be inherited according to the dominant mode: (Warkany, 1947).

brachydactylism
polydactylism
syndactylism
cleidocranial dysostosis
oxycephaly
cleft palate
cleft lip
multiple exostoses
chondrodystrophy (achondroplasia)
osteopsathyrosis
ptosis of eyelids
polycystic kidneys
microphthalmia
aniridia
coloboma iridis
ectopia lentis
cataract
optic atrophy
ectodermal dysplasia (one type)
neurofibromatosis
multiple telangiectasia
spherocytosis
sicklaemia

(a) Apparent exception to Mendelian law. - "skipping" a generation.

It has been seen that an individual who inherits the trait, transmitting it to 50% offspring, sometimes/...

sometimes does not himself show the trait. The explanation is along the following lines:

(b). Expressivity.

In the first instance, there may be reduced expressivity of the gene which may cause a slight abnormality not obvious, although minute examination may show microforms of the defect. Sometimes, special diagnostic methods may have to be invoked, as for example X-Ray to show up skeletal defects in apparently normal progeny arising from hetrozygous parents with dominant transmissable skeletal anomalies. In congenital haemolytic jaundice, all, or one, or some of the following defects may appear in members of the family: anaemia, splenomegaly, hepatomegaly, cholelithiasis, chronic ulceration of the leg. However, all the affected members show spherocytosis and increased fragility of the red blood cells. Or again, in fibrocystic disease of the pancreas, we may have steatorrhoea and bronchiectasis. It is possible that many children suffering from "weak chest" after infancy, may be milder cases of fibrocystic disease.

(c). Penetrance.

In other cases the frequency, or penetrance with which genes show any effect at all is low. Therefore genes have the additional property of increased or decreased penetrance varying according to the particular gene. For example, cataract often skips, neurofibromatosis skips, sometimes showing only the *cafe-au-lait* spots, so that in the case of neurofibromatosis we may say that penetrance is high, and expressivity is variable. (see Susceptibility).

The conception of penetrance is a very important one. If we can discover the factors which influence penetrance, we may be able to subdue, or conceal entirely, undesirable characteristics which have a genetic origin. Here indeed is another worthy goal in the future of Preventive Medicine. Statistics show an increase of the incidence of pyloric stenosis with increasing age of the mother. At the same time there appears to be a definite hereditary tendency. It is therefore likely that non-genetic factors play a part in the production of the anomaly (Stern, 1950.)

(d) Degree of Dominance.

Although rare, there may be more than one abnormal dominant gene. For example, types of brachyphalangy are due to a single dominant gene in the heterozygous state. Where two such heterozygous cousins mated, one child was homozygous for the abnormality, with the result that he was born crippled, showing osseous malformations, including complete absence of fingers and toes. Hence doubling of some dominant genes causes a more marked expression of the abnormality.

Rare dominants are scattered amongst the human population mainly in a heterozygous condition. The question is complicated by the fact that what we regard as "dominant" may be misnomers, because many homozygotes are unknown. If identified, such homozygotes might show the defects much more obviously or, unfortunately, in such a way as not at first in the mind of the observer to relate it to the heterozygous state of expression. Hence the term dominant is often loosely applied in human

genetics/...

genetics to genes manifesting themselves in the heterozygous state. Where rare dominants are mated, 50% of the offspring will inherit the anomaly, (Dr x rr type.)

With common dominants, for example, the blood groups, there is a high proportion of homozygotes in the population and all the following types of matings will occur:

D D	x	D D)	
D D	x	D r)	These will not segregate.
D D	x	r r)	
D r	x	D r	3 : 1 segregation.
D r	x	r r	1 : 1 segregation.
r r	x	r r	all recessives.

Matings of two humans with heterozygous recessive defects often do not give a recessive child, as there is a large sampling error in the case of a small human family.

(e) "Weak" Dominance.

Weak Dominants, or qualified dominants, are dominant genes which can manifest themselves phenotypically in a heterozygote, but expression is largely dependant on suitable environmental conditions. Therefore, only a certain number of the heterozygotes will express the trait. This also helps to emphasise the fact that it is not really "characters" which are inherited but specific capacitites to react to the environment.

(f) Irregular Dominance.

How can we explain the case of a familial trait showing dominant characteristics suddenly expressing itself in the child of apparently normal parents? Very often, the answer lies in faulty information regarding the parents, or in the fact that

a parent/...

a parent may have died before being able to express the trait, - really therefore a case of weak dominance as described above, and called the spurious type.

Genuine irregular dominants occur if -

1. Environmental background is not adequate for expression in other members of the family, e.g. susceptibility to smallpox may not be noticeable, because the person has not been exposed to infection.
2. Other genes exert a disturbing influence. Theoretically, it seems probable that associated genetic factors attached to other genes, modify, or appear to mask the original trait. These modifying characters, by themselves, may have no obvious phenotypical effect, yet they may entirely suppress, dilute or weaken a dominant to the extent of making discovery impossible, or very difficult.

Weak dominants behave very irregularly in families, The parents of the affected zygote usually remain free, although more distant relatives may express the trait, so that the proportion of the affected zygotes is usually low. Weak dominants are common in Man and may be confused with recessives.

6. RECESSIVE MODE OF INHERITANCE.

The following congenital anomolies may be transmitted in a recessive manner (Warkany, 1947):

polydactylism	dislocation of hip
microcephaly	coloboma iridis
anencephaly	microphthalmia
oxycephaly	ectopia lentis
acrocephaly	optic atrophy
cleft palate	albinism
cleft lip	ichtyosis congenita
Laurence-Moon-Biedl syndrome	xerodermia pigmentosa
spina bifida	hermaphroditism
talipes	imperforate anus

Individuals heterozygous for an abnormal recessive gene are apparently normal and produce all normal offspring with mates who have two normal genes for the pathological trait. Mated to another heterozygous person like himself, one quarter of the progeny of this couple, who appear outwardly normal, will be homozygous recessive and express the pathological trait. For example, where r equals the trait (recessive),

Parents	Dr	x	Dr			
Gametes	D	r			D	r
Zygotes	1 DD		2 Dr		1 rr	

Note that one in four of the progeny is homozygous for the recessive defect, which now becomes obvious. Only heterozygotes Dr, and homozygous recessive, rr, can subsequently transmit the characteristics. Dr and DD phenotypically are identical, but are genotypically different in that DD cannot transmit.

Phenotypically, therefore, three quarters of the offspring appear normal, but genotypically only one quarter are normal, and unable to transmit the defect. Half the offspring are heterozygous like the parent, and one quarter are homozygous, showing the defect. Thus three quarters of the children are able to carry the defect. The probability of these heterozygous carriers producing a large number of defective descendants, depends on the rarity of the trait in the population at large. If rare, the chances of meeting, and then of marrying another heterozygote are slender in proportion, but the probability increases if he marries into his own sibship. Hence inbreeding tends to bring out familial defects, as well as good traits, and the

progeny/...

progeny are more likely to be desirable than undesirable in proportion to whether good or bad traits are present in the family. We see therefore, that inbreeding is not necessarily a bad thing. If a homozygote, rr, manifesting the trait marries a normal genotype, all the offspring will appear normal, but be carriers:

Individuals	rr	x	D
Gametes	r r		D
Zygotes (Heterozygous carriers)		Dr	

If recessive type of homozygotes with manifest defects mate, then all the offspring will be abnormal, e.g.

Individuals	rr	x	rr
Gametes	r r	x	r r
Zygotes		all rr	

(7) BLENDING INHERITANCE.

Whereas the chance of a pathological trait occurring in the offspring of two simple recessive heterozygous carriers is, as we have seen, one in four, a recessive trait, dependant on the presence of two genes in different loci not dorresponding, is one in sixteen. If dependant on the presence of four such genes, the chances are one in 256. This indicates that hereditary traits of such a nature may appear in the children of apparently normal parents, and apparently normal families, where individuals may not be carrying a full complement of genes necessary to express the trait. The gametes of the parents of the children in question, contribute genes to make up the full complement in the offspring, where the condition becomes manifest.

(a)/.....

(a) Modifying Factors.

Modifying Factors are genes which have no phenotypic effect of their own, but yet affect the phenotypic expression of another gene and even its dominance, so that in some set-ups the gene may act as a semi-dominant, at other times as a recessive. The modifiers increase or suppress the action of a gene in a heterozygote, and as they are very common, we have yet another explanation as to why a specific gene produces some different effects at different times.

There are some cases where inheritance cannot be explained by a simple gene. There appears to be a tendency towards a particular type of expression. For instance Dunn (1941), investigated a strain of rats showing taillessness. All types of matings, i.e. tailless x tailless, tailless x normal, or normal x normal, within the strain, all give a similar percentage of tailless young. Hence the inheritance of taillessness in this particular case cannot be based on a single gene, but on some other factors of genetic or cellular constitution.

(b) Susceptibility to disease.

In man such a mechanism just described may be operative, as possibly in some forms of cancer, but sampling errors due to small families and inadequate follow-up make investigation very difficult. It is a type of specific susceptibility requiring further elucidation. Bauer (1945), in particular, has studied susceptibility of various organs to disease and has collated evidence in favour of such structural inferiority in certain cases. Here, we have a gene creating an inherited tendency to disease in an organ,

expressing/...

expressing itself should the appropriate stimuli arise.

Because a whole organ or system may be constitutionally inferior, should a certain disease occur, the clinical picture will be coloured by the fact that the inferior organ is the hardest hit by the disease process. For example, should hyperinsulinism develop in a person, manifestations might be abdominal, e.g., with hunger, colic, etc. but if that person be predisposed to epilepsy, then convulsions may overcloud the picture. In the treatment, the response to insulin, anti-convulsants, etc. will vary also from case to case, with those differences in genetic constitutions affecting reactivity to these agents. So we see therefore, that in a disease pattern not one, but many genetic factors are involved.

(8) LINKAGE.

(a) Sex-Linked with Recessive Inheritance.

We have seen that allelomorphs are alternative genes arranged in pairs, governing the expression of a character. The genes are regarded as being present on the chromosomes, of which in the human zygote there are 48. Each of the pair in one gamete (sex cell) has a corresponding mate in the other gamete so that the resulting individual (zygote) also has 24 pairs of chromosomes, of such homologous chromosomes. Actually 23 pairs are coupled in the sense that they resemble each other, the one having come from the father the other from the mother. These corresponding pairs which appear to be morphologically similar are called autosomes. The 24th pair are dissimilar, a long "X" and a short "Y"

(sex /....

(sex chromosomes).

Where a zygote contains two "X" chromosomes, it is a female, XX.

Where a zygote contains X plus Y chromosomes, it is a male, XY.

Note that in the gamete or sexual cell the number of chromosomes is reduced to one half (reduction division). The significance of this is that the chromosome number in the zygotes is kept constant; otherwise with each union of gametes the zygote will keep doubling the number of its chromosomes, until it contains an impossible number. The reduction division is also responsible for hereditary variations depending on different and new modes of linking up in the different zygotes. Sex determination occurs also on these lines. With each chromosome dragged along into the zygote, is the linked together row of genes, so that even the sex chromosome Y drags with it, willy-nilly, a whole string of characters, not directly related to sex *(sex-linked characters)*. Chance however, governs which chromosome goes into which zygote. The Y chromosome has a very small part which is not homologous to the X, containing the so-called Holanderic genes), and of course the X has a very much larger piece for which there is no corresponding part in the Y at all.

It should be understood that the so-called sex-linked recessive characters are linked on to that larger part of the chromosome which has no corresponding homologue in the Y. In other words there is a deficiency of allelomorphic genes in the Y chromosome. Such allelomorphic genes, if present, would dominate the recessive trait, (if dominant),

or/.....

or modifying genes contained in the "missing" part, would influence expression of the trait. The pathological trait in the female may be rendered harmless by a dominant contained in the other X chromosome; or theoretically may be expressed, if the other X chromosome also contains the recessive trait, i.e. the female individual is a homozygote.

HAEMOPHILIA. A female haemophilia carrier, mates with a normal male.

H equals gene for haemophilia (linked to X chromosome X(H).

P	XX (H)		x		XY	
Gametes	X	X(H)			X	Y
Zygotes	XX		XY	XX(H)	X(H)	Y

50% sons have the trait, 50% normal.
50% daughters are carriers, 50% normal.

Normal female mates with affected male -

P	XX			X(H)	Y
Gametes	X	X	XH		Y
Zygotes	2 X	X (H)	2XY		

All the daughters are carriers, but all the sons are normal.

Female carrier mates with affected male.

P	X X(H)			X(H)	Y
Gametes	X	X(H)		X(H)	Y
Zygotes	XX	2XX(H)	X(H)		X(H)

25% are normal females
25% are affected females
50% are female carriers.

However, cases of females suffering from from haemophilia are not well authenticated. It seems logical enough that apart from the fact that the possibility of such a mating must be extremely rare, the haemophilic state may act as a lethal, i.e. a factor not permitting the carrier to live.

The following are known so far to be trans-

mitted as sex-linked recessives (Warkany, 1947).

Microphthalmia
Megalocornea
Leber's Optic Atrophy
Anhidrotic Ectodermal Dysplasia
Haemophilia
Colour Blindness

Some abnormality patterns or entities, e.g. microphthalmia are inherited by different modes, e.g. dominant or recessive as well as sex-linked, and even possibly present as phenocopies which of course are not transmissable.

Colour Blindness. Four per cent of males are red-green glind, although they may be able to distinguish traffic lights by intensity. Inheritance is as for haemophilia (see above) except that certain colour blind females are known ($\frac{1}{2}$ to 1% of the population). The gene for colour blindness is a common recessive in the population, so that colour blindness is a common recessive in the population and the chances of affected males marrying carriers are relatively high.

	Carrier		Normal	
Parents	XX(B)	x	XY	
Gametes	X	X(B)	X	Y
Zygotes	XX	XX(B)	XY	X(B)Y

Hence of the progeny, 25% of females are completely normal;
25% of the females appear normal but are carriers;
25% of the males are perfectly normal.
25% of the males exhibit the trait.

(b) Sex-Limited Factors.

Males and females may inherit genes for a specific defect, which however, only becomes obvious in the case of the male, say, owing to the fact that the male body with its hormones and environmental potentialities enables the expression to occur. The

fact/....

fact that a particular disease is confined to, or predominates in one sex, is not necessarily an indication that such disease is sex-linked. It merely means that the anatomical and physiological soil is really suited to allow such a defect to flourish in the case of sex-limited factors. For example in *hypospadias* the gene for the defect is not carried in the sex chromosomes and yet only males may inherit the defect by virtue of their peculiar anatomical makeup. Penetrance varies with the sex.

Multiple Exostoses are found about twice as often in men as in women, although the dominant gene is not sex-linked, but autosomal, i.e. affected fathers transmit the gene to both sons and daughters. Sex limitation in this case is incomplete or partial. Gaucher's Disease and Niemann-Pick Disease (recessive) and benign cystic epithelioma (dominant) are much commoner in females than in males, while albinism and congenital hypertrophic pyloric stenosis are commoner in males.

Baldness is carried by the same genes in both males and females, although manifested to a greater degree in the male. A female suffering from the condition may possibly, it is thought, show scanty hair, but never complete hair loss.

We have seen how certain characteristics are tacked on to the sex chromosomes, but linkage may occur in any chromosome. Polydactyly may be linked with syndactyly; or hypoplasia of thumbnail may be linked with deficiency of the patella; or in Laurence-Moon-Biedl syndrome, we find obesity assodiated with hypogenitalism, retinitis pigmentosa, polydactyly and mental deficiency; or fragility of bones may occur

together/....

together with deafness and blue sclerotics. The fact that certain characters are inherited in blocks, explains apparent contradictions in Mendel's Third Law of independent segregation of multiple factors; but going a step further, it was found that such linkage blocks where not always complete or constant, sometimes more marked in females than in males, as was demonstrated in experimental work on *Drosophila melanogaster*.

This discrepancy is explained by *crossing over*, a peculiar phenomenon which may occur in the diplotene stage of meiosis. In this process, homologus parts of an autosome are exchanged. In effect, this means that a complete block of allelomorphs is switched, crossing over with the corresponding allelormorphs. In man, we find that the ABO Blood groups may be linked with red hair and with Friedrichs Ataxia. Phenylketonuria, eye, hair and skin colour factors are linked. Even the layman knows about the linkage between freckles and red hair.

This conception of linkage is of great importance in understanding certain patterns of genetic disease.

Crossing over probably occurs during the four strand stage in meiosis, and actual chiasmata have been seen under the microscope (Jennings, 1935). It appears that environmental conditions, e.g. temperature, actinic rays, age of the mother (demonstrated in *Drosophila*) influence the frequency of cross-overs. The number of possible linkage groups, too, is obviously the haploid number of chromosomes in the organism, although they may appear to be less, because of the fact that members of some blocks are as

yet/.....

yet unidentified.

(c) Partial Sex-Linkage.

To recapitulate, partially sex-linked genes are carried in the X and Y chromosome segments which are homologous. In some cases they tend to be carried in the Y, but by crossing over, they may occasionally be taken into the X. In other cases they tend to remain in the X, occasionally crossing over into the Y. The genes appear to be arranged in linear order on the chromosome and hence tend to bear a certain relationship to each other.

Possibly carried along these lines are -

Xerodermia Pigmentoseum (marked cases).
Achromatopsia (complete colour blindness; recessive).
Retinitis Pigmentosa (dominant; only certain families).

(9) LETHAL FACTORS.

Lethal Factors are apparently commoner in plants and animals than in man. There must be very many in humans, but only a few are identifiable, though very definitely so. Many abortions, false pregnancies, stillbirths, in the final analysis, would probably turn out to be examples of such action. and probably the best obstetrical and paediatric care in the world might not save such cases or produce normal children once the genetic constitution is adjusted for lethal effect. In other cases, with proper care, many may be saved. For example, *erythroblastosis foetalis* expresses itself in many ways. Icteris gravis, hydrops foetalis, erythroblastotic anaemia are three main forms of expression, any of which may be fatal; but survival with treatment is possible in some cases, even in children born

with /....

with hydrops foetalis. Premature births may be caused by the same disease, and the result too may be fatal or non-fatal. Erythroblastosis is the result of a complicated set-up. It is the result of a blood group inheritance of a dominant character which only acts when the stage is properly set.

Apart from lethal factors being involved, and inheritance of dominant characters producing effects under certain conditions (irregular action), there is also the factor of delayed action, i.e. permanent sequelae may occur a year or longer after birth, e.g. kernikterus or neurological symptoms with mental deficiency.

In other cases where lethal genes are involved, heterozygous individuals may appear normal, or only have a slight or non-fatal defect, whereas homozygotes cannot survive. Death may occur in utero, or a variable period thereafter. *Brachydactyly* is the classical case of surviving members being heterozygous and showing short fingers (absence of middle phalanges); the homozygous condition is fatal.

D - Brachyphalyngic, dominant.
P: - Brachyphalyngic mates with Brachyphalyngic

P:	Dr	x	Dr
gametes	D r		D r
zygotes	1 DD	2 Dr	1 r r

i.e. 25% DD will die in utero (homozygotes).
50% 2 Dr will show Brachyphalyngy (heterozygotes).
25% rr will be normal

Other lethals are glioblastoma of retina, usually fatal in infancy (rr),

Amaurotic family idiocy, possibly (rr)
Malignant freckles (rr)
Progressive muscular atrophy (irregular dominant)
Haemophilia may be fatal (Gates 1946).

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(10) PLEIOTROPIC ACTION OF GENES.

We refer to a gene as producing a certain character, merely because such a character is observable, but every gene affects the organism as a whole; and the direction in end result (*determination*),will vary according to competence obtaining. Once determination definitely tends in one direction, there is a cancellation of other potentially hindering competences. Any modification of the gene in the sexual cells, or even in the chromosome itself, will also be transmitted throughout the whole organism, being recognisable sometimes even at the morphological level. For example, bombardment of the sex cells of *Drosophila* with electronic rays causes chromosome changes and comparable changes in the chromosomes of the salivary glands, which are observable.

Not only does each gene affect many organs and cells, but "character" is based on many genes, e.g. in *Drosophila*, 30 known pairs of genes influence eye colour. Grüneberg (1938), described a factor in rats causing anomaly of cartilage formation which is transmissable (see Figure 3.) This example admirably illustrates pleiotropic gene action; successions of serial events, lethal factors operating in different ways, all arising from gene action carried through various levels from the physiological to the morphological.

Grueneberg (1943), describes a condition of hereditary dwarfism in mice caused by a recessive gene. Growth ceases, and they remain dwarfed showing histologically under-development of the eosinophil cells in the pituitary. If normal pituitary is transplanted into these dwarfs, they will develop

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DIAGRAM, ILLUSTRATING PLEIOTROPIC AND LETHAL GENE ACTION.

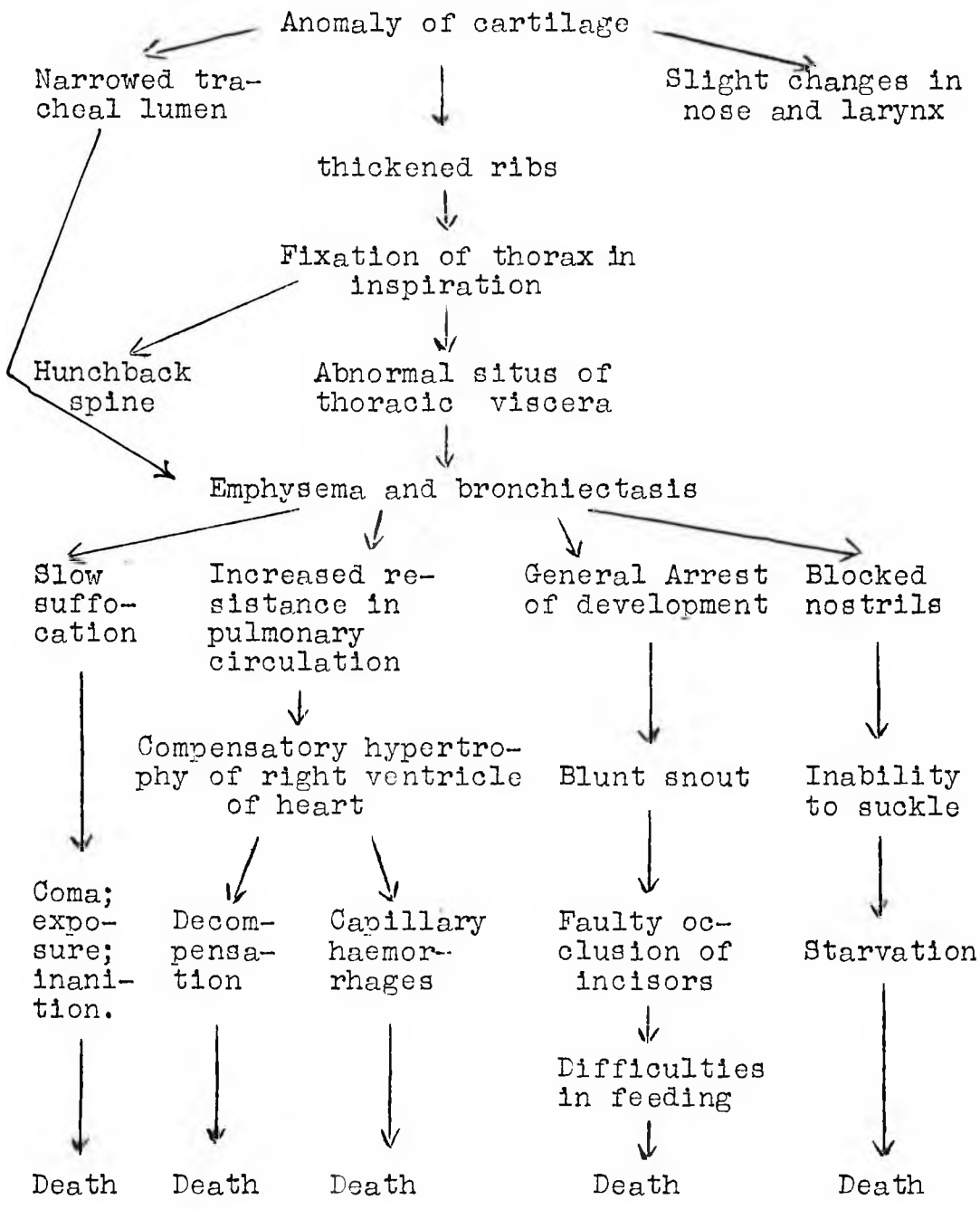

FIGURE 3.

into perfectly normal animals (Smith and MacDowell, 1930). The pleiotropic action in this case acts via the endocrine system, being translated morphologically. Other mice, when X-rayed, produce in the offspring a puzzling array of hairy eye and foot defects of all kinds following no laws of hereditary transmission. (Little and Bagg, 1924). Embryological studies however, showed that the developing zygote developed blebs in the central nervous system according to known laws. Where the discrepancies had arisen, was in the mechanical effects which varied according to where the blebs collected, e.g. in the snout area, eye area or extremities. Again, in children born of diabetic parents, we find hyperplasia of the pancreas to offset the hyperglycaemic environment, this state being associated also with overweight.

In tuberous sclerosis (epiloia), the same gene which causes adenoma sebaceum on the face, also causes mental deficiency, epilepsy, etc. The gene which causes phenylpyruvic acid to be excreted in the urine, also causes mental deficiency (phenylpyruvic oligophrenia). Schizoid personality and Kretschmar asthenic body type may represent pleiotropic action on the part of one gene.

(11) MULTIPLE ALLELOMORPHS.

Genes are present in a zygote in allelomorphic pairs. However, genes may also be represented as two or more allelomorphs. In fact, there may be a whole series of allelomorphs, but usually only two are present in a zygote. If the series be represented A, a1, a2, a3, then the zygote may exhibit any

of the following combinations:-

A A, A a1, A a2, A a3,
a1 a1, a1 a2, a1 a3,
a2 a2, a2 a3, a3 a3.

From the above, we see that the gametes can always contain either A or a1, a2 or a3. The A B O and rhesus blood groups in man illustrate multiple allelomorphism. Groups A, B, AB, O may be further subdivided into two extra types A2, A2B. The type A2 acts as in weak A. A rare and weaker type A3 is known. A1 dominates A2, while O is recessive. B is partly dominant over A2; i.e. A2 reactions are much weaker in group A2B.

To clarify the above: at first it was considered that there were only four groups viz. A, B, AB, and O. Later investigations over a large number of cases indicated that the so-called "A" had in some instances weaker agglutination action than anticipated (Wiener 1943). Thus A2 genotype came to be easily confused with O. In group A2B, it was found that agglutination reactions were weaker than with B alone, thereby indicating that B is partly dominant over A 2. The gametes (spermatozoa and ova) can only contain one allelomorph and the zygote not more than two, viz:

	BLOOD GROUP (Phenotype)	GENOTYPE
"A"	A1 A2	A1 A1, A1 A2, or A1O A2 A2, or A2O
"B"	B	BB or Bo
"A B"	A1B A2B	A1B A2B
"O"	O	oo

The/.....

The various progeny resulting from different types of mating may be seen from the following table:

No.	Mating Phenotypes	Children possible	Children not possible
1	A_1 X A_1	A_1, A_2, O	B, A_1B, A_2B
2	A_1 X A_2	A_1, A_2O, O	B, A_1B, A_2B
3	A_1 X B	All	-
4	A_1 X A_1B	A_1, B, A_1B, A_2B	A_2, O
5	A_1 X A_2B	A_1, A_2, B, A_1B, A_2B	O
6	A_1 X O	A_1, A_2.O	B, A_1B, A_2B
7	A_2 X A_2	A_2.C	A_1, B, A_1B, A_2B
8	A_2 X B	A_2, B, A_2B.O	A_1, A_1B
9	A_2 X A_1B	A_1, B, A_2B	A_2, A_1B, O
10	A_2 X A_2B	A_2, B, A_2B	A_1, A_1B, OO
11	A_2 X O	A_2, O	A_1, B, A_1B, A_2B
12	B X B	B, O	A_1, A_2, A_1B, A_2B
13	B X A_1B	A_1, B, A_1B	A_2, A_2B, O
14	B X A_2B	A_2, B, A_2B	A_1, A_1B,
15	B X O	B, O	A_1, A_2, A_1B, A_2B
16	A_1B X A_1B	A_1, B, A_1B	A_2, A_2B, O
17	A_1B X A_2B	A_1, B, A_1B, A_2B	A_2, O
18	A_1B X O	A_1, B	A_2, A_1B, A_2B, O
19	A_2B X A_2B	A_2, B, A_2B	A_1, A_1B, O
20	A_2B X O	A_2, B	A_1, A_1B, A_2B, O
21	O X O	O	A_1, A_2, B, A_1B, A_2B

In keeping with the contention that the gene affects the organism as a whole, we find that the A grouping is not confined to blood, but is extended to body fluids such as saliva, hairs, urine, sweat, semen, bile and the organs particularly pancreas, kidney, adrenals, liver, muscle, brain and fatty tissues, possibly to every cell of the body (Gates, 1946). This "secretor status" may be implicated in the production of mental deficiency in cases of A B O mother-child incompatibility (Yannet & Lieberman 1948).

The/....

The factors MN, are inherited independantly of the ABO groups, as are the Rh Factors. In addition there are iso-agglutinins present in the blood.

Rh-Isoagglutination: The Rhesus series of blood groups are of great clinical importance as a cause both of neonatal death and congenital disease. Landsteiner & Wiener (1941) found that the blood of Rhesus monkeys, when injected into rabbits, produced a serum which would agglutinate the red cells of about 85% of people. (Rh "positives"). It was found that the sera of women who gave birth to erythroblastotic children, contained an agglutinin which reacted with the red cells of the father of the affected child. Both the father and the diseased child were found to be rhesus positive (Rh), whilst the mother was rhesus negative (rh). The preliminary genetical investigations seemed to indicate that a single gene pair, Rh & rh, were involved, and that the mother, a homozygous recessive rhrh could form antibodies against Rh antigens in her child. The husband's genotype might be RhRh (homozygous) or Rhrh (heterozygous). If the father were heterozygous Rh positive, then 50 per cent of his children would be rhrh and therefore unharmed by the mother's antibodies.

Further blood studies indicated that multiple allelomorphs were involved in the production of Rh positivity. Fisher and Race (1946) found five separate antobodies and postulated the existence of a sixth. They found that everybody had at least 3 antigens, and sometimes in certain cases as much as six. These antigens have been labelled by Fisher

as/.....

as C,D,E, and c,d,e, and he called the missing antibody, anti-d. The original rhesus factor was found to be antigen D. C and E also produce Rh positive effects, though weaker in degree. C, c, D, d, E, e are all determined by different gene pairs, apparently close to each other in the same chromosome on account of their extreme stability. Actually 28 types of chromosome combinations are possible, but three are only really common, namely,

C D e,	c D E	& c d e	(Fisher)
$\frac{Rh +}{R_1}$	$\frac{Rh +}{R_2}$	$\frac{Rh -}{r}$	(Wiener)

Homozygotes have three antigens, whereas heterozygotes have four, five or six, for example;

R_1r (Wiener) = $\frac{C\ D\ e}{c\ d\ e}$ (Fisher)

R_1R'' (Wiener) = $\frac{C\ D\ e}{c\ d\ E}$ (Fisher)

The sensitised serum of the mother produces different iso-immunisation effects on the foetal blood and tissue cells, by diffusion of antibodies through the placenta. In the unborn child there may occur cirrhosis of the liver which eventually leads to foetal death and maceration. Or the child may be born grossly oedematous (hydrops foetalis). During the neonatal period, icteris gravis neonatorum may set in, or congenital haemolytic anaemia. Apart from a raised fatality rate resulting from this condition, remote results in surviving children are manifested by certain types of mental deficiency (Yannet 1950). The most common clinical picture includes the following features (1) severe mental deficiency (2) asymmetric hypertonicity and weak-

ness/.....

ness of the extremities, neck and back, and (3) choreo-athetosis. Anti-Rh antibodies may persist in the maternal blood for many years afterwards.

Not all Rh-negative mothers produce antibodies in the presence of a Rh-positive foetus. Other factors, probably environmental, appear to be implicated as well.

(12) BIOLOGICAL MOMENTUM.

We have seen, that once determination occurs according to a competence in a specific direction, the tendency is to be maintained along that direction. The speed or momentum is specific though different for each part of the embryo to form a co-ordinated growing system. Any disturbance in the rate of growth of an embryonic system, especially during its early critical period may cause abnormalities in development, whether such disturbances act from without, (environmental) or from within, (abnormal gene). According to Stockard (1920-1) an embryonic system during a period of rapid growth, is particularly vulnerable to noxa.

There is a creeper condition in fowls (resembling achondroplasia in humans), which is dominant and hence phenotypically obvious in the heterozygous state (Landauer & Dunn, 1930). The birds are short-limbed in appearance, but so far back as the 36th hour stage of embryological development, general retardation in growth is the first recognisable abnormality. In the homozygous embryos, the presence of two dominants alleles spells death within the first few days of development. In the heterozygous state, the retardation is confined to the limb anlages.

Different/...

Different bones are however, affected in varying degrees, apparently in relation to their different growth rates. Artificially grown legbuds from normal embryos in growth-restricting media produced similar abnormalities. There were also a high incidence of achondroplastic chicks on low glycine diets (Titus & Ellis).

The related condition of achondroplasia in man, is almost invariably caused by a mendelian dominant. Cleft palate and hare-lip may be due to locally reduced rate of growth of bones in the face with consequent failure to unite, though the mode of genetic transmission is not fully known in man. Many cases are undoubtedly phenocopies, very many are hereditary in origin.

Although disturbing events early in the chain may lead to early recognisable, or even lethal defects, yet the effects may not be apparent until after birth, or even later in life. In Huntington's Chorea, the affected members appear normal until after the age of 30 years, when relatively rapid physical and mental deterioration sets in. It is possible that the onset of most diseases is genotypically predetermined and the pathological condition will develop provided that environmental conditions are suited for its development. Even rickets will not develop in every member of a sibship exposed to the same difficiency of vitamin D; or if it does, the extent varies in different individuals under the same conditions.

Viewed from this angle, the aetiology of disease assumes a newer and broader significance.

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It behoves also the pathologist to look for patterns in disease, different diseases representing the same underlying pattern expressed under different environmental conditions.

Our hope for the future in prevention of congenital anomalies lies in the recognition of variable penetrance of many unfavourable genotypes. Why is it, that of those individuals whose genotypes make them liable to have clubfoot, 70% do not develop the trait? We may hope someday to discover the factors influencing penetrance and hence possibly to reduce the incidence of congenital anomalies. In the words of Stern (1950), "recognition of the genetic basis of anomalies does not lend to a fatalistic attitude, but on the contrary, to the search for specific preventive agents."

(13) MUTATIONS.

(a) Origin of Mutations.

At this stage we might ask, "broadly what are genes?". From a practical viewpoint the answer might be, the smallest particles of living matter, actually "atoms" of life, which are handed down from generation to generation, are carried in body after body and maintain unchanged, their specific capacity for producing specific effects under given conditions. They are in a sense, immortal; the body or receptacle dies, while they have the property of syhthesising from cell fluids exact replicas of themselves. This fact explains partly evolutionary processes. Certain environments encourage certain genes to survive and hence certain individuals will be hardier and occur more frequently in certain en-

vironments. However, there is an exception to the above rule of inviolability of genes, namely, the occurrence of mutations. A mutation is an apparently spontaneous change which occurs in one allelomorph, transforming it into another type with a different character, but stable, so that it may be transmitted according to all the laws of heredity. Most of these mutated genes are recessive and hence are passed on in a concealed fashion, becoming manifest with the mating of two hetrozygotes, perhaps generations after the original mutation has arisen. Sex-linked recessive mutations in a female may naturally be phenotypically obvious in sons of the first filial generation.

Although these mutations in Nature are referred to as "spontaneous", yet there may be some factors not understood which affects their incidence, because it has been found that every gene has its own specific frequency rate of mutations. In general, they may be said to occur rarely. In plants, genes are known with a high mutation rate even exceeding 1%. The mutation for a specific gene may always be identified, or yield a series of multiple allelomorphs. They may arise in the somatic cells or in the gametes. Malignant tumors may represent some such mutation process in the somatic cells.

Experimentally, mutations may be produced by X-rays, radium, ultraviolet rays, sublethal temperatures, chemicals, etc. The induced mutation rate is proportionate to the X-ray dose as measured by ionisation, i.e. by degree of electronic bombardment. In the past, cosmic rays and other

natural/.....

natural actinic agents have been believed to cause "spontaneous" mutations, But on the basis of ionisation and rate of mutation a considerable discrepancy is found. This implies that unknown factors are operative. In human blood groups, A2 is considered to be a mutation; and because relatively high A2 frequency figures are found in North Wales, Ireland, Basques, and Negroes, inference is that different races have different mutation rates (Waller & Levine, 1944.)

Mutated hereditary characters are harboured by everybody in the recessive state. Such a mutational process, in itself normal, leads to the concealed accumulation of abnormal genes, and eventually to "abnormal" individuals. Only the rare mutation succeeds. The detrimental ones may or may not become evident. "The threshold of expression" to quote Muller (1948) is "aggravated by inherited physiological weakness, or deviation. It can be estimated that with modern treatments, (including the survival rate of populations,) 1/10, to 1/20 of the population regularly meet what may be designated as 'genetic death', from such causes. At least that is the most probable estimate in flies, and it is not likely, that in humans the amount is less. But the great decrease in mortality which has been achieved in modern times, indicates that a considerable proportion of these deaths are today avoided. This leads to a consideration of the principles, whereby a mutant gene accumulates in a population, and it is shown, that any interference with their dying out, inevitable leads to such genes becoming

increasingly/....

increasingly numerous, as new mutations, continue to arise in each succeeding generation. In other words, our compensation for the mutations, by medical or hygienic means, inevitably though gradually, leads to mutations in their turn compensating for better conditions of living, so as in the end to bring the population to a condition where it has at least as many new ills as it had before, but is, besides, maximally engaged in endeavouring constantly to counteract the original ones."

LETHAL MUTATIONS.

The majority of mutant genes has an effect similar to that of a normal gene, its parent, but less actively produces physical effects. Sometimes it may fail to produce an effect at all; therefore it may be that most lethal genes may show reduced penetrance, actually weakening the organism if not killing it, and rendering it more subject to lethal action by environmental influences. In such cases the hereditary character of the early death may be concealed and we may ascribe it to extrinsic factors alone. If in the meantime the individual has reproduced, the mutation which is permanent, will be passed down the future generations so that every small harmful mutation is in its final effects on the population just as bad, if not worse, than a fully lethal mutation.

Muller (1948) calculated, on the basis of inbreeding results in man, that every person on the average contains in the hetrozygous state at least one lethal gene, or group of genes which in effect act as a lethal together, of such a nature as to kill an in-

dividual who should receive such a gene from both parents. The genetic death may occur at some period between birth and maturity, and this calculation fails to take cognizance of lethals acting at other periods of life.

Auerbach and Robson (1946), have recently found that mustard-gas and related substances have mutational effects. Other workers have found that some carcinogenic products substances produce mutations too. Stone and co-worker (1947), have obtained mutated strains of bacteria from media recently irradiated.

Mutations may be reversible, occurring spontaneously, or after X-Ray treatment, but the actual nature of the change occurring within the gene is unknown. It certainly cannot, except in a very few cases, be due to loss of gene material; it is probably molecular in nature. Particular phenotypical effects however, may be produced by mutations of different genes.

The study of mutation has been done chiefly in insects and plants, but the importance in human genetics is very obvious, especially today in a world experimenting with radioactivity. Also we must remember that certain phenotypical environmental anomolies in humans might morphologically be indistinguishable from mutations. We even see that a particular disease appears as a dominant in one family and as a recessive in another family, but in such cases two different genes are involved, although in both there occurs the same embryological process of maldevelopment.

En passant, relating to the question of evolution we find that most artificially induced mutations are harmful, but not all. "Harmful" is purely a relative term; it applies to environmental conditions prevailing. Some mutations may be very advantageous under certain conditions, others not so under similar conditions. We therefore have a basis for the persistence and increase of mutations based on environment, which allows certain of them to flourish. Many of these mutations are so slight that they may be difficult of detection yet their significance may be high from a point of view of pathological or normal evolutionary processes. We must also not loose sight of the fact that pathological mutation may be modified by a suitable combination of other genes.

As we see, mutations are continually arising, and when they do, they remain stable hereditary units which are transmissable unchanged. We also see that various external forces seem to influence the incidence of mutations. It is noteworthy therefore, that in the final analysis, environmental factors are seen to play a part in the production of purely hereditary characters.

(14) ENDOCRINE FACTORS.

(a) Growth and Development : Intrinsic Genetic Factors.

Although the endocrines influence greatly growth and development, yet a definite relationship between body types and endocrine pattern cannot, except in pathological cases, be substantiated. (Hoskins 1941). It would appear that the limits are set for normal constitutional and racial differences in height, bodily

contour/....

contour, etc., by the genetic constitutions of the skeleton and tissues, quite apart from the endocrine system. And yet, giantism, dwarfism, eunuchoid proportions can and do result from endocrine dysfunction. But an individual, who has a genetic constitution for the development of large stature, may fail to achieve such a stature if his endocrine system is not properly functioning. Should the individual, however, possess directly a gene for abnormal height, the endocrine system, which is the mediator, may be subject to abnormal strain in its effort to carry out the demands of the abnormal gene. In fact, Bauer (1945), records the case of a family of giants, one of whom a eunuchoid, subsequently developed a pituitary tumour, and remaining members exhibited a tendency to giantism with or without eunuchoidism. He records the giantism here, as a primary family trend.

Although deprivation of the gonads retards closure of the epiphyses, all male and female eunuchoids are not necessarily tall, probably because of a genetic trend in some cases towards small stature (Varney et al 1942). Allbright (1942) described a family with small stature and hypogenitalism. He describes the hypogenitalism as being a concomitant abnormality, part of a syndrome of constitutional defects, including in different members of the family, pterygium colli, cubitus valgus, aortic coarctation, cleft palate, strabismus, vertebral "epiphysitis", etc., a combination of familial and hereditary defects.

Pygmies of Central Africa, exhibit no signs of endocrine or other pathology, hence their small stature is due to a constitutionally racial deviation; yet pituitary dwarfs, or "midgets", result from fami-

lial anomalies of the pituitary gland. Achondroplasia results mainly from an inborn defect of cartilage formation. The concomitant hypergenitalism, precocious puberty or advanced sexuality which sometimes occurs, may represent secondary adjustments made by the endocrine organs.

Similarly the rate of growth and ageing of an individual may be genetically predetermined, only to be modified by external factors. A child with genes for longevity (i.e. natural resistance of all the organs to ageing) may yet die at birth from a complicated labour, or in infancy from enteritis, or in childhood from a road accident, or in adolescence from bulbar poliomyelitis. Thus it is, that preventive and sociological medicine increases the expectation of life, although longevity remains unaffected. This increased expectation of life leads to an increase, in the community of older persons, who not only are less fecund, but are also more subject to certain diseases prevalent in their older age-group, just as infants in their particular age-group are subject to enteritis or pneumonia. The question of susceptibility to disease, will be treated later.

Racial and national tendencies are reflected by average size and build of population groups. Physical abnormalities suggestive of endocrine dysfunction are not necessarily so in origin. For example, certain skeletal disproportions, hair distribution irregularities, obesity, etc., are merely due to hereditary traits.

Physiological function in man appears to be under the ultimate control of the central nervous system acting in balance with the endocrine system, it-

self a finely balanced unit, consisting of several glands. They each balance up action upon the effector organs. Actual function, and character or reactivity is therefore a complex intergration based upon the genetic constitution of the endocrine system, the central nervous system, the effector organs, and external stimuli acting upon the various inter-connecting pathways, to obtain, so far as is possible, smooth, equilibrated function. Thus an injury to the Central Nervous System may cause glycosuria in one case. Pancreatic destruction in another case, and a constitutional defect of the kidneys in yet another case, may be responsible for the same symptom. This state of reactivity is bound up with the "personality" of the individual, and is already manifest at birth.

(b) Sexuality.

In more primitive organisms, we find peculiar sexual states, i.e. hermaphroditism (having organs of opposite sex), bi-sexuality (possessing complete set of reproductive organs of both sexes, inter-sexuality (switching from one sex to another), gynandromorphism (each half of the body of different sex), etc. In humans, the concept of sexuality in its widest scope appears to defy adequate definition. It implies more than the presence of male or female sex organs and includes behaviour as well. Every male has a large number of female characteristics and *vice versa*. No single one of these characteristics can by itself be termed masculine or femine. We also have the apparent anomaly of a woman with female sex organs and body contour, behaving as a male. Endocrine

mechanisms and "personality" expressions are usually, but not always, parallel. The "personality" is expressive of *all* intrinsic genetic factors working together, plus the action of extrinsic environmental factors.

It is a remarkable fact, that in the developing embryo, the adrenals comprise a larger proportion of body weight than they do in later life. It would seem that they have a great influence on the development of the individual, both sexually and otherwise. In fact, in many respects the action of this endocrine resembles that of an organiser, particularly with regard to its effect on the gonads, secondary sexual characteristics, and in fact "sexuality" itself. The action of the sex hormones resembles that of evocator substances. Sexual determination appears to be in the first instance dependant on the X, Y chromosomes which set the course for furture development as regards morphological sexual progress ("genetic" sex). But should the endocrine organs get out of hand that course may be seriously disturbed. On the other hand, their proper function is the physiological basis of normal sexual behaviour.

Greene et al (1938) have produced sex inversion of rat embryos by hormonic stimuli, and all pathologists know of the masculinising effects of adrenal cortical tumours pouring out increased quantities of sex hormones.

Sex Hormones: Androgens in female embryos tend to masculinise producing an intersex condition, whereas male embryos are unaffected. Oestrogen in large quentities may have inhibitory effects in embryos of both sexes, but particularly in the growth of the male

sexual/...

sexual organs; the female sex organs however, are actually stimulated. (Warkany, 1947). Witschi (1939) describes male pseudohermaphroditism in certain families which he attributes to excessive action of maternal hormones in the male foetus during the critical stage of its sex development. On this basis, the essential anomaly would appear to be really one in the *mother* whose genetic constitution is such as to cause over-production of sex hormones, operative during pregnancy.

(c) Other Endocrine Factors.

Injections of insulin into chick eggs, pregnant rabbits etc. have resulted in production of deformities (Landauer 1945), while the survival of a foetus born of a diabetic mother is subject to some uncertainty; in fact, without the use of insulin, many female diabetics are unable to conceive at all.

There appears to be a higher incidence of congenital malformations in the children born of diabetic mothers (Murphy 1933). Overweight is another abnormal tendency in the children at birth (Lawrence and Oakley, 1942). This tendency in the child is associated with visceromegaly and hyperplasia of eosinophil cells in the anterior pituitary gland; and in many cases precedes the onset of diabetes mellitus in the mother by some years (Miller, 1945). There is a considerable body of evidence to implicate the pituitary gland in the aetiology of diabetes, and this opinion is weighted by the above pituitary findings, plus the tendency to gigantism. Female diabetics are often sterile, or if pregnant, have been found to excrete excessive amounts of gonadotropins (Joslin et al 1940).

Mongolism/...

Mongolism has been ascribed by Benda (1946) to endocrine factors. He states that, "Mongolism is the constitutional type of hypopituitarism" but autopsies performed by Ingalls (1947) do not corroborate such a statement.

The present tendency to treat pathological conditions in pregnancy with endocrine products may not be entirely free from danger. It has been shown, that the administration of oestrogen to the mother causes precocious development of the uterus and nipples in female embryos, depending on their stage of development. Both androgens and oestrogens apart from specific masculinising or feminising actions, retard in either sex, retrogression of the Wolffian duct systems, with consequent deformities of the external genitalia. In rat embryos, under very special conditions, androgens may cause transformation of ovarian follicles into seminiferous tubules. (Marx 1942). The resulting structure resembles an ovotestis, but complete switch-over has not yet been accomplished.

We are really only on the fringe of a complex branch of an extremely complex subject. Sterility may be caused by an inadequate supply of available oestrogen to the cervix. Apart from infections, absence of oestrogen causes inadequate secretion of cervical mucus so necessary for fertilisation (Barton & Wiesner 1946). Or a deficiency of hyaluronidase in male semen consequent on endocrine dysfunction may lead to a similar result. Such factors may be closely interlinked with environmental conditions, and/or genetic constitution. The subject is further dealt with when the effects of environment in relation to congenital defects are more fully considered (Chap. II).

(15) CYTOPLASMIC INFLUENCE CONTROLLED BY GENES.

It has been shown that there are some maternal influences exerted directly through the female cytoplasin, controlled by gene action. This applies in the case of a certain species of snail's shells. The coiling of these shells, whether dextral or sinistral, is determined by the mother's genes and not its own genes. Although dextral is dominant over sinistral, e.g. where -

L = dextral gene

l = sinistral gene,

then, any female of genotype LL or Ll will produce dextral offspring - even if mated with LL or ll males, and some offspring are ll. That is to say, a homozygous recessive will still show dominant characteristics based on the fact that the mother carried the dominant gene L. In some way therefore, the germ cell cytoplasm is influenced before reduction division, so that the direction for coiling is determined. Apparently the cytoplasm of the maternal germ cell governs the position of the spindles in division and hence direction of coiling. Such dextral offspring will however, produce in their turn sinistral offspring because the cytoplasm of the germ cells is influenced by a sinistral gene (Shull 1948).

A similar action appeared to occur in mice, where breast cancer was apparently predominantly determined by its presence in mother rats, who handed it down to the progeny in a kind of unilateral maternal transmission. However, it was found later that the factor responsible for the production of cancer in the line of rats, resided in the mother's milk. Even un-

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related mice feeding on the milk of a cancerous rat developed a neoplastic condition.

CHAPTER II.

THE RELATION OF ENVIRONMENT TO CONGENITAL DEFECTS.

(1) FUNCTION AND ITS EFFECT ON STRUCTURAL DEVELOPMENT.

Throughout the organism's existence, there is a tendency for growth, in form, of an organ to parallel its growth in function. Hence prematurity, in proportion to its degree, handicaps a child in its attempt to cope with extra-uterine existence. In the neonatal period, new functions are suddenly imposed upon an individual, precipitated into a new environment. Hence this period is accompanied by feverish activity in organs which respond physically to altered physiological function. The ductus arteriosus and cardiac septa become non-patent, the liver, bone-marrow, lungs, in fact every organ undergoes changes in greater or lesser degree according to the extent of demands made upon it. The kidney, as an example, continues in its growth, and even in the formation of glomeruli, for some time after birth.

In the case of the intellect, however, we see what has been described as an "embryology of the mind". (Gates, 1946). A well authenticated case is described which particularly illustrates the importance of function in development. Zingg (1942), relates how two native children were rescued from a wolf's den in India, where the animals had brought them up. They both behaved like animals with many animal conditioned reflexes. They howled like wolves at night, fed on raw meat, lapped their drink and their mode of progression was on all fours. One of the pair, whose age was assessed at about 8 yrs. was rescued, survived for several years

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and was only able to master the art of walking erect after many months of massage. Running was still accomplished on all fours. Sent to a children's orphanage, she gradually acquired human habits, but could only talk with a limited vocabulary of some 40 words. She could never learn to form sentences.

An important question has been raised in modern therapeutics. How successful can we be in changing physiological function, once established? In recent years, surgical procedures have been introduced, as for example in congenital cardiac disease, which radically alter the functioning of parts. Time will provide an interesting answer.

And again, is emphasised, the importance of using every member of the body in its proper functional manner, during infancy and childhood, bearing in mind of course, the limitations imposed by any infantile status at that particular stage of development. It has been shown that the I.Q. of children of professional men is consistently higher, as a group, than that of children born of lesser "intellectuals", dropping lowest in the unskilled labour group (Haldane, 1938). Allowing for the fact that I.Q. is not synonymous with basic intelligence, the influence of a good environment, providing better functional, economic and social opportunities, seems very important. And again, once an intellectual level of function has been established, removal of one or even both cerebral hemispheres causes surprisingly little deterioration of the "mind". Neurosurgeons are demonstrating this fact today. Krynauw (1950), has removed for epilepsy, in childhood and

early/.....

early adulthood, a complete cerebral hemisphere on more than one occasion, and because the brain was yet developing, and adaptable to training, mental function was normal, and not even marked paralysis resulted.

These examples, just cited, serve to illustrate how function affects development post-natally, but the same principle applies in the case of the developing foetus, though in a more limited way. Many workers believe that even the amniotic fluid has a physiological function apart from acting as a protective water cushion. The foetus is continually moving inside his fluid-filled envelope, using his limbs, exercising his respiratory muscles (Barcroft 1947), which latter process may also serve some physiological function. (Smith 1945). Interference with foetal function may affect the development of the foetus.

(2) MECHANICAL FACTORS.

Apart from slowing down the growth momentum, there may be degeneration of whole parts in the embryo after normal development. Whereas intrauterine amputations were originally believed to be the result of strangulation by amniotic bands, they are now suspected to originate by means of a different mechanism, viz. by the action of a vascular anomaly causing excessive dilation of blood vessels, stasis and extravasation with final sloughing of the part. The associated adhesions would appear to be a concomitant rather than an aetiological factor (Browne, 1947).

Although most cases of clubfoot are due to inheritance (Stern 1950), yet Dennis Browne (1947) has shown some to be the result of pressure in utero upon an apparently normally developing foot. He describes

them/.....

them as "moulding deformities" of the osseous system, resultant on abnormal position, with or without abnormal pressure,as well. Where there has been abnormal pressure, the prognosis has been worse, because of the atrophy of muscles and the stiffness of joints.

Ingalls (1947) described an autopsy performed by him on a child with Mongolian idiocy. There was a congenital malformation of the right foot more consistent with an aplastic process, than with a uterine amputation.

"The right foot consists only of the os calcis and the talus. The skin is stretched over these bones, and there are two toenails laterally corresponding to the little toe, and the one next to it, and a rudimentary toenail a short distance medially". Such a condition occurring separately and apart from the concomitant mongolian stigmata, might have been considered an intra-uterine amputation.

Very rarely, bands might possibly cause malformations and distortions, which of course may not be hereditary. (Birch-Jensen, 1949)

Many of these malformations are harmless, others improve in childhood, or are easily remediable. The caudal and cephalic ends, including extremities, i.e. parts most vulnerable to pressure effects, are involved most frequently. Premature infants also show a larger incidence of abnormalities but in these cases mechanical factors are probably minimal and the abnormalities are an expression of the pathological condition which caused the premature birth.

Brachygnathia, torticollis, dislocation of the wrists, elbows, knees and clubfoot, produced mechanically, often improve spontaneously. At least 50% of

neonates/...

neonates (Browne 1947) show deviation of the mandible to one or other side with mal-alignment in relation to the maxilla. Such a deformity is not infrequently associated with a posterior dislocation of the knee, a fact which seems to substantiate the impression that the infant's head had been pressed against the shoulder and fixed by the leg lying against the uterine wall. Similarly brachygnathia may be caused by pressure of the chin on the chest. By "folding" the infant into its most comfortable position, some clue may be obtained as to the mechanism involved in the malformation. At birth, the infant possesses the intra-uterine properties of complete relaxation for a short time. This ability passes off after about a week whereupon the joints or limbs which had previously been locked in abnormal positions, show stiffness, immobility and deformity, not previously obvious (Chapple, 1947). Hence Chapple recommends an orthopaedic examination for all infants at about three months to detect, more especially congenital dislocation of the hip, which at birth is rather a potential, than a true deformity. Congenital dislocation of the hip may be of mechanical or genetic origin, though in the latter case, it is difficult to disentangle the exact point of fault. Is it maternal? (the shape of the maternal pelvis, or faulty hormonal action, etc., allowing of faulty foetal position)? or is it foetal? (exceptional muscular relaxation, laxity of joint capsule, etc.) As it is seven times more frequent in females than in males, what is this predilection due to?

Coxa vara, knock knee, spondylolisthesis, lordosis, are not directly or apparently of congenital origin except possibly in rare instances. (Chapple, 1947)

Ectopic Pregnancy. Ectopic pregnancies usually come to an untimely end, but if surviving, may present abnormalities postpartum. Ectopically implanted ova at a very early stage, already show evidence of spina bifida, encephalocoele, anencephaly, etc. before any effects are likely to have arisen from spatial distortion, and are better attributed to impaired nutrition in an unsuitable environment (Warkany 1947). However, in some cases pressure factors must be operative, as witness areas of skin atrophy, assymetries involving head and neck, marks of compression and constriction etc., Winckel (1902) estimated that 50% of children originating from ectopic pregnancies present malformations of the latter nature, i.e. consistant with distortion locally, as might be caused by oligohydramnios, amniotic bands, distorted amniotic sac, irregular development of containing walls, placental induration, etc. Many of these malformations improved spontaneously after birth.

Asphyxia. Experimental work by various workers (Romanoff, 1930; Byerly, 1946) on incubating chick eggs showed that normal embryonic development could be disturbed by varying the concentration of oxygen and carbon dioxide in the environment. In some animals, however, anoxia does not appear to be of great importance as a teratogenic factor. In guinea pigs, anoxia prior to birth, produced severe cerebral damage (Grunewald, 1947[a]). In man, temporary anoxia of the older foetus stimulates respiratory movements

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(Barcroft, 1947) and may even be responsible for aspiration of amniotic fluid.

Apart from direct trauma to the brain, mental deficiency may also conceivably be caused by anoxia. Gruenwald (1947) cites a case from the literature where carbon monoxide poisoning occurred in a pregnant woman, who recovered from the effects of the gas. Her child which was born 13 days after the poisoning, showed definite signs of cerebral softening at autopsy, when death occurred 9 days postnatally.

Temperature According to Gruenwald (1947) temperature has not been demonstrated in man to have any teratogenic effects, although in animal experiments temperature has been shown to cause various structural defects on the embryo.

(3) ACTINIC FACTORS.

(a) Experimental Observations.

A very reliable method of inducing a high incidence of malformations is by the use of radium or Roëntgen rays. Experimentally this method has proved of great value in the elucidation of mutation rates. It was found that X-radiation retarded the first cleavage of the fertilised ovum, but the highest incidence of severe abnormalities is produced during gastrulation. At a later stage, the vascular and central nervous systems and eyes are affected, probably because of their rapid development during this period. In fact, sensitivity of cells to radiation is found to be indirectly proportionate to their differentiation, and directly proportionate to their reproductive capacity. Foetal death, embryonic

resorption,/....

resorption, and a vast range of abnormalities including hydrocephalus, ocular defects, sterility, incompletely developed organs and limbs, have appeared in the progeny of pregnant female rats depending on the stage of embryonic development at which irradiation was performed.

Goldstein and Murphy (1929) found that 37% of 75 children born after post conception radium or Roentgen irradiation of the maternal pelvis manifested mental or physical abnormalities attributable to the irradiation, while the remainder developed normally. The effects were more common where irradiation occurred during early embryonic life. There even appears to be a suspicion that the irradiation of organs other than the maternal pelvis may possibly cause congenital anomolies in the offspring. (Faober, 1933).

Another significant fact was discovered by Snell (1941). He irradiated male mice, who, before becoming temporarily sterile, sired unusually small litters of normal young which were crossed with normal mice. One third of the resulting progeny also sired, small litters. The litters appeared to be small because intrauterine death occurs in deformed embryos of the litter but only in the second generation after exposure to X-rays. The mechanism is supposed to be that of reciprocal chromosmal translocation, that is, exchange of parts by non-homologus chromosomes.

Today, as a result of the atomic bombardment of Hiroshima and Nagasaki, the inadvertant exposure of workmen in atomic plants, and actual controlled

experiments,/....

experiments, data are gradually accumulating which will shed more light on genetic processes. The emission of very penetrating neutrons and gamma rays, has not only immediate effects of human reproduction causing sterility; but mutational and chromosomal effects in future generations are to be expected. (van Rooyen, 1946).

"Atomic fission is going to add to the sum of future ills", says Muller (1948). "It can readily be estimated that each bomb falling on highly populous areas would probably kill many more people scattered through future generations, than those killed in the generation immediately affected".

The effect of X-Ray is usually considered to be exerted directly upon the product of conception, a fact demonstrable, experimentally. However, no radiation can reach the conceptus without first affecting the intervening tissues, e.g. uterus, placenta, etc. The possibility definitely exists that the metabolism of the surrounding tissues is so disturbed by radiation as to affect the development of the embryo. (Gillman et al, 1948). This metabolic disturbance may be in the nature of protein changes, the formation of macromolecules, which the conceptus is obliged to metabolise or to utilise as building material for its protoplasmic proliferation. This idea introduces another factor into the explanation of defects caused by actinic agents, and the more factors introduced, (some as yet unknown), will eventually elucidate the problem as to why some, but not all, offspring of irradiated mothers are abnormal. Perhaps the factor of genetic constitution is involved as well.

It is/....

It is important for men exposed to relatively heavy doses of radiation to refrain entirely from reproduction for some two months after exposure, on account of the added danger of chromosome breaks in the mature spermatozoa. Such chromosomal translocations may predispose to abortion in the embryo. In commercial use, X-Ray machines commonly used in shoe shops on the feet of customers and little girls, are not free from danger to the gonads by irradiation. Radio-active isotopes also, will have to be used with great care in future (Muller, 1948).

(b) Direct cellular effects.

Apart from molecular or other mutational changes in the gene itself, radiation may cause structural damages to the chromosomes. A small fragment of chromosome may be lost and extruded from the nucleus; or a piece broken off and joined again upside down (inversion); a piece of chromosome may join the other member of a reciprocal pair, (duplication), or a piece of chromosome joins the chromosome of another homologous pair (translocation), a whole chromosome may be lost in one cell, and gained by another (heteroploidy); the whole chromosome becomes multiplied (polypoidy). Such effects have been known to occur spontaneously in plants and animals, or more often after exposure to actinic energy. They almost certainly occur in man under similar conditions.

A "good" mutant, especially if dominant, is selected out naturally and encouraged to remain; bad dominants are eliminated soon, unless they manifest themselves after reproduction has taken place. The foetal malformations resulting from irradiation of the

maternal/....

maternal pelvis however, cannot be attributed to mutations in zygotic germ cells, because fusion of normal gametes had already occurred, and the individual is being integrated. The effect can only be exerted in some directly destructive, or indirectly metabolic way. In some cases, the destructive effects on the somatic tissues may induce somatic mutations, as is possibly reflected by the increased incidence of leukaemia and carcinoma amongst radiologists (Metropolitan Life Insurance, 1948).

There is no safe radiation dose for the gonads. The frequency of mutation is directly proportional to the total dose of radiation, being quite independant of wavelength. The White House Conference report (Vol.1(b)), states that preconception radiation of the female pelvis in non-sterilising doses is harmless. However, there is no threshold dose (Muller, 1948) and the effects are cumulative over an indefinite period throughout life. It has been estimated that a total accumulated dose of approximately 35r to gametes, or about 100 r to the gonads, will double the natural mutation rate, (Crewe 1947), and as most mutations will be recessive, they will remain unknown for hundreds of years.

(4) NUTRITIONAL FACTORS.

Disturbances of the embryo's nutrition may result in any effect ranging from death to retarded development. Disturbances of nutrition are not only caused by a shortage of dietary essentials *per se* but also, by faulty implantation of the zygote, placental diseases, faulty umbilical circulation and various maternal, sometimes footal diseases involving ...

transmission/...

transmission of toxic products. Infections, for example, rubella, actinic factors may also act by affecting early on, the blood supply or other tissues regulating the nutrition of the part. Sterility may be caused by general starvation (Warkany, 1947); post-conception starvation may lead to abortion or resorption of the embryo in the early stages of pregnancy. Later it may cause still-births or underweight offspring. Congenital anomalies may be caused by complete lack of a single dietary essential even though the caloric intake be adequate and the individual does not appear to be starved. Furthermore, the presence of a deficiency disease in a newborn infant almost invariably means that the mother herself is suffering from that disease, excepting in cases of neonatal iron deficiency (Parsons, 1946).

Deficiency of Iodine. Stillbirths and congenital anomalies may occur as the result of iodine deficiency during pregnancy. Endemic cretinism occurs in areas where iodine is deficient, e.g. in the Alps, Pyrenees, Jaucasus, Carpathians, Himalayan districts, and other areas not at the coast. Most, though not all, endemic cretins have goitres, exhibiting low mentality associated with relatively normal physical and sexual development. The endemic cretins without goitres, tend to reach a higher level of mental development but are retarded physically and sexually. Even if the disease should become apparent in later childhood, the defect is actually congenital, having been predetermined *in utero*.

In fact the thyroid is the most precocious of the endocrine glands in its embryological development.

Various /....

Various central nervous system deformities have also been recognised; internal hydrocephalus, brachycephaly, histological changes in cerebrum and cerebellum prognathism, dental defects, etc. Occasionally there is spastic diplegia or quadriplegia with strabismus, ocular defects and deafness. The mental condition varies from slight retardation, (perhaps unrecognised as being due to cretinism), to complete idiocy, and will not respond to post-natal medication with iodine or thyroid. (Benda, 1946).

The children of female cretins may be normal or cretinous, although iodine treatment during pregnancy increases the chance of normal progeny.

Vitamin Deficiencies. Apart from causing sterility, abortions, stillbirths, and other anomalies, congenital blindness due to xerophthalmia or optic nerve constriction may occur in the offspring of animals deficient in Vitamin A. (Moore et al, 1935). Other eye anomalies, e.g. microphthalmia and anophthalmia, as well as accessory ears, hare-lip, cleft palate, ectopic kidneys, and subcutaneous cysts were found in the offspring of sows suffering from Vitamin A deficiency. (Hale, 1937). One of the functions of colostrum would appear to be the provision of Vitamin A for the newborn. (Parsons, 1946).

It was found that female rats on a riboflavine deficient diet, became themselves physically retarded, or produced young with a great variety of skeletal and other anatomical defects. Such anomalies were preventable by administration of liver before a certain stage of pregnancy. This indicated that deformities appeared only during a certain critical period when riboflavine (a tissue enzyme) is required in considera-

ble amounts/...

ble amounts. In other experiments where multiple dietary deficiencies occurred, the addition of riboflavine actually accentuated the deformities. (Warkany, 1947).

Vitamin D causes congenital rickets in new born infants (Maxwell et al, 1939) and this result has been supported by experimental work in animals. Mellanby and Goumalos (1946) investigated comparable groups of children 5 years old, attending London County Council Schools, in 1929, 1934 and 1935 respectively. They found that each group from 1929 onwards showed progressively better dental health, which was attributed to increased calcium and phosphorus intake in the dietary of pregnant women and young children since 1929. The incidence of rickets in general, is falling in Britain. (See report of British Paediatric Association, 1943).

Smith (1947) analysed the physical condition of neonates from mothers exposed to conditions of general under-nutrition in Rotterdam and the Hague during the unhappy winter of 1944-45. He found that the weight and lengths of newborn children declined, reflecting the nutritional state of the mother during the last 3 months of pregnancy. In this trimester or "period of foetal growth" (Warkany), the foetus lays down two-thirds of its calcium phosphate, three-quarters of its protein, four-fifths of its iron, and gains over an ounce a day in the last four weeks of pregnancy. Considerable quantities of minerals, hormones, vitamins, even immune antibodies, are stored for use in early post-natal existence. Hence premature birth, multiple pregnancy, or maternal malnourishment, severely handicaps an infant by cutting into its

reserves/....

reserves. This is reflected by an increased neonatal mortality rate for such "immature" children, and ill results may manifest at any period from birth, right up to even adult life. The above facts provide a stimulus for the already growing consciousness in regard to ante-natal and social paediatrics. Contemporaneous with the raised economic status of the lower social classes, we find a decreased mortality rate for their immature infants. A deficiency of copper in ewes may cause neurological disturbances in offspring resembling Schilder's disease in man. (Warkany, 1947).

(5) CHEMICAL FACTORS.

C.R. Stockhard (1931), emphasises that a particular congenital abnormality could be caused by the action of several different chemical agents. In such cases, the organs developing at the greatest rate during exposure to the injurious agent, seem to be the most vulnerable, probably because organiser action is interferred with. Injuries to primary organisers are likely to cause more serious malformations than injury to secondary or tertiary organisers.

There are some substances which simulate in their action upon tissues, organiser activity. (Needham, 1942). Later work seems to indicate the influence of hyaluronic acid and pteroic compounds. It is possible that some evocator action is related to the cause of tumor growths.

Weller (1917) had demonstrated that male guinea pigs exposed to lead, sired weak and underveloped young with a high neonatal mortality. Cantarow & Trumpar (1944), give figures which show an ....

unusually/....

unusually large proportion of stillbirths occurring in the children of fathers exposed to lead. In 9.5% of cases of congenital cardiac disease with adequate records, the father's occupation involved exposure to lead, as in the case of painters, or workers in battery plants. This evidence is suggestive but not conclusive and requires considerably more research.

In these days, when antibiotics are administered so fully in so many diverse conditions, and also during pregnancy, the question arises as to whether these chemicals affect the embryo in a detrimental way. Speart (1940), tested sulphonamides in rats. He tested concentrations higher than that employed in therapy, but the concentrations were equal in the maternal and foetal blood. Prolonged administration increased the mortality before and after birth, the birth weight was diminished and post-natal growth was retarded. Penicillin was found to have no effect on the embryo (Greene and Hobby, 1944.)

(6) METABOLIC FACTORS.

Gillman and co-workers (1948), have produced congenital anomalies in rats, by injecting the mother rats with trypan blue, a substance which has a binding effect on plasma-proteins. The dye could be demonstrated in the yolk-sac, but not the tissues of the malformed offspring, thus suggesting that its teratogeneous action occurs by virtue of altered metabolism in which the amniotic fluid is implicated. However, the possibility exists that the dye does get carried into the foetus, but is changed into an unrecognisable form. Further investigations along these lines are being eagerly awaited.

Landtman/....

Landtman (1948), found that 42.5% of mothers who gave birth to deformed children suffered from some morbid condition in early pregnancy. More than half of these morbid conditions were not acute infections. In the control series of women with normal infants, only 14.5% had some morbid condition during early pregnancy. This evidence appears to indicate that maternal disease may affect the foetus through some disturbance of the metabolic processes.

Foetal thyroid or iodine deficiency produces congenital cretinism, but the mental development of individuals with congenital hypothyroidism often fails to respond adequately to thyroid administration. Bruch and McCune (1944) suggest that brain damage may be an associated lesion and not a consequence of thyroid deficiency.

Mention has already been made of the tendency for a high incidence of congenitally deformed children to be born in the case of diabetic mothers (Murphy, 1947). Barns (1941), Skipper (1933), and Hurwitz & Irving (1937) produce evidence to confirm this.

In diabetes, the metabolic disturbance and the insulin deficiency of the mother as we understand it, does not cause the visceromegaly in the foetus, because foetal and neonatal mortality are increased during a five year period preceding the onset of maternal diabetes. (Miller et al, 1944). There are therefore early changes occurring at a metabolic level, remaining undetected until relatively late. In fact, there is also evidence of raised stillbirth rates amongst those who subsequently develop the disease. (Gilbert and Dunlop, 1948).

Recent/....

Recent observations have also shown a high coincidence of congenital malformations in children with erythroblastosis (Weber & Scholtz, 1939; Wiener 1947). Javert (1942) described a series of forty-seven infants with erythroblastosis of whom ten showed congenital malformations. Maternal Rh iso-immunisation, when producing defects, tends to involve the central nervous system in a characteristic way, which may be recognisable clinically. Miller (1950) describes the picture as follows:
(i) Severe mental deficiency; (ii) asymmetric hypertonicity and weakness of extremities, neck and back, and (iii) choreo-athetosis. For correct diagnosis, a neonatal history of erythroblastosis foetalis is usually obtained as well as an appropriate Rh set-up in mother and child. There may even be anti-Rh antibodies in the mother's blood many years after the morbid pregnancy. Miller also describes a less common picture of mental deficiency associated with generalised hypotonicity and inco-ordination. It is possible too, that lesser degrees of mental deficiency unassociated with neurological abnormalities may be a consequence of maternal Rh iso-immunisation. Yannet and Lieberman (1948) have published work which indicates a possible connection between certain cases of mental deficiency and maternal ABO immunisation. Although these catastrophes of maternal iso-immunisation are described here under the heading of metabolic factors, it appears however, that several other factors are also involved.

(7) INFECTIOUS FACTORS.

It has been remarked upon, that in spite of the

common/...

common lay opinion that external factors in pregnant women may cause abnormalities in the child, it was not until 1941, that Gregg recognised the relationship between rubella incurred during early pregnancy and foetal abnormality. (Gregg 1941). Syphilis during pregnancy had long been known to cause foetal disease. Wesselhoeft (1947[b]) states that "following rubella, the mother may recover, may be delivered of a premature stillborn child with deformities, may be delivered of a living child with serious congenital deformities, or may go to term and give birth to a perfectly normal child".

Toxoplasmosis in recent years has been known to cause microcephaly in the child of an affected mother. (Levin and Moore 1942; Cowan et al, 1942). Other manifestations may occur, namely, hydrocephalus, microphthalmia, persistent pupillary membrane and chorio-retinitis. These malformations are not so much the result of arrested development during organogenesis essentially, as the effect of foetal disease during the growth period (Warkany, 1947). Apparently the infective agent attacks the foetus via the placenta relatively late in foetal life, because there is an absence of major developmental defects. In this respect there is a similarity to syphilis, and also in the fact that the mother herself shows no sign of the disease except for positive neutralisation skin tests. Probably in her, the infection is latent. There may be extrinsic factors operative which determine the mother's passing on infection to the child, because healthy children may be born before and after the affected child. Familial cases also occur.

Parental/....

Parental tuberculosis may possibly be related to the production of congenital defects in the offspring (Murphy, 1947; Landtman, 1948). Virus infections such as mumps, varicella, morbilli, influenza, common colds, poliomyelitis, if occurring during the first trimester of pregnancy, may possibly influence the incidence of congenital disease in the newborn. However, the subject is dealt with at greater length, in the second part of this work.

CHAPTER III.

CONGENITAL AND HEREDITARY DISEASES.

Though we do not usually regard it as such, the potentiality for disease transmitted from parent to offspring genetically, is really congenital. In these cases the genetic constitution is such at birth, that it may only require the passage of time, or suitable external factors to bring about the expression of a particular disease. Where actual expression occurs at birth, we use, as we have seen, the term, "congenital". Thus, hereditary diseases, may be defined as diseases manifesting themselves in an individual as a result of his genetic constitution, in an environment suitable for the expression of the disease. On this basis, a hereditary disease may be congenital and familial as well, but not necessarily so. A particular "character" may express itself in one particular way, in one particular member of a sibship, and in another fashion in other sibs, because the same gene is acting in a different "set-up". For example, allergy, may be familial, but only one member may express it as dermatitis (hereditary), several other members exhibiting the allergic tendency in the form of asthma (familial), or a condition may arise in a person as a mutation for the first time, so that there is no familial history of such a condition. The condition, however, is still hereditary, if it can be shown to result from intrinsic genetic constitution, or be transmissible to future generations in one way or another; and therein lies the rub. Many hereditary conditions, are today, not recognisable as such, due to mutations, re-

cessivity/...

cessivity, variations in penetrance, pleiotropism, modification, etc.

"Because a gene for a given ailment is hereditary, it does not mean that it cannot be improved, avoided or cured completely. Such a correction of abnormal character can be regarded," says Muller, (1948) "as one of the major functions of physicians, agriculturists, and in fact civilisation itself. By rectification, we have in effect changed an undesirable gene into one less undesirable, although that gene will still continue to be subject to the same laws of inheritance as before. But in making it a less detrimental gene, we automatically lessen the rate of its elimination, thus encouraging its presence in the general population. Hereditary ills are unlike other diseases because in 'curing' one today, we are creating another case of the same kind tomorrow. This conception is exercising the minds of the eugenicists to no small degree. 'Genome' or genetic death in a future descendant as a result of that individual's inherited constitution, is a term coined by them."

Penrose (1950) draws attention to the fact that many cases of inborn methaemoglobinaemia and de Toni-Fanconi syndrome may be successfully treated by methylene blue and vitamin D respectively. However, this successful treatment in no way minimises the hereditary nature of these defects.

It must also be emphasized that although the term congenital as applied to a morbid condition implies recognition of that condition at birth, the responsible aetiological factors may be genetical and/or

environmental, but too often defy detection.
A more detailed analysis of the term "congenital"
is given in Part II of this work.

CHAPTER IV.

FAMILIAL DISEASE.

The term "familial" applied to disease, merely indicates, that an abnormal variation occurs repeatedly in a family or sibship. Such a variation is not necessarily genetically determined, e.g., familial toxoplasmosis, (infection in several members of a family due to the prevalence of infecting organisms in a particular locality); silicosis in members of a family who are all employed in mining; cretinism, due to absence of iodine in diet, etc. Threadworms may affect several sibs living under the same roof, as will measles, whooping-cough, and the exanthemata. Such conditions are really community diseases. Bad economic conditions in a particular family may even lead its members to participate in crime. The opinion is therefore here held, that family conditions based on genetic constitution, should be called heredo-familial, to indicate their true nature. A lesion occurring in a member of a family apparently for the first time, may on more detailed examination prove to be present in other members, though in a lesser or somewhat modified form, more easily missed. Thus a human pedigree should be very closely investigated. As will be seen, below, congenital syphilis, may be both familial and congenital, but is not hereditary. We have mentioned toxoplasmosis as causing familial deformities in children born of apparently healthy mothers, yet no genetic factor is involved.

Even in the case of rheumatic fever there is often to be discerned a familial element. Griffith

et al/....

et al (1948) studied over 3,000 patients with rheumatic fever and three control groups (1,397 individuals). The authors found that the occurrence of rheumatic fever in the family increased the risk of the individual developing the disease while in contact with the family, but not after separation from it. There does not therefore appear to be a strong, inherited susceptibility. The occurrence of multiple cases in families could be explained either on the basis of contagion or common environment. These authors regard the data as indicating the dominant role of contagion in the development of rheumatic fever.

Thus, we see that an investigation should search out even details, which at first sight appear to be irrelevant, but which may later turn out to have a possible bearing on the main "character" under investigation. Descriptions must be full and lucid, accompanied by drawings, photographs and genealogical tables. In the pedigree, individuals unable to be seen personally, should be indicated, and the source of the information supplied in order to assess its true value. Ages must be clearly stated, because some members of a family may die before manifesting any hereditary defect. Illegitimate children, abortions, stillbirths, sex, consanguinity, even remote, must all be shown. All normal members of the family, with their respective ages, and sex must be included, together with individuals marrying into the family. In doubtful cases, the pedigree of the latter should also be investigated.

With the present day trend in lowering of general mortality rate, even little ailments tend to

become/...

become familial and eventually to be found in the population at large. Although an anomaly may occur in a family during one generation and never before or after, genetic transmission is not ruled out.

The albino infant in the vast majority of cases will have normal, non-albino parents and all his earlier ancestors and relatives will probably be normally pigmented. Only among the sibs may there be one or more additional albinos. A genetic analysis indicates that recessive inheritance is involved. An albino results where two parents each contributed an abnormal gene for the defect. The parents themselves are normal appearing since they each carry one dominant normal gene and one recessive gene for albinism. Half of the parents' germ cells contain the albino, and the other half the normal gene. Therefore, there is 1 chance in 4 that an egg with the albino gene and a sperm with the same constitution will meet to produce an albino child. Hence any further conceptions of the parents of an albino again have one quarter chance of producing albinos, and a three quarter chance of producing normal children. The prospects for future offspring of the albino, are paradoxically more favourable than for offspring of his non-albino parents when the albino marries, the mate will most likely be a normal person, genetically free from albinism. Thus all their children will receive a normal gene from the normal parent, in addition to carrying the albino gene from the albino parent. They will therefore appear normal like their albinism-carrying grandparents. Usually therefore, albinism occurs "sporadically" or "familiarly" in one generation and not for generations before or after (Stern 1950). Lethal multiple telangiectasia may behave on similar lines.

P A R T T W O.

RUBELLA : EPIDEMIOLOGY, SYPTOMATOLOGY, DIAGNOSIS AND TERATOLOGY.

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P A R T II.

RUBELLA.

CHAPTER I.

HISTORY.

The disease which we know today as rubella was first described by the German physician, de Bergen, in 1752, and Orlow in 1758 (Wesselhoeft, 1947[a]). Because of its original association with German investigators, it came to be called "Rötheln" in England and America. The first epidemic of what must have been rubella was recorded by Jahn in 1807, and the clinical features were set out by Wagner in 1834 (Harries and Mitman, 1947). In 1866 Henry Veale introduced the preferable term rubella. Much confusion has arisen in the past, as it was originally confused with scarlet fever and ordinary measles. The latter disease eventually came to be called "rubeola", or "morbilli".

Rubella as a disease was described in America in 1845, but even after that, all over the medical world doubts were expressed as to its position in Medicine as a separate entity.

The identity of rubella was established at the International Congress of Medicine in London, 1881, (Michael, 1908). Filatov in 1885 and Dukes in 1900 stated that two diseases were described under the name of rubella (Michael 1908). Filatov called the one type of rash, rubella scarlatiniforme, and believed it to be distinct from rubella. Dukes called this same type "Fourth Disease", but today it is fairly

generally/...

generally accepted that all are clinical variations of rubella. Forchheimer described the spots named after him, in 1898. This was round about the time that Koplik described those particular spots, which today are known to be pathognomonic of ordinary measles. To this day, in consultations of foreign literature, confusion may arise as regards terminology. In Sweden, German measles is called Rubeola, in Spain it's called Rubéola, in France it is called Rubéoli, and in Austria, it is called Rötheln, or Rubeolae. In Holland, the name given to this exanthem is Roode Hond, but Afrikaans-speaking South Africans occasionally use the term "Rooihond" to designate scarlet fever. Until 1941 there was never any relationship suspected to exist between rubella and foetal malformations. Gregg, (1941) an ophthalmologist working in Australia, was impressed by the increased incidence, and peculiar morphology, of congenital cataracts seen by him in children. By calculating backwards from their ages, he came to the conclusion that these ocular defects originated during a severe outbreak of German measles in Australia. Soon afterwards, much evidence began to accumulate from various sources that, indeed, these eye defects did occur in children whose mothers had had rubella during the gestation period. The government subsidised investigation into the matter, and much painstaking work was done by Doctors Swan, Tostevan and Black (1943, 1944, 1944[a], 1946), not to mention many others. The results of their labours disclosed that many other congenital defects were also related to the epidemic of German measles.

The rubella epidemic in Australia was at its maximum during July and August of 1940. This period was one of great military activity, mobilisation and crowding of population. An epidemic of sore throats occurred about the same time, and was believed to have originated from military camps before spreading amongst civilians. The Australian investigators retrospectively investigated these epidemics to establish the identity of German measles, and differentiate it from any other possible condition. The question of scarlet fever with an atypical rash, misdiagnosed as rubella was given consideration. Forty-nine such cases were investigated in 1943, (Swan et al) and of course, difficulties were met with in obtaining satisfactory histories. Some mothers of congenitally defective children appeared to be more intelligent, and more observant than others, whereas the history of a few was incomplete. Out of 35 cases recorded, 26 were primipara, suggesting that younger people were more susceptible. Prior to 1940, there had been no rubella epidemics, so that the epidemic flourished in a non-immune population. The identity of the maternal infection which caused cataracts and other deformities in the child, was definitely established to be rubella and since then, confirmation of the teratogenous effects of this mild exanthem has come from different sources all over the world. (England, Clayton-Jones, 1947; America, Miller, 1950; Denmark, Mogens Bardram et alter, 1947; Scandinavia, Grönvall & Selander, 1948; Switzerland, Franeschetti, 1947;

France,/....

France, Gerard-Lefebvre & Merlen, 1948; Mexico, Alarcon, 1949. In South Africa, the association between rubella and congenital malformations many times has been seen by the present writer and his colleagues.

CHAPTER II.

AETIOLOGY.

The nature of the Rubella virus and similar agents.

Burnet (1945) concludes from the evidence available, that in prehistoric times, from the beginning of the Pleistocene period to about 10,000 years ago, practically no specific infectious disease flourished among the human species. The limited communities and lack of gregariousness peculiar to Mankind at the time, did not provide conditions suitable for the spread of micro-organisms. Obviously, small bands of human beings would either become completely immunised by infection, or extirpated. Under both sets of circumstances, the disease could not spread further and would itself become extinct.

When agricultural communities started to grow in size, conditions became more suited for parasitic, bacterial and virus spread, amongst human beings. Presumably, viruses which had originally flourished, amongst birds and mammals and other gregarious creatures, became adapted to live with man. Mutation and natural selection were, probably the processes involved. Yellow fever and typhus appear to have become standardised infections within the historic period, and psittacosis, today, appears to be in imminent danger of becoming specifically adapted to human beings, with spread from person to person, although the specificity, at present, is predominantly avian.

The origin of viruses in general, and rubella in particular, is obscured in the nebula of the bio-

logical/....

logical cosmosphere. These particles vary in size from 10 millemicrons to 300 millemicrons, and in case of rubella, approximate no doubt, the lower figure. Like most viruses, the rubella agent is probably that of a nucleoprotein predominantly, and represents a very low form of life. It does not however, arise *de novo* but from parent forms which reproduce under special circumstances. How the first viruses arose is conjectural. According to some, it arose as a more or less complex nucleoprotein in a cell, which became detached to lead, a semi-independent existence. In fact, some biologists deny that the term, "living" fits the description of the lower viruses, and indeed, it is difficult to define what is meant by a "living organism".

Broadly speaking, a living organism has the property of synthesing from other elements, a replica of itself. A "gene" would also fit such a description, and in point of fact, viruses have been likened to genes, which have become detached from the genetic apparatus within the cell, to live a more or less independant existence, while yet deriving sustenance from within the living cell. (Shull, 1948). It has evolved its own character without being closely controlled by interacting forces exerted by other genes. This theory is not very probable, because on every hand we see infectious agents such as vaccinia and psittacosis becoming adapted to symbiotic existence in human cells, while they themselves have not originated from cells of vertebrates. Crystals in a solution, have the property of growing and reproducing themselves, and yet are not regarded as

living/....

living organisms. On the other hand the tobacco mosaic virus, obtained in the crystalline form, yet exerts its full pathogenic and virus effect.

Another theory of virus origin, also tenuous, is that they are the evolutionary descendants of primitive precellular forms of life, which became a adapted under changing environmental conditions, to a symbiotic life, parelleling evolution of higher forms.

The most probable explanation, however, for virus origin is that they have degenerated into their present forms from other larger micro-organisms.

Glaser (1930) presents evidence to show that the rickettsias have probably evolved from bacterial symbionts in different arthropoda. Apparently mutational forms have been selected, which depend for existence on the presence of enzymes found in living cells. The rickettsia, in fact, is a "link" between bacteria and viruses, and a scale of various gradations exists. In *anaplasma*, (a protozoon), and in *spirochaeta recurrentis*, degenerative processes and forms are recognisable (Burnet 1945). Such regressions are likely to occur if some enzymes are not supplied, as in the case of Neurospora (Beadle and Tatum, 1941). Röentgen irradiation of this mould, produces upwards of 200 mutational degenerates, many of which require, for their continued existence, the addition of different amino-acids to the nutrient medium (Burnet, 1945); the original form is however, able to synthesise these amino-acids. By some similar process, we can conceive of certain organisms becoming dependant on certain enzymes available solely in the living cells of a particular species. Such

an organism/...

an organism then becomes a specific symbiont or pathogen.

Amongst the lower organisms, with their excessively rapid reproduction rate, spontaneous mutations must be constantly occurring, and natural selection, in a great degree determines the final form of the organism. Chance, or accident, also plays no inconsiderable part, as regards the types of mutation, the suitability of the host, the mode of existence, etc. For survival, too, there must be operative a process for transferring the organisms from one host to another. In rubella, spread apparently occurs from the respiratory tract to the outside of the body, but intimate details and intermediate stages are not understood as yet. In other virus infections (e.g. poliomyelitis) this part is even more mystifying.

During the course of its history, the virus has probably changed its host several times, itself been modified countless times, and its pathogenicity expressed in altered ways. Apart from the biological dictates of survival and multiplication, there appears to be no reason for its continued existence, and in many cases, pathogenicity is a mere accident occasioned by increased susceptibility on the part of the host, or increased "virulence" on the part of the organism, as Burnet points out.

That the degree of modification from the original virus strain to the present strain of rubella must be considerable, is borne out by the fact that rubella is not transferable to any other animal except, with difficulty, to a rhesus monkey.

(Habel, 1942). Among monkeys, there is no spread from one individual to another, so our premise must be, that the rubella virus, though derived from another species of micro-organism, or virus, has by now lost its pathogenicity for the original host.

Mutational changes and chromosomal alterations, such as inversions, etc., have been studied in higher cellular elements, and are the result of bissexual reproduction. Though some of the viruses, e.g. vaccinia exhibit evidence of internal structure, other virus particles including probably, the rubella agent, are devoid of cellular structure and certainly no chromosomal apparatus is visible, not even in the case of bacteria, which are more easily visualised. Yet these variations occurring in such primitive organisms must be based on some kind of genetic process. Variants breed true: attenuated or virulent strains retain their character. Huxley (1942) says that, "the entire (bacterial) organism appears to function both as soma and germ-plasm, and evolution must be a matter of alteration in the reaction system as a whole", probably in the nature of a change in chemical equilibrium.

Genes, in the final analysis, are probably molecules with an enzyme-like function, and in the case of virus bodies, are present without being attached to any visible chromosomal elements. They represent the most rudimentary forms in which genes can exist in some special molecular arrangement. The border between life and non-life is seen to be more relative than real. Some writers, however, still hold that bacterial and virus variations are

due to changes essentially somatic in nature, a concept which is somewhat indefensible. De Kruif (1921) and Arkwright (1921) demonstrated variants in bacteria arising by discontinuous processes. Burnet and Lush (1936) working with bacteriophage found evidence of a similar process. Mass transformation of pathogens therefore "represent selective survival of one or more mutant types".

Now on the horizon, there seems to be gathering evidence pointing to a form of sexual reproduction in viruses. Virus particles have the power of penetrating bacteria and reproducing on a large scale. When the bacterial body then ruptures, the virus particles are set free as bacteriophage. Infection of a particular bacterium with a particular type of virus seems often to preclude invasion by some other types of virus - the "interference phenomenon (Andrews, 1948). Delbruck and co-worker (1948) worked with two different viruses genetically related and capable both of entering and existing in a particular bacterium. When both viruses were grown jointly in the bacterium, both types were found amongst the descendants, as expected. But in addition, a third type of virus was found with partial characteristics of both parents. This "switching" of characters, suggests that an interchange of parent factors had taken place, i.e. a primitive form of sexual reproduction.

Luria of Indiana University (J.A.M.A. 1949) indicated on experimental grounds that several elements in the make-up of a virus structure may be destroyed by ultraviolet radiation, and the virus

rendered/....

rendered unable to reproduce itself. When two or more such damaged viruses enter a single bacterium, it is claimed that a combination of the undamaged elements occurs, resulting in a new individual, destructive to the bacterium and capable of self-reproduction. A comparison is drawn between this process and the selective destruction of genes in *Drosophila* by chromosomal irradiation, and an alternative mechanism is postulated for the production of new disease-producing germs amongst viruses.

The rubella-producing agent is believed by most to be "filterable virus" which Steinmaurer (1938) claimed to have cultured on the chorio-allantoic membrane of the chick embryo, and to have visualised under the fluorescent microscope. Hiro and Tasaka (1938) injected subcutaneously filtered saline washings from the naso-pharynx of eruptive cases. Of the 16 non-immune children thus injected,

4 showed a characteristic rubella rash
and
2 showed lymphadenopathy without any eruption.

The incubation period thereby determined, was,

7 days in 3 cases
8 days in 1 case
11 days in 1 case
17 days in 1 case

Habel (1942) used washings collected within 24 hours of appearance of the exanthem and injected this into *Macacus mulatto* monkeys, by intranasal, intraperitoneal, subcutaneous, intramuscular, and intravenous routes. The monkeys were affected by all routes, provided the washings were collected on the first day of the disease. If obtained on the third day, all results were negative. The clinical

course/....

course in monkeys was mild, being initiated by leucopaenia, relative lymphocytosis, and slight pyrexia. On the eleventh day, a light scattered macular rash became visible on the face, abdomen and thighs, and was followed by desquamation.

Habel describes the culture of the rubella agent on the chorio-allantoic membrane of developing chick embryo. Eggs incubated 11 to 13 days were opened and 0.15cc of human rubella blood was inoculated on to the chorio-allantoic membrane. After 4 or 5 days incubation at 36°C, these membranes were removed and ground in a mortar with sterile sand plus the addition of 3 c.c. of broth per each membrane. These passage embryo membranes were inoculated with 0.15 c.c. of supernatant from this emulsion. Four strains were carried through for 5 egg passages, after which 5 c.c. of supernatant was inoculated into monkeys. Rubella (with rash) was produced in one case, possibly in two (the second had fever, leucopenia, and lymphocytosis on the 14th day without a detectable rash). Habel also passaged 3 human strains transferred in monkeys by blood given intravenously and 2 were positive, 1 after one passage and 1 after five passages.

Monkey passage material has not yet been inoculated back into susceptible human beings. Infective material was found by Habel to become weaker on monkey passage, and frozen stored material proved to be non-infective.

Burnet, Anderson and co-workers (1948) were not successful in their attempts to cultivate the rubella virus on developing chick embryo. They

did/....

did, however, transmit the infection to 9 out of 16 student volunteers. These volunteers were made to inhale filtered throat washings atomised by compressed air. The 7 who did not develop rubella remained in close contact with the infected volunteers, and were assumed to be immune. It was confirmed, too, that the virus is present in high concentrations in throat-washings taken from patients at the height of the eruption. Such washings remain active indefinitely when frozen, and can be used to produce the disease when desired. This is in contrast to the work of Habel (1942) who did not use the same freezing technique. Burnet and his coworkers were induced by the success of these latter experiments, to recommend deliberate active immunisation of women at convenient times, instead of by change infection during an epidemic.

Anderson (1949) obtained the throat washings from typical cases of rubella. The material was sealed in ampoules at the bedside of the patient and stored in a mixture of solid carbon dioxide and absolute alcohol. The washings were taken from the patient and stored at -70°C. within five minutes. Various experiments conducted on 40 young women volunteers showed that typical rubella could be produced by use of a hand operated De Vilbuss spray, which delivered the atomised material into the nasopharynx. The rubella-producing agent was found to remain viable in the presence of 200 oxford units of penicillin per millilitre, and apparently after filtration through a millemicron membrane. The agent responsible was present in throat washings taken on

the/...

the first day of the rash, and remained infective for at least 90 days when stored at - 70°C. as above described. This and all the above evidence seems to definitely indicate that the rubella agent is a virus. The experimentally produced disease was also found to be infective, and did not differ from the natural type of infection. Experiments done by Habel (1942) demonstrated lack of cross immunity with morbilli. Two methods were employed, viz:

(1) injection of convalescent morbilli blood, and

(2) inoculation of morbilli virus into a previously rubella positive monkey.

That roseola infantum is not the infantile manifestation of rubella has been proved by the fact that children may develop the two infections at different times. Better evidence, however, is provided by James and Freier (1949), who observed adult cases of roseola infantum contracted by nurses and parents from children in a maternity hospital in England. The adults presented the same general clinical picture as the infants.

CHAPTER III.

EPIDEMIOLOGY.

(1) EPIDEMIOLOGICAL PATTERNS:

Rubella is widely known in the Americas, Europe, Africa, Asia and Australia, but it differs from measles by not being unduly severe when coming into contact with a non-immune population. (Burnet 1945). However, in its epidemiological pattern, it seems to parallel measles in many respects. Correct evaluation of epidemiological factors is extremely difficult on account of the fact that in most countries it is a non-notifiable condition. In the United States, although it is notifiable, there is considerable neglect in reporting cases with consequent inaccurate statistics.

When a small number of virus particles enter into an individual, rapid multiplication may occur, so that within 48 hours, the virus population may total several billions. Only an infinitesimal proportion of these, however, propagate, and the remainder of the virus inhabitants dies out entirely, at least, so far as we know to date. Only a few induce fresh infection in other susceptible persons. It appears that in a very few individuals, however, (possibly one in 10,000 say), the virus remains latent to initiate a new epidemic when conditions are so suited.

In such larger virus populations as occur during epidemics, some mutations must inevitably arise, more of course, if the epidemic is large. Persistence of such secondary strains is enhanced, only if they should possess some added advantage for survival

under/.....

under the conditions prevailing. Chances of the variant entirely replacing the original are small. Burnet (1945) estimates that a variant with such advantages occurs once in about 10^6 generations roughly, and that not more than $1/10^7$ of the virus particles in a given host find an opportunity of originating further infection. Then of (say) 10^{10} particles present in the host, about 10^5 will consist of the new form, and 10^3 of the original strain will be present in infecting dosage. Thus the variant is outnumbered 100 to one, in spite of its survival advantages.

We see therefore, that high pathogenicity depends on short term survival advantages. If such a form should succeed in becoming predominant, then there occurs a sub-epidemic of unusual proportions, as may possibly have occurred in Detroit during the rubella outbreak round about 1942. But survival of a new strain actually depends on a small number of individuals, and for survival purposes, variants of low rather than high virulence will tend to be selected. That this fact is borne out in practice is the general experience of common uniformity of a disease from year to year, with short exacerbations of unusually high or unusually low virulence. The main strain tends to persist in the long run. Bennett and Copeman (1940) who observed more than 300 cases during February and March 1940, found that the severe cases all occurred towards the end of the epidemic with a progressive increase in the severity as the epidemic progressed.

From the chart (Figure 4) which is taken from Aycock and Ingalls, (1946), the periodic pattern of

rubella is evident. There is a difference from measles in that the individual prevalent periods tend to extend over a period of 2 - 3 years. The intervening periods of low incidence last for 2, 3 or 4 years. Therefore the seasonal incidence resembles measles except that during "high" years, the infection remains at a distinctly raised level in the "off" season. Another factor, illuminating the question of mode of spread, is that, in the "highest" years, the reported cases of rubella reach the same proportion as in the highest years of measles; whereas in lower years, the incidence is only one-tenth that of measles. The latter discrepancy is believed to result from neglect in reporting cases. Swan et al (1943-4) obtained retrospectively figures for congenital defects in the Australian epidemic as follows:-

8 cases (pregnant women)	1939	- 8	children with congenital defects.
6 cases	1940	- 6	do.
7 "	1941	- 6	do.
28 "	1942	- 12	do.

These figures support the above statement that "peak" period extends over about three years. It was also noticed in the cases investigated, that the distribution was wide, actually, 15 in country districts, and 30 in the urban area of Adelaide. Aycock and Ingalls further state that there is no seasonal difference between rubella and morbilli; their curves for seasonal prevalence being closely similar. Bedford and Brown (1937) believe that large epidemics tend to occur at intervals of 10 to 20 years. The outbursts are frequently seen during late winter or spring.

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In their chart, Aycock and Ingalls show, that in Massachusetts, (Northern Hemisphere) rubella had sharp rises in incidences in the early months of each year from 1917 to 1945. This would imply that a preponderance of defective children would be expected to be born in the latter months of each year. Such a preponderance was actually found recorded for the United States as a whole by Miller et al (1949). The latter workers, also found evidence that the peaks of prevalence occurred simultaneously in different parts of the United States during the spring of 1943, and 1946, and they supply illustrative charts. If future epidemiological studies indicate this synchronism to be a recurrent tendency, then investigations of teratological effects would be assisted by such relation of data. Judging from previous records, another pandemic of rubella may be expected within the next few years.

High Schools, colleges, army and navy cantonments, provide a happy hunting ground for the rubella agent. We often see resident medical officers and nurses attached. Margolis et al (1943) noted that 9,000 cases in the general population were reported in Detroit during the first 6 months of 1942.

Worcester et al (1950) analysed the gestational characteristics of 677 congenitally malformed infants born in the Boston Lying-in Hospital during the period 1930 - 1941, and they found that the total anomaly rate was significantly high in 1935 (Cf. Figure 4), when births of defective infants reached a peak seven months after a widespread epidemic of rubella. These data were recorded before the teratogenic properties

of/.....

of German measles were suspected, and hence represent unbiased information.

Patton (1947) gives graphs based on data supplied by Health reports on the City of Manchester. Rubella "peaks", in 1920, 1931, 1935 and 1940 respectively were followed in each case, one year later, by "peaks" in infant mortality. This may have been coincidental, or possibly due to weakly post-rubella infants with congenital anomalies failing to survive longer than one year when encountering infections. It is, however, mentioned as well that during the years of high infant mortality, diseases such as whooping cough, measles and diarrhoea also showed a high incidence, thus tending to invalidate the usefulness of these graphs which purport to show a relationship between rubella and infant mortality. Hence great care should be taken in interpreting Public Health data.

Candiotti (1949) makes the interesting observation that rubella is more prevalent amongst Anglo-Saxon races and comparitively rare in France, where symptoms are often so slight that they escape notice. This observation helps to confirm the previous statement by other French writers (Gerard-Lefebvre and Merlen, 1948) that in France, rubella in pregnancy is very rare, mild in type, and plays little part in the causation of foetal abnormalities.

Alarcon (1949) states that in Mexico, rubella is endemic and every woman has had it in childhood, so that the adult population appears to be relatively immune.

In South Africa, rubella is not uncommon, but

as it is not a notifiable disease, no figures are available. As to the incidence of rubella amongst the non-European population of South Africa, one cannot even hazard a guess. During the war years 1939 - 1945), when rubella was so prevalent in South Africa, the writer, with the courtesy of the Director General of Medical Services, undertook an investigation into the records of non-European military personnel who were isolated in camps and institutions as a result of infectious disease. While all the other common exanthemata and infectious were diagnosed, the auther was unable to find recorded a single case of rubella. This negative finding is no doubt due to the difficulty in establishing the diagnosis in dark-skinned individuals. It also seems unlikely that there can exist any non-human reservoirs of infection in the case of rubella (Meyer, 1950).

(2) AGE.

Bradford (in Brenneman's "Practice on Paediatrics"), quotes Scholls as having reported a case of congenital rubella. Bradford also mentions cases encountered in children a few weeks old, where the infants' mothers were non-immune. Corlett (1902) also mentions cases of infection in the neonatal period, but like measles, rubella is rare in the first 6 months of life.

In the literature, there are several reports of rashes with enlargement of the posterior cervical and occipital glands occurring in small infants. Such rashes are called rubella but further diagnostic

criteria/.....

criteria are meagre. Hadfield (1940) quotes the case of his own daughter who developed a typical rubella rash at the age of 18 days. Another member of the household had had the infection about 2 weeks previously and both his wife and infant contracted the disease from this patient.

Measles in early infancy is usually mild, and presumably rubella, too, so that non-recognition of the disease may occur. Wesselhoeft (1947[a]) collected reports on 5 cases in infants varying in age from 18 days to 2 months. After the age of 6 months, the infection pursues its usual course, but because of its short duration and mild character, is not often treated by a doctor, and hence, in America, is often not reported. In children's institutions, the disease spreads rapidly. Out of 190 children, Michael (1908) reported, 80 contracted the infection, with a nearly 100 per cent attack rate in all under the age of 6 years. Humphrey and Ekermeyer (1937) found that 48 per cent of exposed children were attacked, but Geiger (1918) reported a 12 per cent attack rate in school children.

Michael's figures for children in an institution are quite interesting:-

Under the age of 6 years all children were infected except 3,

Over the age of 6 years, 25 per cent were infected.

Of infected cases -

3 children were less than 2 years.

43 children were between 2 and 6 years.

25 children were between 6 and 10 years.

9 were older than 10 years; the oldest infected child being 14 years.

Unfortunately, no figures are given to indicate how many children there were in the different age groups of the institution as a whole.

Adults are, of course, more susceptible to rubella than to morbilli, due to the fact that practically every person becomes actively immunised by morbilli during childhood. Manchester is the only area in England where rubella is notifiable. Of course an unknown number of cases are never notified. In the age-sex distribution of cases notified during the rubella epidemic of 1940, Clayton-Jones (1947) remarks that his epidemic was peculiar in attacking a high proportion of women of childbearing age.

On the basis of the above figures, it would appear that the attack is higher in children's institutions, than in day schools. However, the

fairly/....

fairly high incidence of rubella amongst young adults in colleges and in military life, suggests that more children escape rubella than they do morbilli. Infectious Fever Hospitals also usually have more cases of rubella amongst young adults than in children, probably because rubella cases are never hospitalised, excepting when they occur in dormitories or barracks.

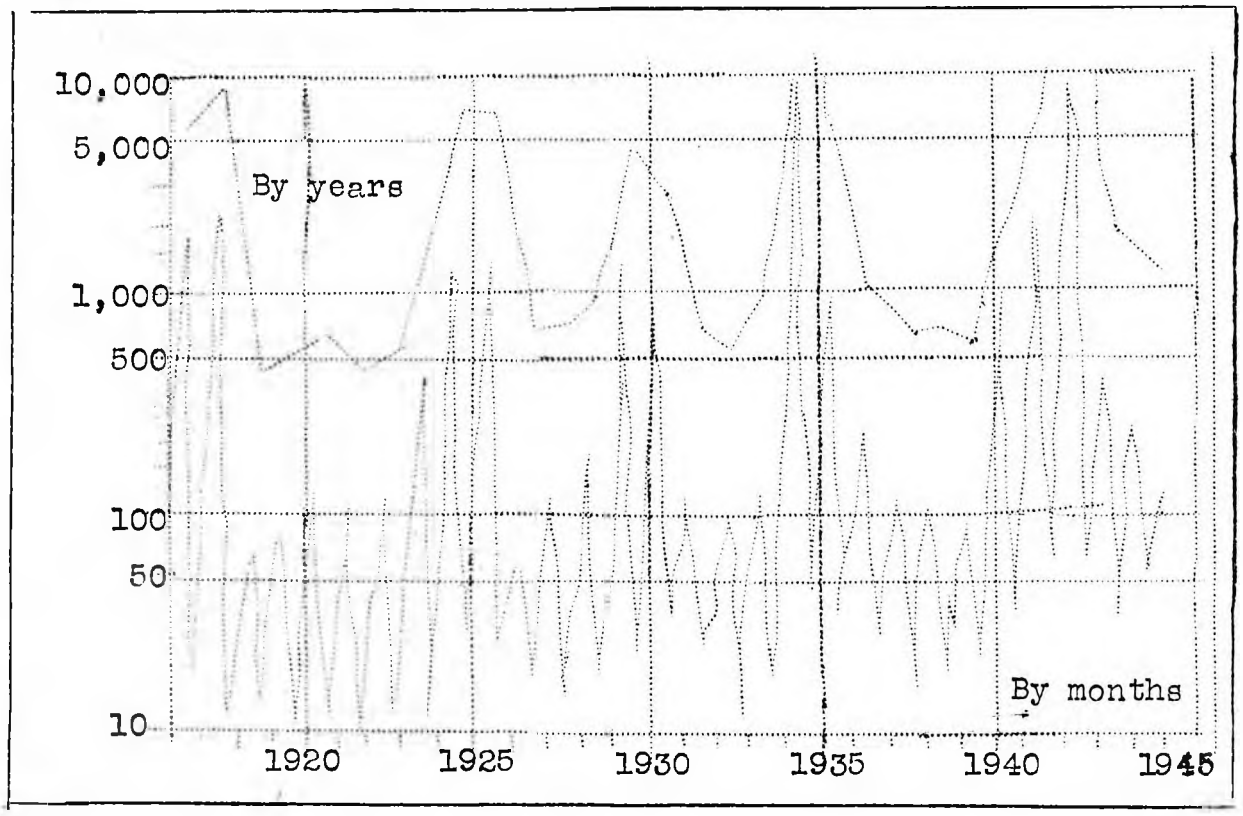
The disease is rarely found over the age of 40 years, (Clayton-Jones 1947), although Simpson (1940) reported infection in an 82 year old patient in England. Aycock and Ingalls (1946) present a chart showing the age distribution for rubella in Massachusetts in 1943 for 7 largest cities, and for towns under 5,000. In the rural population, the age group is slightly higher than the corresponding figures for urban areas, where opportunity for childhood infection and immunisation is more favourable. (See Figure 5.)

(3) SEX.

Chart (Figure 6) taken from Aycock and Ingalls indicates that in reported cases, the incidence in females, becomes increasingly greater in the older age groups. Perhaps this is because more women than men remain longer at home in closer contact too, with their children, so that there is greater opportunity to acquire infection; or their close association with children leads to their being reported along with them. What is important to note, in regard to congenital defects is, that -

14% of all female cases are in females of childbearing age.

8% of all cases are in females of childbearing age.



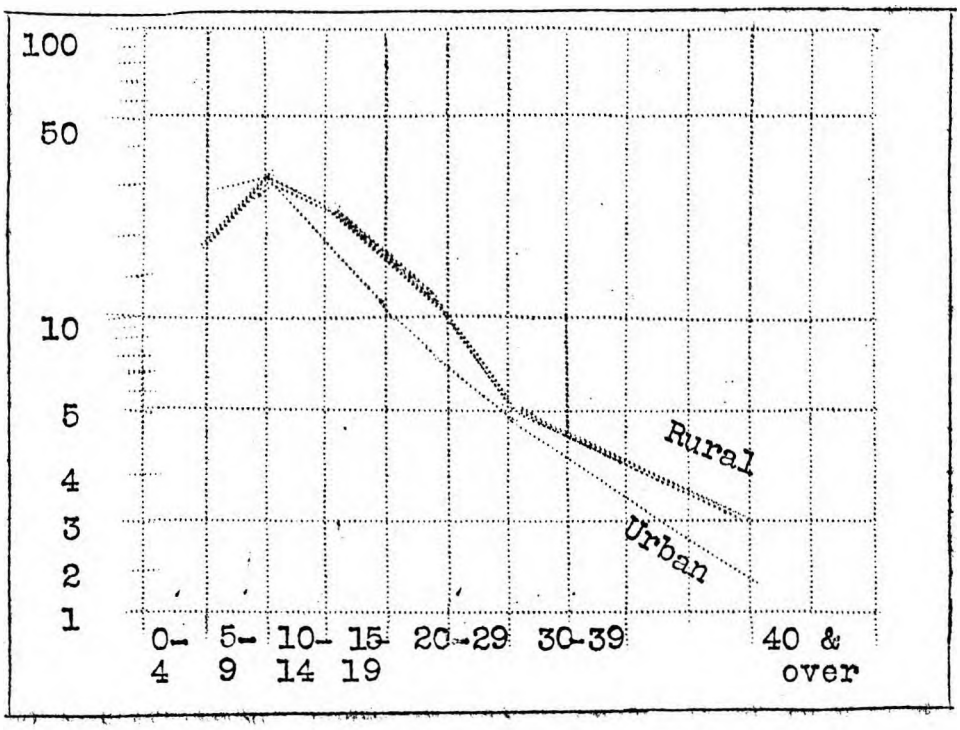
CHART

Reported incidence of rubella by years and by months in Massachusetts. (After Aycock and Ingalls).

FIGURE 4.

RUBELLA

Percentage Age Distributions.



CHART

Comparative age distribution of rubella in urban and rural Massachusetts in 1943. (After Aycock and Ingalls.)

FIGURE 5.

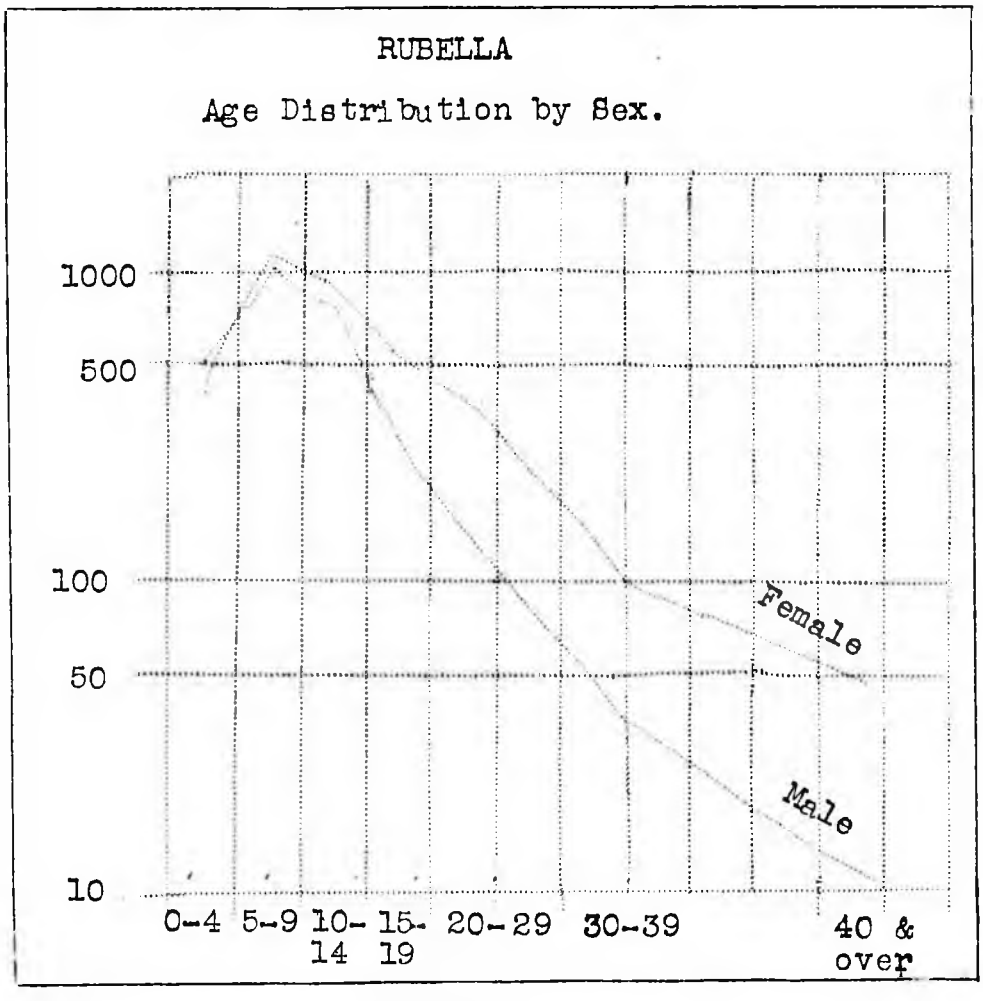


CHART.

Reported cases of rubella by age groups and sex in Massachusetts, 1943)
(After Aycock and Ingalls).

FIGURE 6.

Clayton-Jones (1947) also publishes charts which bear out the greater reported preponderance of rubella in women of older age groups relative to men. This finding was more especially noticeable in 1940 as compared with 1941.

There are no figures available as to whether pregnancy influences susceptibility or not.

CHAPTER IV.

IMMUNITY.

(1) POSSIBLE MECHANISMS.

Immunity following an attack of rubella is generally life-long (Bradford), although occasional second attacks have been reported (Aycock & Ingalls, 1946). Immunity in the mother is, so far as general experience goes, communicated in some way, transplacentally, to the foetus. The actual method whereby immunity is established, is unknown, but is specific as there is no cross immunity with morbilli or other exanthemata (Habel, 1942).

It yet remains to be seen whether the congenitally deformed children, born after maternal rubella, will be immune to the disease in postnatal life.

Burnet (1945) describes immunity as resistance to symptomatic infection. It may arise out of a balanced inter-action between host and virus, and is engendered by (1), a prolonged period of association between the two, (2) opportunity for infection to involve a large proportion of the host species, (3) absence of important means whereby the pathogen can survive indefinitely apart from the host. Such conditions are suitable for a "standard, low-grade, widely prevalent infection, only exceptionally producing significant mortality in the host". Any infection which is highly fatal in the host is prejudicial to the virus' chances of survival, and is likely to end in the complete extinction of the virus itself. Nature has provided a fair balance between the two

forces/....

forces, with a swing of the scale, now a little up, now a little down.

The epidemic of rubella especially prevalent in Australia and America during the war years was a result of the combined deficiency in the first two of the above conditions. Rubella was practically absent in the country for 20 to 25 years prior to 1937. Hence the stage was set for an epidemic which attacked not only children, but young adults as well, and sometimes gave rise to graver manifestations than usual.

Under non-epidemic conditions, the virus invades the cells of the host, invoking only mild systemic reactions, which subside, and therefore the virus is not permitted to be further transferred to other potential hosts, except under very special circumstances. How does such a state arise?

There is some evidence that in some virus infections at least, (e.g. influenza), the "interference" phenomenon (Andrews 1948), is operative, i.e. the host cells are already "blocked" by some other, though somewhat similar virus, thereby becoming too full to receive fresh virus infection. Such a mechanism may be responsible for producing mild or abortive attacks in certain cases. There is also the question of individual susceptibility based on genetic factors; factors probably of indirect and secondary importance in rubella. In the ferret, influenza causes destruction of the respiratory mucosa with resultant incapacity of the virus to damage the regenerating basal epithelium, to which it is not "acclimatised". (Francis and Stuart-Harris, 1938). The fact that ...

influenza1/...

influenzal immunity is shortlived, and the influenza virus is localised to the respiratory cells (never having been found in the blood), also suggests that the type of cell invaded, influences the degree of susceptibility to infection (Rivers, 1943). And indeed, virus bodies sometimes exhibit considerable cell or tissue specificity; less obviously so in the case of rubella.

Of all immunological factors, antibody formation, is however, the most reliable defence measure, and may exists under the following conditions:

(1) The host eliminates the virus completely with subsequent prolonged immunity.

(2) Infection persists asymptomatically, due to a symbiotic relationship existing between pathogen and host. That this situation may possibly arise in rubella is suggested by reports in connection with congenital defects following pre-conception rubella. (see Chapter XXII(9)).

To stimulate antibody formation and effective immunity, the virus must at some stage enter the bloodstream. Furthermore, should the host be re-exposed to infection, there must be operative some method whereby the invading agent is exposed to circulating antibody and knocked out before it can reach the cells towards which its attack is being directed. Some such mechanism appears to function in rubella. Habel (1942) claims to have identified the rubella agent in the blood of patients during the first 30 hours of infection, though not later. The initial infection in non-immune subjects, is, in the first instance, probably localised to the naso-pharyngeal

mucosa, afterwards spreading; in immune subjects it remains strictly localised without any obvious development or external manifestations. In influenza, immunity is shortlived; in herpes simplex, the virus persists in spite of circulating antibody.

Where permanent immunity is induced with elimination of virus from the body, the epidemiological pattern of the disease follows a certain type, i.e. an acute epidemic attacking susceptibles, followed by complete disappearance of the disease for several years (see chart, Figure 4) It reappears again when a mass of susceptible subjects re-accumulates. Isolation and public health measures tend to prolong an epidemic while lowering its intensity.

Age plays some part in the immunity-producing mechanisms, and throughout infancy, childhood, adolescence, adulthood, and senescence, it in itself, apart from other immunological factors, influences resistance to infection. In very early infancy, there is likely to be an immunity to rubella, irrespective of whether the mother is susceptible or non-susceptible. (Rivers, 1943). There is at present no test for the detection of specific antibodies in rubella.

Re-accumulation of susceptibles occurs by the addition of neonates chiefly, of immigrants, less commonly, to the general population. The common viruses then produce a permanent immunity in surviving members of a susceptible community in the event of infection. The younger the patient, the more severe and dangerous is the infection usually, after the initial period of immunity has passed. However, in the

case/....

case of rubella, because of its mild nature, this is of little consequence. Generally speaking, a normal child population between the ages of 6 to 12 years, can resist any infections disease better than the population of any other age-group, child or otherwise. (Burnet 1945). Yet again, in rubella, age is of little consequence except in females of childbearing age, because of the rarity of serious complications. During the widespread rubella epidemic in 1942, all age groups appeared to be equally susceptible to the uncommon complication of encephalitis (Margolis et al, 1943.)

When a disease passes from the non-endemic to the epidemic stage, there appears to be a greater susceptibility in young adults or adolescents. The only significance this has for rubella, is that females of childbearing age may be affected during pregnancy, (Clayton-Jones 1947). In fact, young adults are very susceptible to infections in general, and if exposure does not occur in childhood, young men and women make up a large proportion of the susceptible population. Such increased susceptibility in young people may be related to precisely this question, namely, an application of biological principles of survival, whereby young adults under natural conditions, having already contracted diseases during childhood, are immunised by the time adolescence is passed, and capacity for immunisation is of less import, thenceforth. In general, however, physiological reactivity appears to be greater in young adults than in children.

Whereas/....

Whereas in the case of some infections, immunity is maintained by repeated attacks of subclinical infection, in rubella immunity most probably follows one attack. The possibility of permanent immunity being maintained by repeated exposure cannot be entirely excluded ; especially, when we consider that rubella is uncommon over the age of forty years. In the case of many other infections, pathogenicity is accentuated after the age of forty.

Immunity following an attack of rubella is generally life-long and many a "second-attack" represents a misdiagnosis. "In 4 pairs of epidemics analysed in detail, 2 boys at school, N.B. were attacked in both epidemics, the diagnosis being made by the same school medical officer". (Aycock and Ingalls, 1946). Yet the parents, doctors, nurses, teachers, etc. are continuously exposed to reinfection, without any signs of the disease ever developing. The type of epidemiological curves obtained also confirms the statement regarding permanent immunity. Each wave of prevalence is followed by a period of greatly diminished incidence.

(2) RECRUDESCENT INFECTION.

Recrudescence may occur, however, and is often confused with subsequent new infection. Amongst the laity (and even some members of the Profession), belief is widespread that subsequent attacks are not uncommon. The majority of relapses follow shortly after the first attack. Humphrey et alter (1937), noted a 6% incidence of relapse, occurring from 12 to 41 days after the beginning of the first attack. The diagnosis was so careful as to appear unimpeachable,

and/....

and in 3 cases, complications developed during the recrudescent period. The rash was typical and generalised in both relapse and original attack, although in general, the relapse was of milder nature and shorter duration. Geiger (1918) reports three successive attacks in 5 cases and in one of these, the third attack came at the proper incubation period after another exposure.

The cases observed by Humphrey, occurred in an institution, which of course, provided plenty of opportunity for re-exposure to infection. In this author's opinion, the results suggest that immunity does not develop for about 3 weeks after the onset of rubella, thus permitting of re-infection. The interval between attacks in one case was 41 days and in the remainder averaged at 26 days.

15 cases relapsed in 3rd week.
3 cases relapsed in 4th week.
1 case relapsed on 41st day.

In Hopsital practice, the patients are often discharged before relapse occurs, except where they happen to be detained for long periods as for example in cases of complications following scarlet fever. In another series of 65 cases, one recrudescent attack occurred, following the primary by an interim of 18 days. Tidy(1940) reports recrudescence of the adenitis three or more weeks after the initial attack and after the adenopathy had almost subsided. The recrudescence was sometimes accompanied by pyrexia and constitutional symptoms. Bennett and Copeman (1940) had an 8% relapse rate in their series of over 300 cases. Some of the relapsed cases were very mild,

but/.....

but three were very acute and for 24 hours simulated meningitis. Wesselhoeft (1947[a]), in the relapsed cases observed by him, found them to be identical in severity with the first attack.

Anderson (1949) using concentrated infective nasal washings was not able to transmit rubella artificially to 14 out of 25 volunteers. These 14 remained immune to subsequent natural intense exposure. Five of these people gave a history of infection 6 to 9 years previously, and the other 9 had probably undergone sub-clinical or inapparent infection. According to Anderson, these facts provide sufficient circumstantial evidence to indicate that infection confers a high degree of immunity for at least 9 years. An artificially induced infection in a woman of 20 could therefore be expected to provide protection from re-infection with rubella during the usual childbearing period.

Relapses, as recorded in the literature, are supported by experimental work. Five monkeys that had developed rubella with a rash, and two without a rash, were re-tested by Habel (1942) after a varying interval of from 4 to 11 weeks, by re-inoculation of infective material. This material, which was shown to be infective, by its disease-producing effect on fresh monkeys, was obtained either from human blood or monkey passaged rubella blood. Only two monkeys were thus proved immune, over the period above stated.

CHAPTER V.

INCUBATION PERIOD.

Very little is known about what the rubella virus is doing during the incubation period. It has been assumed that during this period, the virus is multiplying in the host. Recent work was done by Fenner (1948) on ectromelia, a virus infection in mice, (mouse-pox) which is the murine representative of the mammalian pox viruses, especially varicella, as determined by serological tests (Fenner 1947). This work serves to act as a "model" for the study of virus infection. He found that multiplication of the virus at the site of its entry reaches almost its highest titre before any lesion is evident macroscopically. From the site of entry, the ectromelia virus passes rapidly to the regional lymph glands, and from there into the blood stream, whence it is removed by the liver and spleen. The virus then multiplies in these organs and sets up a secondary viraemia. The skin first shows virus on the 6th day after infection, and thereafter the virus content rises rapidly to reach a maximum at the time the rash becomes clinically apparent on the 9th day. As the antibodies rise in titre, so does the virus diminish quantitatively in the liver and spleen. Hence, virus deposited in the skin multiplies for several days before any macroscopic lesions appear. "Clinical phenomena lag behind the multiplication of the virus, and symptoms do not appear until after the virus proliferation has reached its peak, when the battle may be already lost. The incubation period

is/....

is thus revealed as the most vital of all phases of the disease". (Lancet 1948).

Fenner postulates a similar mechanism in other exanthematous diseases, including rubella, where the "primary lesion", however, not necessarily apparent clinically, is in the respiratory tract and not in the skin, as in the case of mouse-pox.

Various authors corroborate the statement that the incubation period of rubella is about 18 days. Lindberg (1924) described an infection which developed exactly 18 days after a three hour exposure to a commencing rubella eruption. This period was also confirmed by investigating an epidemic in a boys' boarding school. (Aycock & Ingalls, 1946) :-

One hundred out of the 106 cases consequent on the initial infection occurred within 15 to 23 days of exposure (see chart, Fig. 7). This represents an average of 18 (± 3) days.

The interval between cases can be used as a diagnostic aid to differentiate rubella from morbilli, where the incubation period is given as generally 10 or 11 days to the commencement of the catarrhal stage (Harries et Mitman, 1947). The incubation period of rubella, determined experimentally in children by the injection of infected nasal washings varied from 7 to 17 days. (Hiro & Tasaka, 1938).

Anderson (1949) noted that, in general, the longer the incubation period after artificial inoculation with infected material, the milder was the attack of induced rubella. He infected susceptible young women with rubella artificially by means of throat washings from established cases. These

volunteers/...

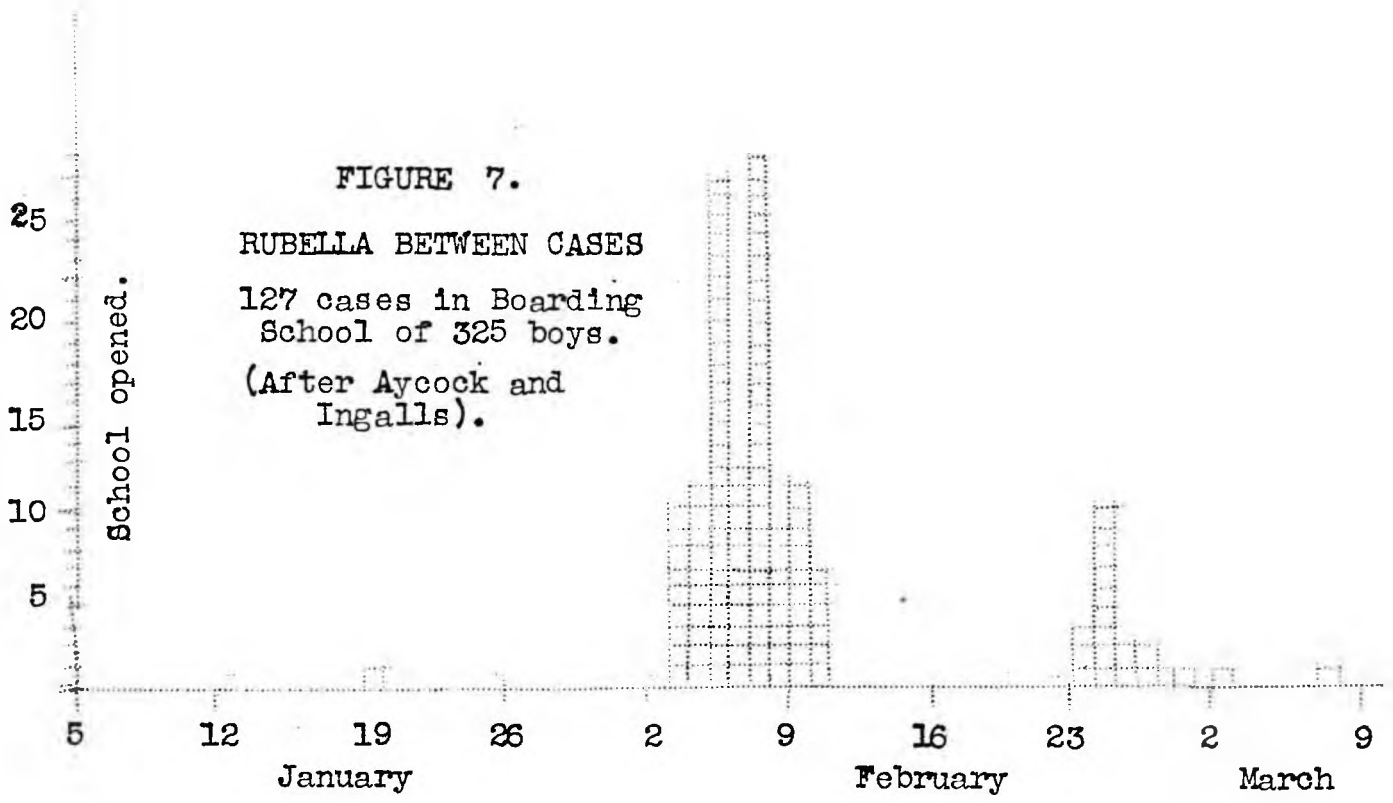


FIGURE 7.

RUBELLA BETWEEN CASES

127 cases in Boarding School of 325 boys.

(After Aycock and Ingalls).

volunteers were kept in hospital under observation from 20 to 72 hours, but none showed during this period any signs suggesting "illness of infection" as has been described in cases of measles (Harries and Mitman, 1947 p. 250).

CHAPTER VI.

PERIOD OF INFECTIVITY AND MODE OF INFECTION.

Bradford in Brenneman's "Practice of Pediatrics", states that, "the communicability rate (of rubella) is decidedly lower than that of measles, and more nearly resembles that of scarlet fever". It would appear that the infective agent of rubella and other exanthemata, lie in the upper respiratory tract during the prodromal period, before the infection is recognised, and before adequate isolation measures can be instituted. The mechanism of virus spread in measles can be easily ascribed to droplet infection, encouraged by coughing, sneezing and speaking. Chicken pox, however, is a disease without any catarrhal symptoms, and yet is very infectious. In fact infection will pass from one cubicle to another, if there is air communication between them. Moreover, in German measles, catarrhal symptoms are often lacking.

Anderson (1949) sprayed infective material (taken from the throat washings of patients with typical rubella) into the nostrils and oro-pharynx of volunteers and obtained almost 50% "takes". In one experiment, a laboratory worker standing at least 10 feet away from where this spraying was going on, contracted rubella. Cases of artificially induced rubella were not found to differ in any way from the natural disease.

Habel (1942) demonstrated virus infectivity in the washings taken from the nasopharynx during the first 48 hours of eruption, but not afterwards.

In/....

In practice, too, it has long been realised that cases follow on contact with infection, before the appearance of the rash. Habel also demonstrated the presence of the virus in the blood of patients during the first 30 hours, but not in blood taken on the third day. The available evidence, therefore, indicates that the infecting agent is in the upper respiratory tract of the patient in the first 48 hours; that infectivity commences before the appearance of, but terminates with the fading of, the rash. Because the rash is of short duration, only partial success will be gained by isolating all patients who exhibit the exanthem. Geiger (1918) recommended that cases be isolated during the stage of lymphadenopathy. The impracticability of such a plan becomes evident when we consider that lymph glands may remain enlarged for an indefinite period, especially in children. The clinical and epidemiological experience, also, is that transmission is by direct, or close contact. Infection through the medium of fomites, or a third person, is doubtful.

For practical purposes, isolation of a patient for five or six days is adequate.

CHAPTER VII.

PRODROMAL PERIOD.

The prodromal period generally lasts 12 to 24 hours, occasionally being prolonged beyond this period with influenza-like and catarrhal symptoms, such as coryza and conjunctivitis, in addition to the common symptom of enlargement of the posterior auricular lymph nodes, Bennett & Copeman (1940) during an epidemic of over 300 cases noticed in 4 cases, prodromal swelling of the mucous membranes of the nose, palate and gums without catarrh, "giving rise to considerable trouble".

Humphrey and associate (1937) in a series of 305 cases, found that posterior auricular gland enlargement was the most constant prodromal sign. Anderson (1949) induced artificially, in susceptible women, rubella by means of throat washings from typical cases of rubella. In some of these cases, the lymphadenopathy preceded the rash by as much as six days.

Constitutional symptoms, on the other hand, may be very slight, a fact convincingly borne out by the fact that in school epidemics, many infected boys fail to report sick. In children, a slight pyrexia in the 24 hours preceding the eruption, may be the only prodromal sign, while in adults, the severity of prodromal symptoms tends to be proportional to the degree of the rash, and include in severe cases, prodromal fever, headache, muscular pains, and posterior auricular adenopathy. Anorexia, nausea and vomiting are rare events (Harries and Mitman (1947). Stiff-

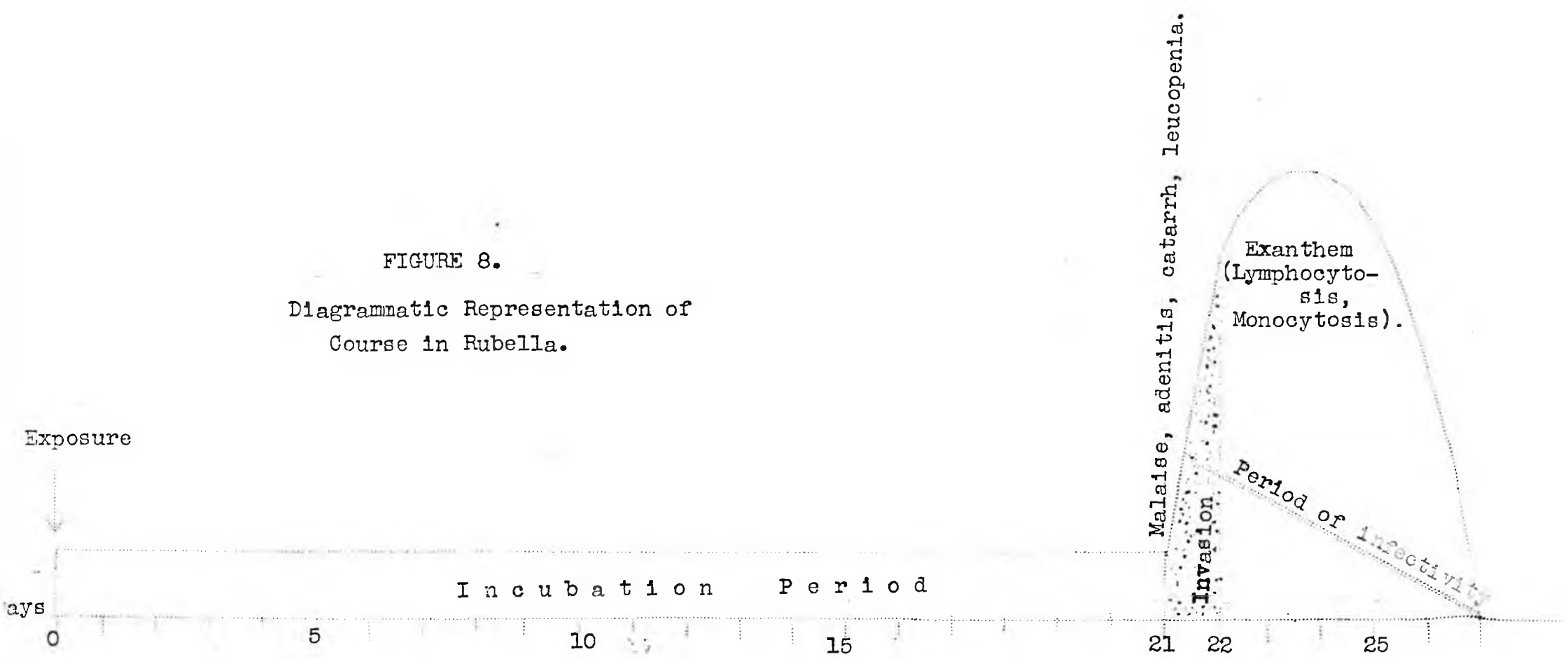
ness/....

ness of the neck is a characteristic symptom in some epidemics, and at least one case of encephalitis has been described, which occurred during the prodromal pre-eruptive period. (Holliday, 1950).

In the blood, a marked leucopaenia may occur in both children and adults, the leucocyte count even falling to 2,000 per cubic m.m. The leucopaenia, however, is not invariably present. When eruption occurs, a lymphocytosis with slight monocytosis, is apt to set in, but any blood findings are not pathognomonic. (MacBryde & Charles, 1935).

FIGURE 8.

Diagrammatic Representation of Course in Rubella.



Incubation period ± 14 to 23 days (average 18 days)

Exanthem 2 - 5 days (Average 2 - 3 days)

CHAPTER VIII.

SYMPTOMATOLOGY.

(1) COURSE.

The course in rubella is the mildest of all exanthems, being associated with no or relatively little discomfort in the vast majority of cases. The prodromal symptoms are occasionally so slight as often to be missed. The cardinal signs are pyrexia, exanthem, and lymph gland enlargement, but no individual sign is pathognomonic, and diagnosis is often made by the presence of one or two of several signs. In mild or modified types, assistance for diagnosis may be obtained by reference to the calculated incubation period. During epidemics, the onset may sometimes be acute, simulating meningitis or encephalitis, following on a period of malaise lasting 24 to 48 hours (Bennett & Copeman, 1940). There may occasionally be pain, or even stiffness, in the muscles of the neck, but in most cases, such symptoms are probably muscular in origin, or due to the adenitis.

(2) EXANTHEM.

The pathogenesis of the eruption in rubella is largely deduced by inference, and may be due to fragility of the minute vessels in the skin. Recent work on ectromelia or mouse-pox, is claimed by Fenner (1948) to indicate the probable mechanism in exanthematous diseases of humans. He showed that the virus is already present in the skin of mice a few days before the rash occurs, and he attributes the rash to focal infection in the epidermal cells.

Von/.....

Von Pirquet's theory of allergy as the basic mechanism of rash production in the exanthemata, he disposes of on the following grounds:-

(a) In mouse-pox, focal multiplication of virus in in skin was shown to cause the rash.

(b) An allergic reaction to the mouse-pox virus could not be demonstrated in the animals until the seventh day after infection, when the virus had already become localised to the skin.

(c) Congenital variola, vaccinia, alastrim, measles, (and even a case of rubella), have been known, and the rash in the child, develops in the usual way, although the infection occurs in utero. Fenner cites work by Grasset (1929), and Burnet (1941), to show that the foetus *in utero* is incapable of forming antibody, although the human placenta will transmit neutralising antibodies which probably assist in controlling foetal infection, and is incapable of passing sensitising antibodies (Sherman et al, 1940).

(d) Animal experiments are quoted where intravenous infection of vaccinia and simian measles virus is followed by typical skin lesions after a very short incubation period, i.e., when the internal organs are "short-circuited".

Clinically, the exanthem in rubella may be preceded by intense facial erythema, lasting only 12 to 24 hours, and especially heralding the severer types of rash. Generally, however, the eruptive stage commences with the appearance of small, pale rose-pink macules on the face and scalp. They vary in size

from/...

from a pinhead to a split pea, and may be round or irregular in shape, even confluent. (Michael 1908). They first cluster in small groups, usually appearing initially behind the ears and on the forehead, and then they spread downwards over the trunk and extremities. Lesions are pale, rose red, slightly raised maculo-papules. By the time they appear on the lower extremities, the rash is disappearing from the face, tending to leave the circumoral ring clear as in scarlatina, and at examination, the legs, the dorsum of the feet particularly, may be the only parts evidencing any signs of eruption. In the initial stages, the circumoral area is invaded, but often sparsely. (Harries and Mitman, 1947). By the time the rash is profuse on the face, it appears sparingly on the trunk, usually in the first 24 hours, and although the rash tends to fade rapidly from the face, it may persist in that situation throughout the eruptive phase. Rarely, it may be confined to the face only; but an eruption may never appear on the face at all. However, by the time the general practitioner is called in to see the case, more often than not, in the writer's experience, the rash has already faded from the face and is to be seen on other parts of the body.

In severe cases, the macules may coalesce in certain areas, particularly over the lower back and buttocks, producing erythematous areas of considerable extent. In children, Michael (1908) found confluence on the buttocks and popliteal regions common. Pressure due to clothing on lying in bed may cause such

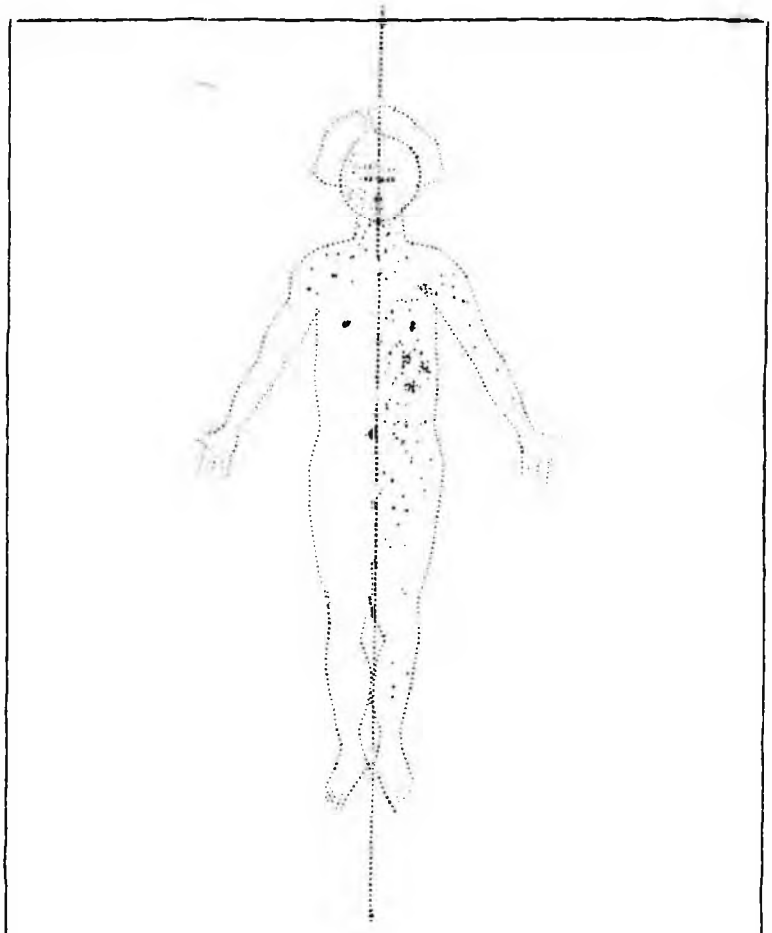


FIGURE 9.

Diagram showing development of rubella rash.

Note early involvement of face, as well as rapid disappearance of rash from face.

erythymatous lesions or punctiform lesions, especially on the buttocks and inner sides of the thighs (Osler & Macrae, 1926). Such erythematous areas in rubella formed by confluence of lesions, are however, pink rather than punctate. Only in severe cases are macules found in the axillae, popliteal spaces, the palms and plantar surfaces (Wesselhoeft, 1947a). Michael (1908) who investigated an epidemic of rubella in 80 children, observed the eruption frequently in the palms and soles. On the trunk, the eruption tended to be more profuse than elsewhere. In the second 24 hours, Michael observed that the chest lesions in children were paler, but on the lower part of the body they were profuse especially on buttocks and behind knees. It is rare for the rash to be equally intense all over the body (Atlee, 1937). In fact, it is quite characteristic for the rash to appear in one area, and then to fade wholly or partially before erupting elsewhere. The lesions, therefore, do not necessarily commence fading gradually from above downwards, but may show up brightly in some skin areas, and less so in others. (Osler and MaCrae, 1926).

In children, Michael (1908) found, the severer the eruption, the longer it remains, and in bad cases, a coppery tint may appear as in scarlet fever. Such cases evidence high fever followed by furfuraceous desquamation of the face and trunk as the rash subsides, and are often confused with scarlatinal eruptions. In 9 out of 21 undoubted cases of rubella seen by the writer in general practice in Pretoria from June to September, 1949, the rash on the body

could/...

could be described as having a brownish rather than a pink colouration. These brownish rashes tended to be very intense, though associated subjective symptoms were sometimes minimal.

From the preceding description, it can be seen that the rash may assume various characters. In general, the macules remain discrete, and the eruption comes out suddenly on the face, from whence it tends to fade somewhat abruptly in milder cases. By the second day, the rash has begun to fade on the face although it may be well marked on the trunk. It tends to be polymorphic, fine, rose-pink, "kalaedoscopic", changing from an initial macular appearance to a more punctate appearance, resembling measles on one day and scarlet fever on the next. (Wesselhoeft, 1947a). The fading of the rash from the face on the second day may suggest scarlet fever, which however, only rarely involves the face. Occasionally the macules may be as large as a pea, rose-red, darker, and may coalesce on the trunk, but they do not show the robust character of measles. The ordinary case is simple enough to diagnose and differentiate from scarlet fever, but in exceptional cases, distinction is difficult.

In children, Michael (1908) found, that as the eruption faded on the third day, it looked pimplish and mottled, especially on the posterior surfaces of arms and legs where it remains longest. In many cases the rash disappeared entirely within three days, but in some cases it was observed to clear from the face and trunk in 24 hours, but persisted as a...

mottling/...

mottling on the back of the arms and legs for 5 or 6 days. Sometimes the rash appeared to have gone, but after exposure reappeared again. Amongst 80 children, the period of eruption was found to be as follows:-

Rash in		9	cases,	lasted	3	days.
"	"	18	cases,	"	4	"
"	"	24	"	"	5	"
"	"	22	"	"	6	"
"	"	6	"	"	7	"
"	"	1	"	"	8	"

In a few cases the rash itself was indistinguishable from that occurring in measles. These were probably cases, where the rash had a brownish colouration as noticed by the present.writer.

Desquamation is rare, but pigmentation, as in morbilli, may follow, and the intensity of eruption may be out of all proportion to the degree of pyrexia. (Bradford). Occasionally, particularly in adults, the rash is itchy, and it is then easily confused with drug eruptions. Michael (1908) noted fine, branny desquamation in 35 out of 80 cases occurring in children at an institution. Such desquamation tended to occur after profuse rashes, and was most marked on the face, less evident on the body, and very rarely on the palms and soles.

Bennett and Copeman (1940) found desquamation to affect the hands particularly, in an epidemic studied by them.

There is no true ENANTHEM, merely a diffuse injection of the naso-pharynx occasionally preceded by a fleeting spotty rash, of deep pink colour, and occasionally vesiculation. (Stokes, 1948). Humphrey and Ekermyer (1937) found no enanthem on 305 ....

cases. Forchheimer described spots named after him, inside the throat, as being rose-red, and fading in 24 hours leaving yellowish-brown pigmentation. This latter finding cannot be substantiated, but the early, fleeting, spotty, discrete, rose-red rash in the throat (also described by him), has been observed in early cases (Harries and Mitman, 1947; Wildman and Teasey, 1940).

(3) PYREXIA.

The rise in temperature persists only for one or two days, and generally ranges between 99° and 100°F. Less commonly, it rises to 101°F., and very rarely to 102° or 103°. Aycock and Ingalls (1946) give excellent charts illustrating of the different types of temperature records met with in rubella (Figures 10a, 10b, 10c & 10d). The records are from 20 adolescent boys taken at random, and it is apparent from them, that there is no characteristic curve. Many curves indicate an afebrile, or even sub-normal course throughout the illness. In severe cases there may be chilliness and temperature up to 104°F., though even so, the patients concerned are not very uncomfortable as a rule.

Michael (1908) who inspected 80 infected children in an institution, found that in 48 of these patients, the pyrexia was 99°F. or less and lasted only 2 days. The pulse corresponded with the temperature.

Bennett and Copeman (1940) noticed a secondary rise in temperature in about 10% of cases occurring in an epidemic of over 300 individuals in the British

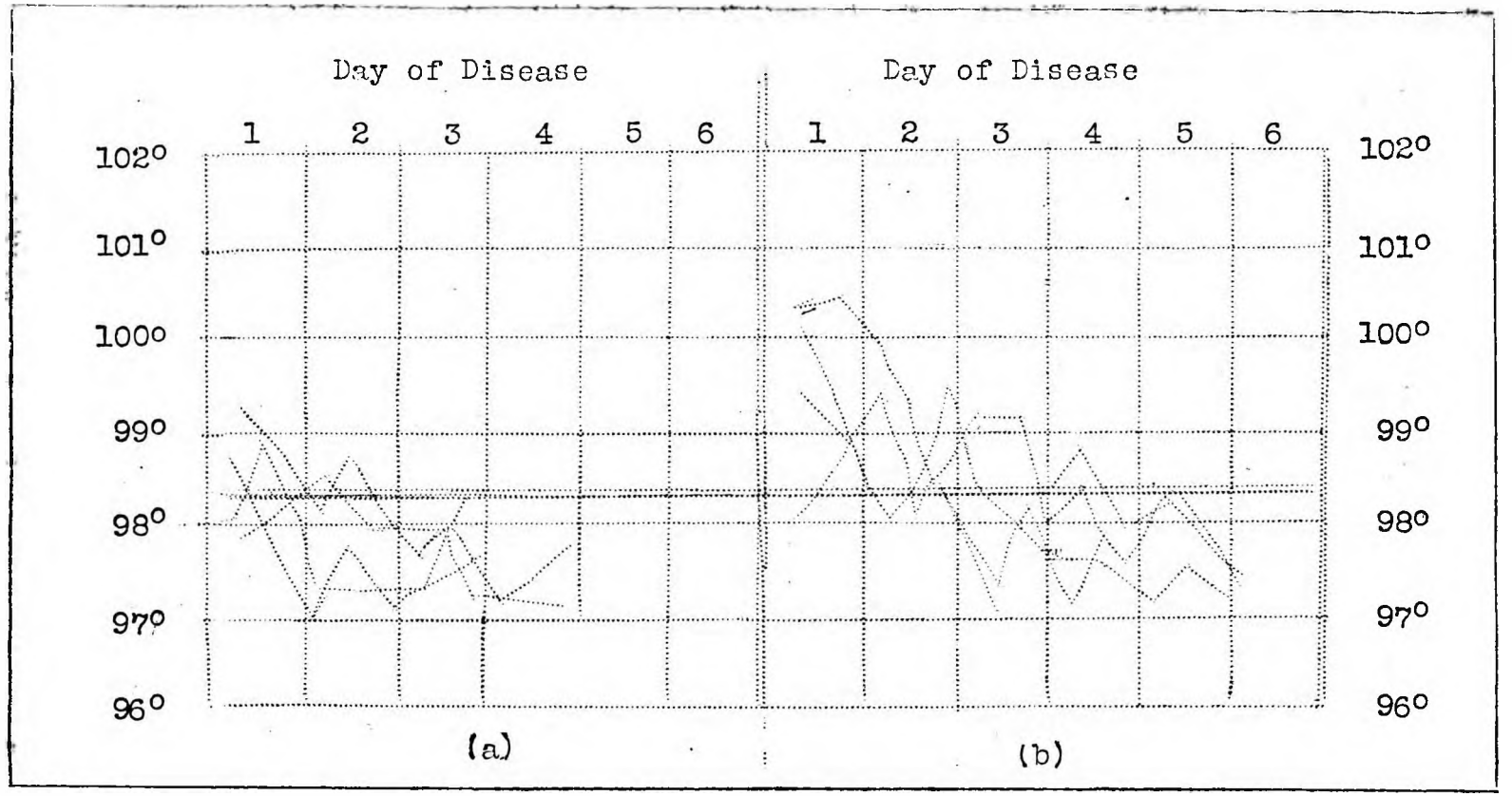


FIGURE 10

TEMPERATURE CHARTS TAKEN FROM 20 CASES
OF RUBELLA DEMONSTRATING THE VARIOUS TYPES OF CURVES OBTAINED.
(AFTER AYCOCK AND INGALLS)

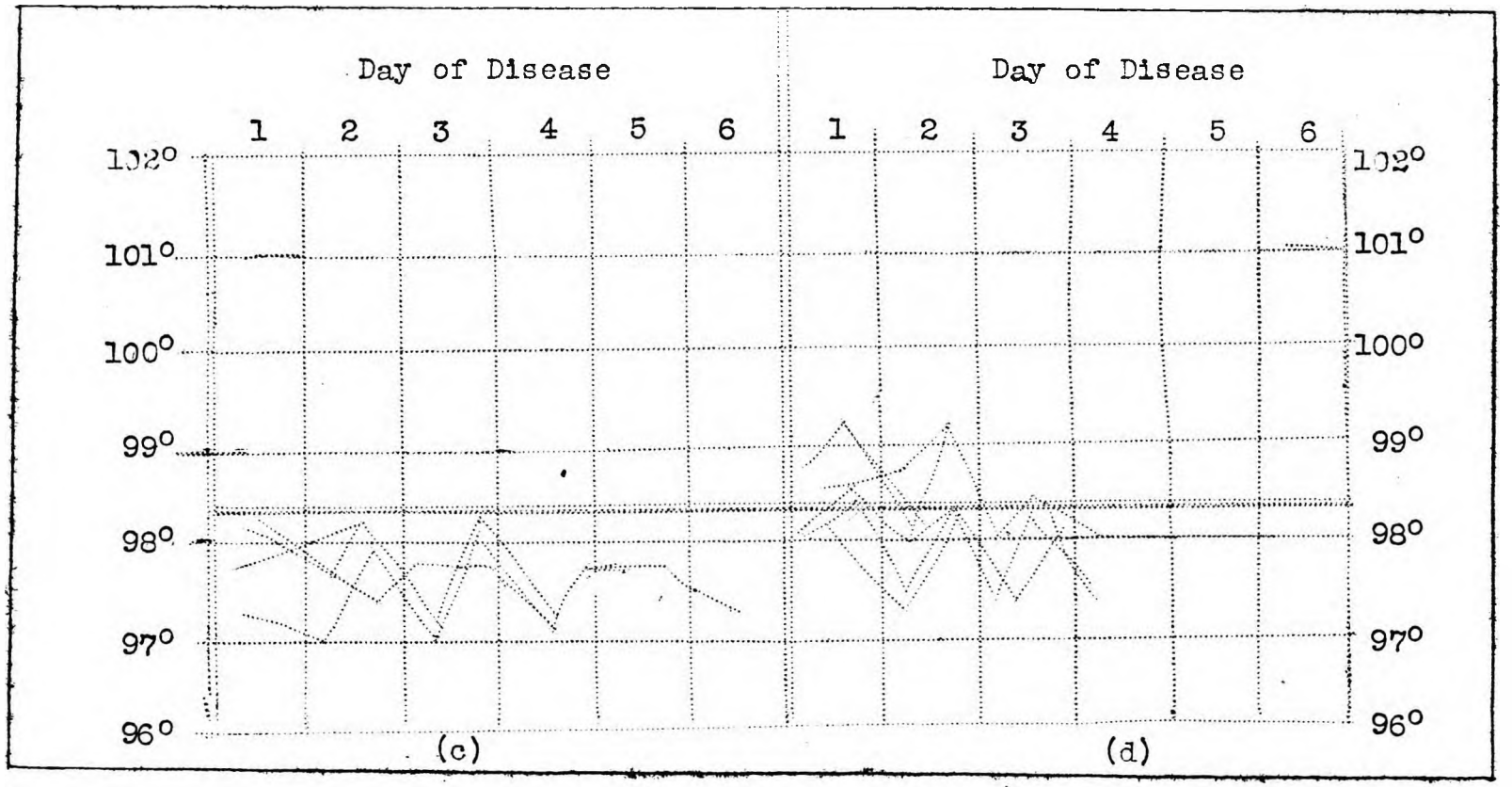


FIGURE 10

TEMPERATURE CHARTS TAKEN FROM 20 CASES
OF RUBELLA DEMONSTRATING THE VARIOUS TYPES OF CURVES OBTAINED.

(AFTER AYCOCK AND INGALLS).

Expeditionary Forces. The secondary rise of temperature, which usually reached about 101°F, followed an apyrexial period of 48 hours or more, and was accompanied by malaise and increased swelling with some pain in the enlarged glands.

(4) CATARRHAL SYMPTOMS.

Catarrhal symptoms are absent, unless due to a secondary infection such as the common cold. Cough is actually a very uncommon symptom. The mucous membranes of the nasopharaynx are very injected, and the ocular conjunctiva is pink, rather than inflamed, as is the tendency in measles. Also there is no palpebral conjunctivitis, no lachrymation or sticky discharge and rarely photophobia, as in morbilli. In Britain, it has been noticed that rubella and "pink eye", (acute catarrhal conjunctivitis) are often prevalent at the same time, (Atlee, 1937), but the association is probably accidental.

Bennett and Copeman (1940) reported pharyngitis, follicular tonsillitis, nasal congestion without catarrh, and soreness of the gums in a severe epidemic breaking out in the British Expeditionary Forces. Todd (1940), a school medical officer, who herself contracted the disease, complained that her gums were painful, as though her "teeth were falling out". Harrison (1940) also mentions painful bleeding gums, while Bennett and Copeman (1940) under epidemic conditions found painful gums or "toothache", a common complaint, which usually lasted 48 hours and sometimes disturbed sleep at night. This complaint usually started on the second day, but sometimes was marked at the beginning of the illness.

Tonsillar/....

Tonsillar exudate is very uncommon, (Harries et Mitman, 1947). Michael (1908) observed a diffuse redness and the eruption on the soft palate in 17 out of 80 infected children, although there was no complaint of sore throat.

The TONGUE may sometimes have a bright strawberry appearance, which however, is only localised to the tip, and does not spread over the whole surface as in scarlet fever. Of course, in scarlet fever, as in rubella, the tongue may appear normal.

(5) LYMPHADENITIS.

Lymphadenitis may occur during the prodromal period, or after the onset of the eruption, and the most characteristic feature, is its situation over the mastoid region. The glands vary in size, usually from that of a pea to a marble, in the latter case being actually visible under the skin. Mastoid lymphadenopathy should always give rise to a suspicion of rubella. Children often complain about earache, without any evidence of otitis media, and present on examination, enlargement of lymph glands in the neck and scalp. There is often no associated tenderness or pain over these glands, and they never suppurate. Pain or tenderness in the glands is however, not infrequently noted by the patient, but when present, is not usually very acute. Stokes (1948) states that there is no other disease which causes tender enlargement of the retro-auricular, posterior cervical and postoccipital glands in the same way as rubella.

Moderately enlarged suboccipital, and posterior cervical lymph nodes are often palpable as in measles,

and/...

and sometimes even the groins and axillae may be involved. Bradford (Brennerman's Practice of Pediatrics), emphasises that the posterior cervical lymph nodes may be enlarged both in measles and in scarlatina. Rubella may occur, however, without any posterior auricular lymphadenopathy, and the latter, if it occurs, may persist for weeks, months and sometimes even for years. It is an interesting question, though an unanswered one to the writer's knowledge, whether the virus remains dormant in such glands. Other superficial glands, e.g. the epitrochlears, may also be enlarged.

Bennett and Copeman (1940), found generalised glandular enlargement to be a prominent feature of the epidemic studied by them. A few of their cases were admitted with pyrexia, fairly sore throat, and generalised lymphadenopathy, but no hepatomegaly or splenomagaly. The clinical picture apart from the rash suggested glandular fever, but white blood counts showed that the majority of these cases had a leucopenia with a relative lymphocytosis. The adenopathy remained for ten days or more, and a further blood count in some of the cases before discharge from hospital showed a return to normal.

Anderson (1949) produced rubella experimentally in human volunteers and found that lymphadenopathy may precede the appearance of a rash by as much as 6 days in some cases. Michael (1908) found that lymphadenopathy was the last symptom to disappear. The latter author also found splenomegaly in two out of 80 cases of rubella occurring in a children's institution.

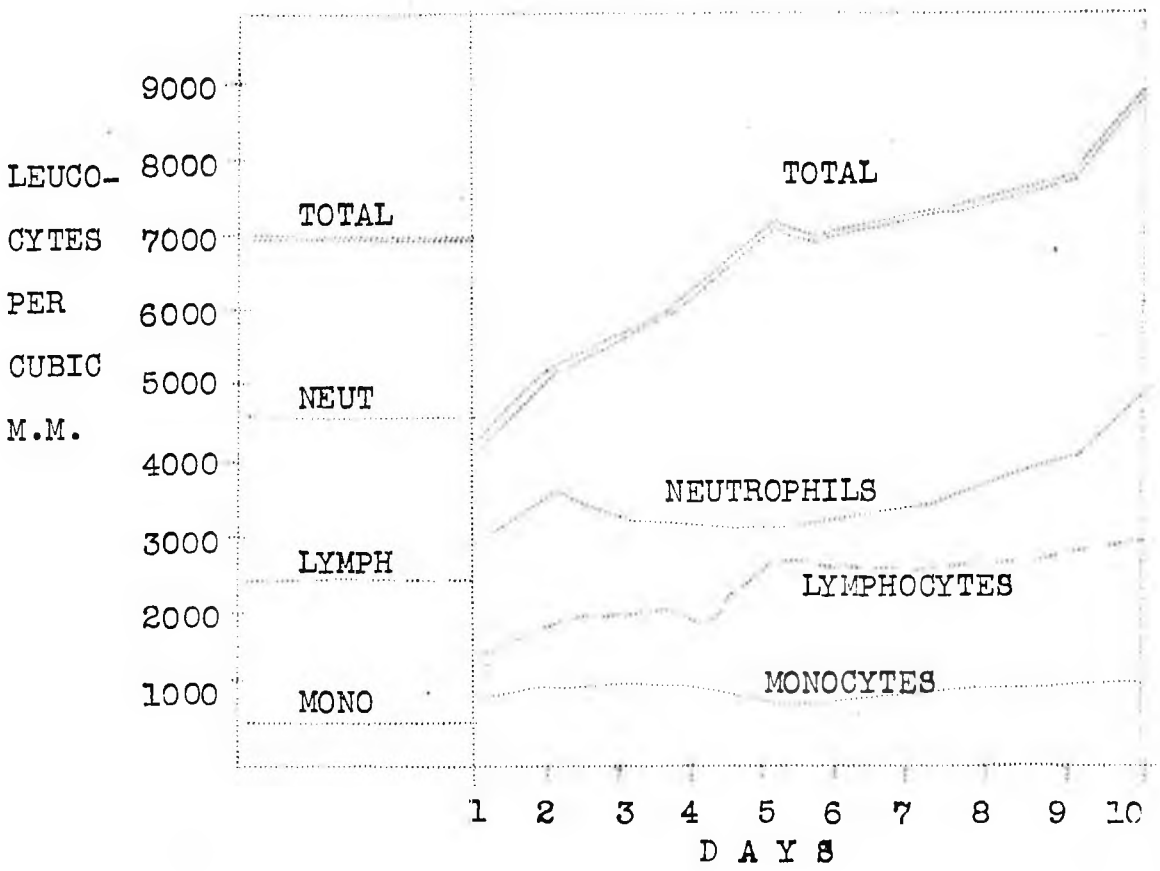


FIGURE 11.

MEAN LEUCOCYTE COUNTS IN RUBELLA (after Hynes)

Day 1 is onset of rash. The horizontal lines at the side show the normal mean.

(6) THE BLOOD.

The blood changes in rubella are somewhat similar to those occurring in whooping cough, measles, mumps, glandular fever, and agranulocytosis. In the PRODROMAL stage there occasionally occurs a marked leucopaenia. When the eruption appears, there is a tendency to lymphocytosis, along with the appearance of a few monocytes. Hynes (1940) investigated 61 affected adults by serial blood counts. Absolute leucopaenia and neutropenia generally occurred at first, changing to absolute lymphocytosis on the 6th day, and a neutrophilic leucocytosis after ten days. These findings are exactly similar to those occurring in measles. The initial leucocytosis of scarlet fever contrasts strongly with the leucopaenia of rubella. With the onset of encephalitis, the blood picture appears to change to one of leucocytosis. (Margolis et al., 1943). In scarlatina, lymphocytes are low in number, being 14% or less. Eosinophils tend to remain and to rise in number, during the recovery stage (Mac Bryde & Charles, 1935; Carrol, 1934).

Hynes did not find that the recovery stage of rubella was associated with a "high grade shift to the left in polymorphonuclear cells", as originally described by Whitby and Britton (1939). MacBryde and Charles (1935) found that the Schilling haemogram indicated an increase in the number of lymphocytes and monocytes as the rash disappears. "At the onset, the neutrophils constitute only 60% of white cells, but there is a marked rise in stab cells.

The/...

The appearance of juvenile forms (metamyelocytes) is relatively rare". These authors found no significant differences between the count in children and adults. Out of 30 cases, their youngest were two aged 7 years. Carroll (1934) also noticed a constant post-infective lymphocytosis commencing about the fourth or fifth day and often paralleling the lymphocyte rise.

MacBryde and Charles also found that eosinophils tended to remain in their normal numbers, and not to disappear as in most other acute infections. They may reach 10% between the 3rd and 6th days, an average of 2%. The highest figure recorded by Hynes was 770 per cubic millemetre, between the 6th and 11th day. (Normal, 150-400 per cubic millimetre). The basophils remained numerically unchanged. Türck cells were always present, commonly numerous, and reach a peak about the fourth day. Plasma cells were also common in the first week. The earliest form of Türck cell which was seen most usually at the outset, is a large oval cell, 25 to 30 microns in diameter, with a nucleus of 15 to 30 microns. The nucleus has a well formed, fairly light reticulum with 2 to 5 prominent nucleoli. The cytoplasm is lilac and often vacuolated, or exhibits a clear space at one side of the nucleus. These cells actually differ from lymphoblasts. As the disease progressed, more mature Türck were seen, eventually exclusively. As the cell matures, it becomes smaller, the nucleus loses its nucleoli, and it condenses, thus finally emerging as a typical plasma cell.

Plasma/....

Plasma cells were present in from one half to two-thirds of patients during the first week. The plasma cell is an oval cell about 8 to 14 microns in diameter, with an eccentric nucleus, 5 to 7 microns in span, showing cart-wheel chromatin condensation. The cytoplasm is deep lilac in colour with a clear space on the central side of the nucleus. Hynes says that only cells strictly conforming to this description should be regarded as plasma cells, and "intermediate" cells should be classified as Türck cells, not as plasma cells. American authors do not stress the point about Türck cells so much, as the latter are non-specific and may be present in measles, too. Carrol (1934), who included all types of plasma cells in his blood counts, found them in all of 30 cases of rubella, whether relatively severe or mild. He thinks they begin to appear during the prodromal stage of lymphadenopathy. There are not often plasma cells in roseola infantum (Zahorsky, Brenneman's Practice of Pediatrics).

The erythrocyte sedimentation rate was increased in 25% of cases, (Hynes 1940) and there are no serological diagnostic tests. The Paul Bunnel reaction is negative. According to Hynes, a leucocyte count is sufficient to distinguish between rubella and scarlet fever, but not between rubella and measles. MacBryde and Charles however, do remark on the tendency towards a lower percentage of lymphocytes and a higher neutrophil count with juvenile forms in measles. Carrol (1934) confirms the tendency for an early variety in the genetic scale of cells to appear in rubella, and he got a picture of general confusion and disorder in the blood of measles as regards, size, morphology and staining. Hynes states that the characteristic blood

picture/...

picture in glandular fever, together with a positive Paul Bunnel reaction serves to clearly distinguish infectious mononucleosis from rubella. However, it should be remembered, too, that the Paul Bunnel reaction may only become positive at a late stage, or during the recovery stage of infectious mononucleosis (Tidy, 1948).

MacBryde & Charles remark on the fact that in drug or toxic rashes, the total leucocyte count may go up slightly, with a slight rise in neutrophils and stab cells and usually also in eosinophils.

(7) THE URINE.

Michael (1908) examined 76 cases of rubella for albumin and diazo reaction, but these tests were positive in only two cases, namely, one who had rubella following on chicken pox (incompletely recovered), and the other, a marasmic baby aged twenty months. In the first case, the diazo reaction was positive on the first day only, and in the second case was positive for three days. The diazo reaction occurs in typhoid fever (from the end of the first week to the end of the second week), miliary tuberculosis, scarlet fever, pneumonia, and erysipelas (Boyd, 1944). It was pointed out by Kennedy (1942), that even a small dose of sulphapyradine results in a positive diazo reaction, although this is not the case with sulphanilamide or sulphaguanidine.

(8) INAPPARENT ATTACKS.

Habel (1942) transmitted rubella to rhesus monkeys by inoculation of blood and nasal washings via the nasal, subcutaneous, intraperitoneal and intravenous routes. Fever and leucopenia usually

occurred/.....

occurred within 8 days, and the virus could then be recovered from the blood, although sometimes a rash was not present. Hiro and Tasaka (1938) transmitted rubella to children by the subcutaneous injection of filtered nasal washings from typical cases. Of 16 children presumed susceptible, 4 developed typical rubella, but 2 showed characteristic leucopaenia with lymphadenopathy and no rash whatsoever.

The National Research Council England (1938) noted in one school that, during a rubella epidemic with an attack rate of 17.1%, 539 boys were still at school and not attacked in 1933, when the rubella attack rate was 20.4% in "new" boys. The conclusion is, that either these immune boys had never shown clinical infection in 1932, or their original attacks, possibly pre-school, had been so mild as to have been overlooked.

Floystrup (1923) reported "inapparent" infection in his child 2 weeks after definite exposure to infection in school. There was no rash except for a few pale macules on the child, lasting for a few hours; but vomiting, conjunctivitis, slight pyrexia and characteristic lymphadenitis were present. Two weeks later, the child's own brother developed typical rubella. Habel (1942) produced infection in monkeys from naso-pharyngeal washings taken from a 4 year old boy in a doctor's family, who was definitely exposed to rubella on 3 consecutive days, but who also never exhibited any rash, only fever, malaise, slight rhinitis and posterior auricular gland enlargement. Many cases of "inapparent" infection are merely cases of modified rubella, due to the patient's high resistance,

where/....

where the rash is so fleeting as not to be observed. Floystrup's son falls into that category, except that in this case, the infection was recognised because of the father's medical knowledge. In South Africa, amongst the dark-skinned Bantu, rubella rash easily passes unrecognised, and lymphadenopathy due to other causes is so common, that the diagnosis of rubella is very infrequently made, if at all.

In the original Australian series, one case in the retrospective follow-up, was reported of a woman who apparently got the infection from her husband. He had never been known to have had the disease (it had probably been missed !) but he had visited a friend suffering from rubella. Simpson (1944) writes about a severe rubella epidemic in his district, Dorset, England. During this period, 3 anencephalic monsters were born without any rubella history. Thirty-five per cent of the cases with rubella had polyarthritis.

The writer also had a case worth while recordings:-

> A schoolgirl of 14 years was attended for slight pyrexia. There was an associated lymphadenopathy, and a typical rubella rash. The conjunctivae were slightly pink, but otherwise there were no catarrhal symptoms. About 3 weeks afterwards, the girl's mother (aged 41 years) complained of severe pains involving the larger joints and especially the knees, elbows and wrists. There was no pyrexia and no swelling of the affected joints, but the occipital and posterior cervical glands were enlarged. She had no rash, and gave no history of one, but the articular symptoms and the enlarged glands subsided after 8 days and did not recur thereafter. The case was therefore apparently one of "polyarthritis" associated with inapparent rubella.

(9) UNUSUAL FORMS OF RUBELLA.

ECCHYMOTIC FORMS of rubella have been described where both the exanthem and enanthem are ecchymotic in character/...

character. (Wesselholft, 1947[a]). Such cases present also increased capillary fragility, but are not associated with any blood loss from the body or viscera; nor are the constitutional symptoms severe. The permeability of the capillary endothelium may be affected in all types of inflammation, and apparently rubella is not excluded from this vascular effect. A coppery hue which occasionally follows a severe eruption is due to such ecchymoses.

One case is described (Schamberg & Kollmer, 1928) in an adult who exhibited severe prodromal symtoms for five days, followed by a rash. The latter was macular in type, appeared below the knees first, and then spread, upwards with some crescent formation, finally involving the face on the third day, and disappearing on the sixth. Irregular spread of rash, involvement of the palms and soles, abnormally long persistence of the rash, and a fine papular condition of the eruption have been described (Osler and McCrae, 1926).

CHAPTER IX.

COMPLICATIONS.

Complications are rare except for foetal damage when the mother is affected by the illness early in pregnancy, and a few other conditions described below.

(1) MENSTRUATION.

Menstruation may rarely be delayed or brought on prematurely.

(2) POLYARTHRITIS.

Polyarthritis, mild in type, may occur a few days after subsidence of the eruption, involving the knees or feet in children, or the fingers in adults. Such a complication is almost invariably associated with a mild pyrexia. Potter (1930) described a polyarthritis on the 3rd day of the eruption, involving fingers, wrists, ankles and feet, but unaccompanied by fever. Geiger (1918) reported 36 cases of arthritis in approximately 180 cases of rubella occurring in Ankansas, U.S.A. Simpson (1940) reported a mild migratory type of polyarthritis in 25 out of 72 patients with rubella in an English outbreak, and Copeman and Bennett (1940) noted the same complication amongst the British Expeditionary Forces. These observers found that the muscular pains usually commenced on about the third day of the disease, though occasionally were dealyed to the ninth day. The grades of severity ranged from transient muscular pains lasting one or two days, to cases which were indistinguishable from rheumatic fever. In the majority of cases the shoulder girdle was affected, but sometimes the gluteal and thigh muscles were chiefly involved. Gregg, in

Australia/...

Australia, found in the retrospective histories of some rubella patients with malformed children, a story of joint and limb pains labelled as "arthritis". Wesselhoeft (1947[a]) cites from the literature a case of polyarthritis during the acute stage of rubella. The present writer has seen two cases in women aged 41 and 45 years respectively, the latter having the complication during the acute stage of rubella.

(3) NEURITIS.

Neuritis is described as presenting itself clinically by some workers in general practice (Hodge and Whitney, 1940) although no true cases of neuritis have been seen in any institution. Cases seen by Harrison (1940) and Hodges (1940) developed "neuritis" 3 - 6 days after the rash. There was pain, numbness, or paraesthesiae of wrists, hands, fingers, shoulders or ankles, with some weakness in about 50% of cases. In 4 such cases, the average age was given as 32 years. Possibly this condition may have been arthritic, because there is some suggestion of joint involvement with swelling rather than true neuritis. The "transient motor weakness" described, may also have been due to disability consequent on pain and tenderness when the affected limbs were moved. It should be borne in mind, however, that an encephalomyelitis could cause true paresis. According to Hodges (1940) who saw over 300 cases of rubella, about half of which were children, adults only were affected by neuritis. A possible explanation for this is that the pyrexial metabolites, and decomposition of infective material in infectious diseases produces antigenic substances which activate old centres of healed lesions (Brock, 1940).

(4) THROMBOCYTOPENIC PURPURA.

Thrombocytopenic purpura has been met with.

Up/....

Up to 1946, 10 cases had been reported according to Wesselhoeft (1947a). He cites a case of Pitten, where thrombocytopanic purpura occurred in a 9 year old girl with no previous history of hemorrhagic tendencies. Gunn (1933) described a case, also in a 9 year old girl, who however, gave a previous history of mild nose-bleeds, since the age of five, but no other manifestations. There was, in addition to the thrombocytopenia, a prolonged bleeding time, a leucocyte count of 13,000 (79% neutrophils). In both cases, the spleen was not palpable, the purpuric lesions over the whole body were severe, and epistaxis was prolonged. After the sixth day there was complete recovery in both cases. Two mild cases in children, reported by Fox and Walton, are also cited by Wesselhoeft (1947a). One was in a nine year old girl occurring on the fifth day of a mild case of rubella. The platelet count was 40,000 per cubic millemetre, the bleeding time more than 45 minutes, and the petechiae were widespread. Recovery occurred in 3 weeks. The second case was a 16 year old boy with rubella relatively severe and an initial temperature of 103 degrees F. The petechiae developed rapidly and spread all over the extremities. Red cells were found in the urine, and recovery occurred in 2 weeks. In both cases, there was no family history pointing to hemorrhagic diathesis. Two cases in adults (Warren et al, 1946) made a recovery in 2 months and 5 months respectively. From the above case it is obvious the severity of purpuric complications is not necessarily proportional to the severity of the rubella attack, although purpura is one of the few diseases which, ...

occurring/...

occurring concurrently with rubella, is aggravated thereby.

Occasionally otitis media, croup, bronchitis, with secondary invaders, "bronchopneumonia" may even occur in children. A few instances of glomerulonephritis have been reported and also endocarditis (Bradford). All of these must be excessively rare, because resistance to pyogenic organism does not appear to be lowered by the disease, and one cannot help feeling that some of these conditions just enumerated, might well have been coincidental, having existed before the onset of the exanthem and not aggravated thereby. As so many of the above complications have been reported in hospitals, institutions and military camps, it is obvious that exposure to other infections may have occurred.

(5) SECONDARY INFECTIONS.

Secondary infections are indeed rare, but Hamburger (1944) presented evidence to show that the recovery stage of rubella is associated with susceptibility to streptococcal infection, as follows on in the case of measles. Wesselholft (1947[a]) however, ascribes this to the fact that streptococci may have been prevalent in the Hospital from which Hamburger's cases were drawn. He, Wesselhoeft (1939) surveyed 100 cases of rubella occurring in patients convalescing from scarlet fever, and found no indication in the different age groups of heightened susceptibility to streptococcal infection. In the case of measles contracted during convalescence from scarlet fever, however, he found a much higher incidence of suppurative otitis media in all age groups. He also quotes

Florand/...

Florand and Fiessenger's case of steptococcal septicaemia occurring 6 days after rubella.

In the epidemic of 305 cases investigated by Humphrey & Ekermeyer (1937) there was an unusual number of complications and relapses, viz:

15 cases tonsillitis – 5%
3 " suppurative otitis media – 10%
(Still much lower than the incidence in scarlet fever or measles.);
2 cases suppurative cervical adenitis – 10%

(6) ENCEPHALITIS:

This complication usually occurs between the 2nd and 6th day (Briggs, 1935). Harries and Mitman (1947) mention that certain epidemics of rubella tend to be complicated by encephalitis, and they make a comparison with measles, where there is also an association between encephalitis and certain epidemics.

Encephalitis is extremely rare, occurring in one in 6,000 cases according to Margolis, Wilson & Top, (1943), which is about the same incidence for encephalitis following measles and chicken pox. In mumps, a benign encephalomyelitis occurs, of which the estimated incidence (if carefully looked for) is given as 11% in some epidemics (Fox et al, 1949).

Out of the 14 cases of rubella encephalitis described by Margolis and co-workers, 4 were fatal, and 10 recovered, 6 being very mild. All the fatal cases, and some of the non-fatal cases evidenced severe and protracted convulsions, but the course of the illness was short irrespective of the outcome. The fatality rate works out to 20.8%, when 34 cases previously reported are included. The latter series of 34 had 6 deaths. Death occurred

within/....

within 3 days of the onset of encephalitic signs or "with striking consistency, 4 days after the onset of the disease". (Margolis et al, 1943). The mortality from this complication occurring in all cases of rubella based on the above information, is about 1 in 30,000. The mortality of rubella in general is probably about one in 60,000. All age groups appeared to be equally susceptible.

The manifestations may be those of a mild meningo-encephalitis, or of encephalo-myelitis, but the pathogenesis is vague. One theory is that some latent encephalomyelitic virus is aroused into activity by the rubella agent. Another theory is that of damage to the central nervous system, either directly by the virus of rubella, or indirectly by dissemination of its toxin. The picture resembles that of encephalitis associated with measles, chicken pox, and vaccinia.

Putnam (1941) postulates some allergic mechanism related to the establishment of immunity, causing disturbed clotting function. He emphasises the thrombotic and vascular nature of the pathological findings. And yet, as Wesselhoeft (1947[a]) remarks, the onset of the eruption is the result of lowered capillary resistance in the skin, whereas encephalitic symptoms may occur after the rash has disappeared.

Davison and Friedfeld (1938) found on histological examination, a mild meningitis, perivascular infiltration of grey and white matter of the cerebral cortex, brachium pontis, superior cerebellar peduncle, dentate nuclei, cerebellum and brain-stem.

These/....

These lesions, therefore, do not differ from those seen in any other form of encephalitis, except that Margolis and co-workers were not able to demonstrate perivascular demyelination as is so frequently seen in post-vaccinal and measles encephalitis. They found marked swelling of the brain, with flattening of convolutions, narrowing of sulci, pressure cone in cerebellar region, and generalised capillary hyperaemia of cerebral white matter. The cells infiltrating the perivascular tissues were plasma cell in type. Mononuclears with yellowish brown pigment were seen in the Virchow-Robin spaces, and neurone damage was non-specific in nature. There were capillary hemorrhages especially in the floor of the fourth ventricle.

There may be any of the usual non-specific signs of encephalitis, namely, headache, vomiting, stiff neck, fever, reflex speech aberrations, etc. In encephalitis, the leucopenia of rubella becomes a leucocytosis, as was determined in the Detroit epidemic, 1942. (Margolis et al). In this outbreak, stiff and painful neck or extremities were common (10 out of 14). Diplopiae, bulbar palsies, thickness of speech, muscle twitching, weakness of limbs, urinary retention, convulsions may be present. Owens and Greenway (1940) report an unilateral temporary retrobulbar neuritis with diminished vision in an adult who was not very ill. Wesselhoeft (1947a) cites from the literature a case of Revilloid and Long, where "polyneuritis" occurred in an 8 year old boy, 10 days after rubella. This child had diplopia,

marked/....

marked muscular weakness of the extremities and loss of tendon reflexes, and doubtless was actually a case of encephalomyelitis. Hodges and Whitney (1940) observed 15 cases of neuritis, 3 of which were brachial. Even with severe neuritic signs, the patient need not necessarily appear to be ill, and encephalitis if not carefully looked for, may be missed in mild cases.

The course of the complication is relatively short, and does not appear to exceed 2 or 3 weeks, although sequelae may be persistent. Margolis et co-workers found that in the shortest case, symptoms cleared up in 8 days, and in the longest case they cleared up in 120 days.

In cases reported by Margolis and associates, the cerebrospinal fluid was increased in pressure to between 120 and 180 millimetres of water. Cell counts varied from 8 to 500 per cubic millimetre, averaging 91, while mononuclears predominated in the field. Margolis and co-workers further found that the sugar varied between 67 and 100 milligrams per 100 millelitres. The protein was moderately raised, averaging 67.5 mgm. per 100m·l.

There is nothing specific about the signs and symptoms. A history of German measles within a week prior to the onset of central nervous system signs, associated with a fading maculo-papular eruption, or enlarged post-auricular glands is highly suggestive. A history of exposure should be taken into consideration too. It is worth while freely quoting a typical case described by Margolis et al., to fix a basic picture in the clinical investigator's mind :

A 10 year old boy complained of headache and vomiting. His speech had become thick, and he was disorientated. Six hours after the onset of his illness, he fell suddenly to the ground with eyes rolling and severe generalised convulsions. His temperature was 103°F., and he was found to have a few faded macular spots on the buttocks, some enlarged posterior auricular glands, and both Kernig and Babinski signs positive. He was cyanotic, and respiration was of the Cheyne-Stokes type. The cerebrospinal fluid pressure was 180 millimetres; there were 80 mononucleated cells per millilitre; sugar was 80 mgm. per cent, and Pandy's test was plus. There was a history of a generalised rash for the previous 3 days, without however, any fever, and he had not been confined to bed. He remained stuporose for 36 hours, with occasional attacks of spasticity, tremulousness, or convulsions. His fever subsided, breathing became easier, consciousness gradually returned, and complete recovery occurred. Five days after the onset of convulsions there were no abnormal neurological signs.

SEQUELAE: Margolis and his co-workers (1943) noted that 2 out of 48 collected cases had persistent sequelae, namely ataxia involving all limbs, tremor of right hand, with partial facial paralysis all clearing completely up to 2 months in the one case, and in 4 months in the other case. The latter case presented ataxic signs, staccato speech, and propulsive gait during the acute stage. This tendency for sequelae to clear up is in contrast to what tends to occur after measles encephalitis. In measles encephalitis, there is a high rate of permanent sequelae, (Ford, 1938), up to 65%, and even after chicken pox, there are sometimes permanent sequelae. In mumps encephalitis, the prognosis is good. (Wyllie and McKissock, 1949).

PRE-ERUPTIVE RUBELLA ENCEPHALITIS: Although most of the cases of rubella meningo-encephalitis are reported in the literature to have occurred subsequent to the eruption, Margolis et al (1943) mention three cases where the occurrence of the exanthem coincided with

the exhibition of neurological symptoms. However, Holliday (1950) describes a case of what appears to have been pre-eruptive rubella encephalitis. A two-year old girl developed neurological symptoms three and one-half days prior to an eruption which was typically that of rubella. Pyrexia, convulsions, coma, disorganised movements, muscular twitching and hypertonia were apparent. Sluggish pupillary reactions to light, and ataxia were apparent. No Koplik spots were seen. Cases of rubella had been seen in the neighbourhood, and three siblings developed a disease indistinguishable from rubella. Investigations were done to exclude the possibility of lead encephalopathy, infectious mononucleosis, dysentery, uraemia, acute bacterial meningitis and brain tumour. The cerebrospinal fluid, when examined on two occasions, was found to be sterile and clear with normal sugar and protein content. Cell counts showed only 10 and 4 mononuclear cells per millilitre. This patient also exhibited the leucocytosis (34,000 per cubic c.m.) so often seen with the encephalitic complications of the eruptive contagious diseases. This child improved somewhat in hospital, but at a six months follow-up study, she demonstrated personality changes and residual ataxia.

If more such cases are reported, they would provide confirmative data towards the contention that post-rubella encephalitis is not of anaphylactic origin, but rather a definite virus invasion across the barriers into central nervous system territory. The same writer describes over 20 cases of pre-eruptive measles encephalitis, several cases of pre- ....

eruptive roseola and varicella encephalitis, which data suggest that in these cases the neurological condition is of virus origin. The probable deleterious effect of pyrexia on the central nervous system as another cause of encephalopathy cannot entirely be excluded however. Harries and Mitman (1947) describe stiffness of the neck as a characteristic sign in some epidemics. Although this finding may have been due to cervical adenopathy, it is not improbable that some of these cases may have a neurological basis.

CHAPTER X.

DIAGNOSIS.

(1) MEASLES (MORBILLI, RUBEOLA).

Measles (morbilli) is under ordinary circumstances easily distinguishable from rubella. The rash is more robust, catarrhal symptoms are more evident in the former, but it must be admitted that in mild cases, or in modified cases as after the injection of protecting serum or gamma-globulin, the two diseases may be indistinguishable clinically. Koplik spots, if present, and circumstantial evidence will assist in making a diagnosis. Other factors of assistance are, in morbilli, the shorter incubation period, the pre-exanthematous catarrhal stage, the darker tint of the eruption and its gradual fading in the order of appearance. A severe measles rash may sometimes be followed by branny desquamation of palms and soles.

(2) SCARLATINA.

Scarlatina, if mild, is also difficult to differentiate, as rubella on the second or third day may present punctiform type of eruption, most confusing, and probably giving rise in the past to an artificially created entity called Fourth Disease (Dukes, 1900), supposedly intermediate between rubella and scarlatina. The scarlatinal eruption is not "kalaedoscopic" but may occasionally involve the face on the forehead and temples, where it feels rough to palpation. Otherwise, there is flushing of the cheeks and circumoral pallor. On the limb flexures, Pastia's sign (brown staining and minute petechiae) is apparent. The other signs of scarlatina may be..

present/...

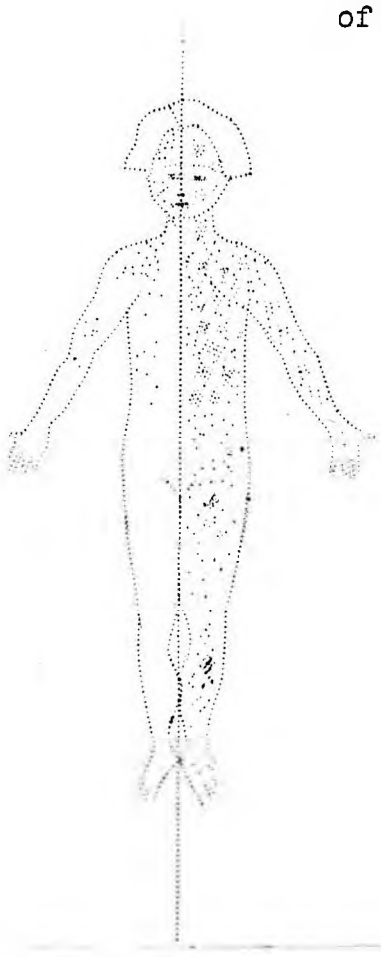


Figure 12.

Diagram showing development of measles rash (adapted from Harries & Mitman 1947). Note that the face including the circumoral area is invaded early and the density of the rash is greatest on the face and trunk.

present, e.g. strawberry tongue, sore throat etc., but it must not be forgotten that in rubella, a secondary throat infection may be present as in children with chronic tonsillitis, or the fauces may be injected from heavy smoking. The anterior cervical lymph nodes rather than the posterior group are more prone to enlargement in scarlatina than in rubella. Although late peeling under the fingernails is retrospectively pathognomonic of scarlatina, yet mild cases of that disease, may never desquamate. A positive Schultz Charlton test is pathognomonic of scarlatina.

Small infants, especially with scurfy scalps, often have enlarged mastoid, occipital and posterior cervical lymph nodes, and if a fleeting roseolar or papular rash of gastro-intestinal, allergic or sudaminiferous origin occurs, rubella is apt to be suspected.

(3) ROSEOLA INFANTUM (Exanthum Subitum, "Sixth Disease")

Roseola Infantum however, is generally confined to infants up to 2 years, rarely 3 years, and occurs no doubt more commonly than is generally recognised. When occurring in adults, it may be misdiagnosed as rubella (James and Freier, 1949). The rash closely simulates that of rubella, lasting only about 48 hours, and preceded by a stormy 3 or 4 day period of pyrexia, with restlessness, or misery and even sometimes a convulsion. (Veeder & Hempelmann, 1921). The eruption appears first on the shoulders and trunk, and may, in parts, become confluent. It involves the limbs and face later, leaving the peri-nasal area ...

relatively/...

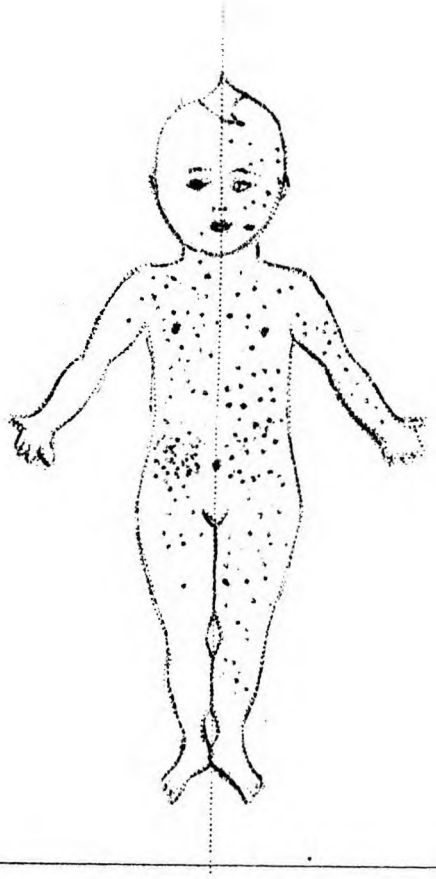


FIGURE 13.

Diagram showing development of rash in roseola infantum.

Note initial involvement of shoulders and trunk, later involvement of limbs and face leaving circumoral region relatively free.

relatively free. The maximum concentration of the eruption is on the buttocks and lumbar region. (Zahorsky, 1940). Confluence may cause a morbilliform or scarlatiniform appearance (James and Freier, 1949). Lymphadenopathy is often mild and generalised, frequently pre-eruptive (Jennings, 1940), but the posterior auricular nodes are not enlarged. The laboratory findings may be normal or leucopaenia with relative lymphocytosis and monocytosis may occur. Plasma cells are not commonly found.

(4) INFECTIOUS MONONUCLEOSIS (Glandular Fever).

Infectious Mononucleosis in the early stages may also be confused with rubella, more particularly when there is a scattered, pinkish macular rash and cervical adenopathy. The rash, however, tends to occur sparsely on the face, if, at all, and more profusely on the trunk; sometimes there is a tendency to papule formation. In the first few days, too, the blood picture may resemble that of rubella, but later there may be an increase of monocytes, and the typical mononuclear cells with fenestrated nuclei may be evident. There is great tendency for severe faucial anginal infection to occur with white fibrinous exudate. Later the Paul-Bunnel Test may become positive, and where the Davidsohn modification is employed, such a positive result is very significant. (Davidsohn, 1937).

(5) RICKETTSIAL DISEASES.

Rickettsial Diseases, especially Tick-bite fever and Typhus, in South Africa, should be borne in mind in considering the differential diagnosis of

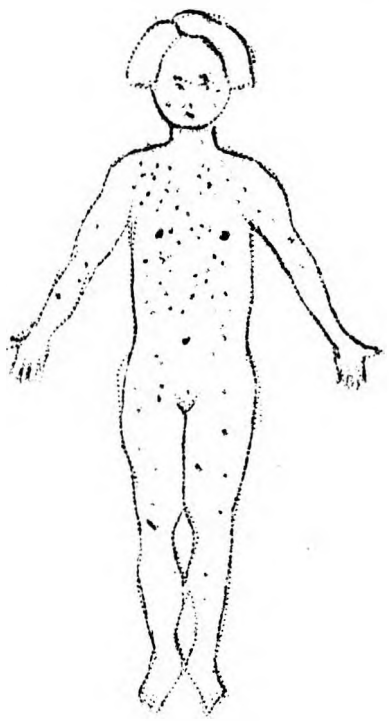


FIGURE 14.

Diagram showing distribution of rash in Infectious Mononucleosis.

Note sparse involvement of face and somewhat greater distribution on trunk.

In TICK-BITE FEVER, a rubelliform or morbilliform eruption may be present and if not diligently searched for, e.g. in the scalp or external genitalia, the typical tick-bite may escape detection, thus leading to difficulties in diagnosis, more especially in mild cases. Enlargement of the regional lymph glands may provide a clue as to the whereabouts of the tick-bite. The agglutination reactions in the blood only become positive when the clinical symptoms are subsiding or have actually subsided, i.e. usually after the tenth day of illness.

In this disease, the rash usually begins appearing from the third to the fifth day. The macules and papules may be sparse or very profuse according to the severity of the infection. The papules appear in fresh crops daily for several days and they feel shotty to palpation. Their colour is dusky and in addition to the body, which may present a dusky mottled appearance, the face, palms and soles are characteristically involved (Gear, 1941). Fever which is usually prolonged from 1 to 2 weeks, may last only a day or two in mild cases, particularly in infants and children. Injected conjunctivae are often present, giving rise to a superficial resemblance to rubella or morbilli. In LOUSE-TYPHUS (as in Tick-bite fever), there is a tendency for the rash to involve the palms and soles as well, and petechiae tend to be present. The face however, is not affected. Prostration is generally marked, and the fever is high with delirium. In children, nevertheless, the disease tends to be mild, and the rash often evanescent....

(Gear,/....

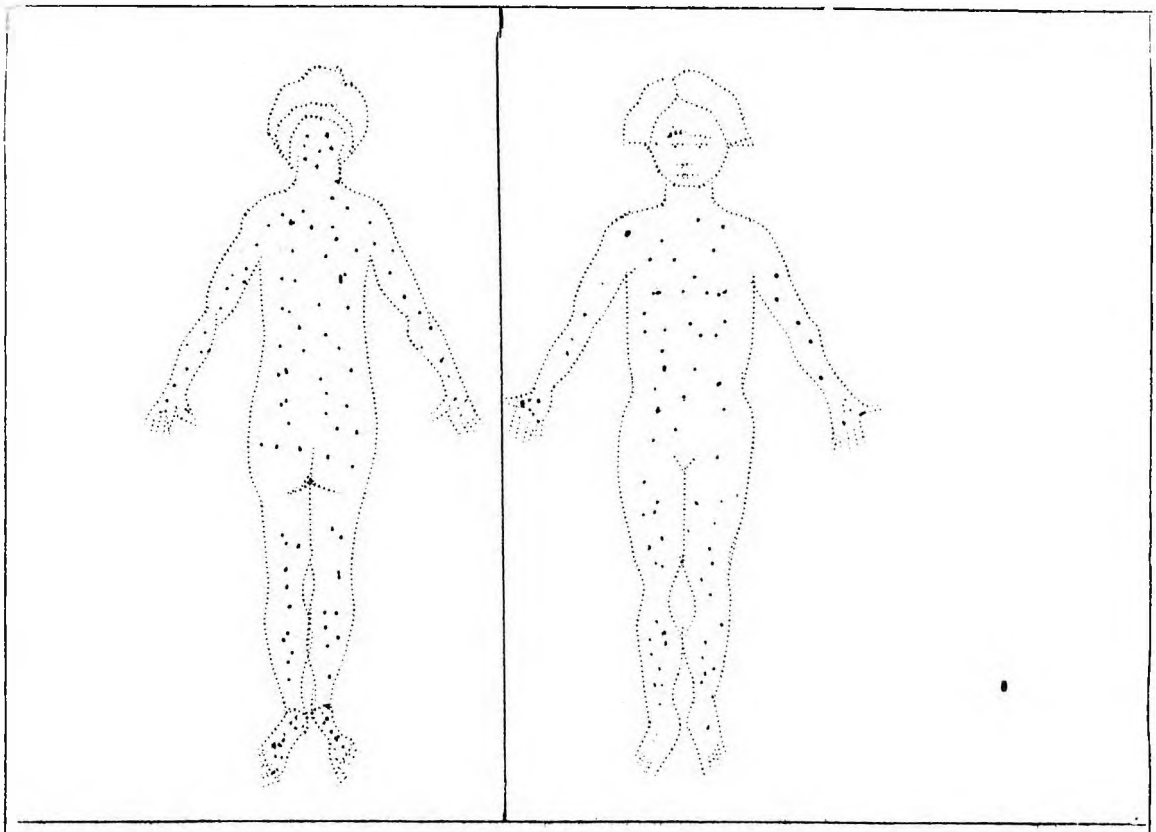


FIGURE 15.

TICK-BITE FEVER	LOUSE TYPHUS
Note generalised maculo-papular shotty rash involving face, body, palms and soles. The rash tends to be dusky in colour.	Note rash, often petechial in character involving palms and soles, but leaving face free. When petechial, the rash is to be distinguished from that of cerebrospinal fever.

(Gear, 1941). MURINE TYPHUS clinically presents as a milder form of louse typhus. In the typhus diseases, agglutination reactions become positive after the first week, and latterly complement fixation tests have been successfully employed.

(6) ALLERGIC RASHES.

Allergic rashes of all kinds are common in children, and may result from the administration of drugs, sera, foodstuffs, etc. There is a tendency to whealing, pruritus is intense, and the eruption tends to "wander". Drug eruptions, especially those following administration of sulpha derivatives, barbiturates, quinine etc., lack the "kalaedoscopic" course of rubella and may be very irregularly distributed. In allergic cases, the eruption is more deeply coloured and "blushing" than in rubella and there may be an increase in neutrophils or eosinophils of the blood. A history of previous attacks is not uncommon.

(7) PITYRIASIS ROSEA.

Pityriasis Rosea occurs very rarely in children and tends to last several weeks, although in the early stages the rash may superficially resemble that of rubella. The lesions are however, dimorphic, viz: small irregular pink macules of varying sizes, and large oval scaly plaques changing in colour from pink to fawn, one of which, the "herald spot", tends to appear first, and is larger than the rest. The maximum distribution is in the trunk, where the lesions tend to run parallel to the rib spaces, and in the proximal parts of the limbs.

(8) OTHER CONDITIONS.

Secondary syphilis may cause a roseolar rash

with/....

with lymphadenopathy. The lesions are not itchy, rarely occur on the face, tend to be coppery, and are more prominent on the flexor than on the extensor surfaces. Other signs of syphilis may be present. Erythema infectiosum (Fifth Disease) apparently does not appear to be diagnosed in South Africa, at any rate on any epidemic scale. An initial erythematous rash with "butterfly distribution" on the face precedes a polymophous eruption, on the proximal parts of the limbs gradually extending to the distal portions and finally sometimes involving the trunk as well. (Harries & Mitman 1947). Gyrate and annular patterns are very common, suggesting that the disease may be a variety of erythema multiforme (Banks H.S., 1949).

In differential diagnosis, one should always bear in mind the possibility of a rash being prodromal. For instance, smallpox and chicken pox are occasionally preceded by a scarlatiniform eruption. In the latter exanthem, too, the eruption itself may be maculopapular in the early stages prior to vesiculation.

CHAPTER XI.

RUBELLA : PROPHYLAXIS AND TREATMENT.

Now that we are cogni zant of the possible damaging effects which rubella may have upon the unborn child, the problem of prophylaxis becomes a practical issue, and one which is part of the growing branch of "antenatal paediatrics". As soon as pregnancy is diagnosed, all febrile illnesses, upsets, accidents, shocks, etc. just before, as well as after conception, should be noted. Likelihood of exposure to infection should be considered, especially during epidemics. This is in the interest of both the patient and of clinical research. A good family history extending back on both sides, to at least three generations if possible, should be obtained, to gain insight into any history of hereditary, or familial or transmissible conditions which might possibly be confused with the teratological effects of rubella, should that exanthem occur during gestation. It has been urged that rubella should be made a notifiable disease, and the fact of pregnancy occuring at the same time, should be noted. In the United States, rubella is a notifiable disease, but according to Margolis et al (1943), only about 1 in 10 cases are actually notified, due to neglect, missed diagnosis, faulty diagnosis or other causes, so that control is rendered most difficult indeed. Aycock and Ingalls (1946) who found 5 cases of congenital defect in children after the mothers had had German Measles during pregnancy, noted that in 4 of these...

cases/...

cases, the rubella infection had not been reported to Health authorities.

Women about to become pregnant, or already pregnant should be protected by propaganda and instruction. Patients of all school-going children with rubella should be warned of possible teratological consequences, and in this connection there should be encouraged a better *liaison* between obstetrician and paediatrician. All infectious diseases occurring in pregnancy, should besides having all possibly relevant, even apparently trivial facts noted, be also adequately followed up. More extensive virus research work is needed, and it is to be hoped that the present intensified virological work on poliomyelitis, may also shed light on the mysteries of rubella.

In mumps, bed-rest does not diminish the possibilities of orchitis, so that in rubella it is unlikely to affect the incidence of complications, whether neuritic, encephalitic, teratological or otherwise (Wesselhoeft, 1947[a]).

All cases should definitely be isolated, only because of the danger to pregnant females. Some writers have recommended exposure during childhood especially in females. The danger of such a procedure however, is that infected children may pass the disease on to their mothers or other females likely to be pregnant. Many mothers do not know, or remember if they have ever had rubella. Wesselhoeft (1947[a]) adopts a practical approach when he writes that, "although it is safe to say that an epidemic of rubella

should be allowed to run its course in asylums, and in boarding schools, and in such colleges as can be isolated for the time being, the same statement cannot be postulated for day-nurseries, kindergartens and day-schools, or colleges situated in metropolitan centres".

Communicability occurs just prior to the eruption, and diminishes rapidly with the disappearance of the rash. Thus isolation measures during the eruptive period are not very successful although they should be carried out nevertheless. During an epidemic, enlargement of the posterior auricular glands alone may be grounds for quarantining a suspected case of rubella (Geiger 1918).

According to Barenberg et al (1942), pooled sera prevents rubella in children for an unknown period, but there are certain dangers pertaining to such agents, viz:-

(1) Reactions due to the large quantities of serum required to be used, although Barenberg and his co-workers rarely observed any reactions;

(2) possible infection of child with homologous serum jaundice;

(3) if used upon the mother in the early stages of pregnancy, there exists the possibility of altering the protein metabolism of the mother with consequent deleterous effects upon the foetus (see Gillman's work, Chapter XIII).

Barenberg and co-workers, in an American Hospital, from 1934 to 1937 used pooled parental blood serum intramuscularly for the routine prophylaxis of contagious disease. During this period, they maintained a medical paediatric ward constantly open and free from outbreaks of contagious disease, whereas in the surgical paediatirc ward, used as a control, (no prophylactic serum being employed), ...

there/...

there was an annual loss of 34 hospital days due to contagious disease. They emphasized, too, that although it is rightly recommended to isolate all clinical cases, yet since the incubation period of communicable diseases varies from 5 to 21 days, 2 or 3 days detention in an observation ward of the hospital will not suffice to exclude all such cases from developing exanthems after admission to general wards.

They also studied the effect of the pooled parental serum upon children with a positive Schick reaction, and they found that the Schick reaction was reversed, while the blood antitoxin titre rose. (Barenburg et al, 1940). Human serum protected one half of the children for over 20 weeks, whilst in the other half (a younger age group), immunity lasted for 3.2 weeks.

From 1938 to 1941, their technique was to inject intramuscularly into the buttock of every child admitted, over the age of 3 months, 30 c.c. of either the pooled parental serum, or later, pooled bank plasma. (Barenburg et al., 1942). When a case of primary contagion occurred, all the children not having had plasma within the previous 10 days, were re-inoculated with the same amount of plasma as soon as they reached the 10th day following the previous inoculation. The problem was to confer protection once the incubation period had been initiated, and they found a significantly lower incidence of infections than in the control group. As they say, "considering the fact that the epidemic of measles in 1940-41 was the most widespread in the history of New York, and that very few children escaped the disease, the low...

incidence/...

incidence of primary cases ..... is almost inconceivable" (in the wards where prophylactic serum was being used).

It was also pointed out that there may be a vast difference between the serum obtained from a person with low antibody titre, and pooled serum containing a higher concentration of antibodies. They consider 5 - 6 cc. of convalescent measles serum sufficient for protection if given early in the incubation period, but unfortunately, except in the case of diphtheria, it is impossible to measure the antibody titre of the exanthemata and other contagious diseases so prevalent amongst children. As the initial infection confers passive immunity for ten to 14 days, an additional injection was given to patients not receiving an injection 10 days prior to exposure. In the first 2 days of the incubation period, small amounts of serum will modify the disease, while large amounts protect. After the fifth day, larger amounts rarely protected.

As regards rubella, the same investigators were faced with presumptive evidence of the efficacy of pooled serum. A resident medical officer and a ward attendant went down with rubella. However, all the children except 2 (who had previously had definite measles, and hence had not been inoculated like the rest within the previous 10 days), escaped the disease, notwithstanding the fact, that when rubella develops in a ward, there is great difficulty in stopping the spread, and these children had been exposed to rubella repeatedly and intimately

during/....

during its most infectious stage.

The value of gamma globulin in preventing rubella appears to be doubtful. Greenberg (1947) cites two series of cases. In the one group of 40 infants between the ages of one and two and a half years, who had been exposed to rubella, every alternate child was inoculated with 5 cc. of gamma globulin one to four days after exposure. Six children, all controls, developed German measles 11 to 19 days later. However, the group studied was too small, and the exposures in an institution too irregular to draw definite conclusions. In fact, in the other series cited by Greenberg, 29 out of 58 exposed children in an institution were injected with 2 cc. gamma globulin. In from 12 to 23 days after the inoculations, 5 cases occurred in the injected children, and 7 cases in the controls. Was the dose of gamma globulin perhaps too small? Or is it not a very efficacious prophylactic agent? Gamma globulin extracted from convalescent serum was given to 22 presumably susceptible pregnant women all of whom had been in proved or possible contact with rubella. Although none developed a rash, the evidence in favour of the efficacy of gamma globulin is still not overwhelming. Nor is it certain that it will modify an induced infection without interfering with subsequent immunity (Lancet 1948).

McLorinan (1949) obtained encouraging results in 63 pregnant women by inoculating them less than a week after contact with rubella. He used an individual dose of 2 millelitres of gamma globulin derived from the sera of 55 patients in a Naval Depot convalescing from German measles. The average time of

collection/...

collection was 23 days after the attack, and the gamma globulin fraction was prepared showing an eight-fold concentration of antibodies commonly found in pooled serum. This serum was given over a 12 month period to 63 female contacts, who with 3 exceptions were in the first four months of pregnancy. Most were given the serum less than seven days after contact, and fifty-eight showed no symptoms of rubella. No reports had been received from five others. Up to the time of McLorinan's report, 13 had been delivered of apparently normal babies. Two had aborted hydatidiform moles at four and a half, and five months respectively. In all but one of the others, pregnancy appeared to be progressing satisfactorily.

McLorinan admitted that there might be a doubt as to whether all the infected persons with whom contact had been reported, were definitely suffering from rubella. Nor was it certain whether any of the women, who had been treated with gamma globulin, had not had rubella previously. He also mentioned the possibility of some of these treated women having developed subclinical attacks of rubella, which might yet be associated with teratogenous effects.

At present, it would seem that the answer lies in the perfection of a vaccine of modified rubella virus, which would produce immunity without being communicable. If sexual reproduction does occur in virus as is claimed (Delbrück et alter, 1948) then we have another potential mechanism for creating such a beneficial variant strain.

F.M. Burnet, et al. (1948) on the basis of...

successful/....

successful experimental transmission of rubella to volunteers by filtered throat washings, which can be kept active indefinitely by refrigeration, has proposed mass active immunisation. He suggests the "possibility of a seaside holiday camp where a woman could spend a fortnight to be immunised without any risk of infecting others". Such a procedure hardly seems to be practicable, however. The danger of artificial immunisation by means of infective material, lies in the inadvertent transmission of other virus diseases, as for example poliomyelitis.

Also, in considering the prohylaxis of rubella, the use of a mask in special circumstances, and such a mundane method as the application of soap and water on the hands, should not be forgotten, because the possibility exists that a virus may be transferred from nose or mouth of one patient to another susceptible person via the intermediate contamination of the hands. (Wesselhoeft, 1946). A mask, too, once adjusted should never be touched with the hands.

Should a woman who has developed rubella in early pregnancy be therapeutically aborted? This question is discussed at a later stage (See Chapter XXI)

Post-rubella encephalitis is a rare complication, but one which should always be looked out for, especially as residua may only become obvious after the acute symptoms have passed off. Of such residua, the most important are personality changes. The major problem facing such children is readjustment to their social environment, and this applies to the teratogenous effects of rubella in children as well.

As/.....

As a result of the child's illness, adverse environmental factors may arise which not only affect the child, but its parents as well. Financial and social embarrassment may consequently ensue, and the unity of the whole family may be threatened as a result of an abnormal child within its midst. The child too, has to establish relationships with individuals who fail to realise that they are dealing with a sick child. Hence early recognition of such cases is urged so that prophylactic measures may be taken to help the family as a whole. One should assess the time needed to keep such children out of school. Since great improvement tends to occur in the first year following encephalitis, a year's vacation may be advisable in many cases. (Spragins et al., 1950).

There is to date, no evidence as to what value are the newer antibiotics such as aureomycin, terramycin and chloramphenicol in the prophylaxis of rubella, or the treatment of severe complications such as encephalitis.

CHAPTER XII.

TERATOLOGY.

1. CONGENITAL DEFECTS: DEFINITION AND INTRODUCTION.

It would be advantageous at the beginning to indicate most clearly what is meant by the term "congenital". "Congenital" implies present at birth, even if not manifestly so to the naked eye, and the term has no aetiological significance at all. The opinion is held in this thesis, that whenever an abnormal process at birth is demonstrable, whether by biopsy, radiology, laboratory or later autopsy findings, the term "congenital", may be applied in description. Sometimes a distinction is made between "congenital" disease, (where the accent is on the pathological process), and congenital "anomaly", "defect", "malformation", "deformity" (where the accent is in increasing degree according to the term used, placed upon the morphological aspect.) A foetus with very marked malformations is called a "monster", and the scientific study of the abnormal end products of embryological development is termed "teratology" (Arey, 1946).

Included under the term "congenital" as defined above, are the group of injuries incurred by the foetus while in the process of birth itself. To distinguish these, they are better called "birth traumata" or "natal" or "neonatal diseases". Examples are:-

Fractures:	e.g. of clavicle, extremities, skull, vertebrae, jaw, etc.
Visceral injuries:	rupture of lungs, liver, brain, etc.
Haemorrhage:	cephalhaematoma, haematoma of sternomastoid, intracranial haemorrhage, adrenal haemorrhage, soft tissue injury, caput succedaneum, etc.

Peripheral/....

Peripheral Nerve Injuries:	e.g. Erb-Duchenne, Klumpke Paralysis, sciatic palsy, facial palsy, etc.
Post-anoxic injury.	e.g. cerebral palsies after long labour, narcosis during parturition, Iso-immunisation, etc.

Many cases of mental deficiency have their origin prenatally in non-genetic causes. After the birth of such mentally defective children it is often difficult, and sometimes impossible to determine into which group the case falls. Yannet (1950), in a study of institutionalised defectives assessed that about 45% of cases were due to gentically determined factors. About an equal number, 46%, were due to factors operative before birth, but of unknown or questionable nature. Here he includes mongolism, congenital cerebral palsy, and undifferentiated types. Thus almost 90% of all admissions to the institution were due to developmental anomalies resulting from a wide variety of aetiological prenatal factors. Only about 10% were caused by natal and postnatal factors, there being twice as many of the latter group.

Congenital disease, apparently often represents the expression of foetal injury short of causing death. Thus measles may be lethal and cause an abortion, while German measles which is a milder injurious agent causes malformations. All forms of interference, whether chemical, nutritional, infective, actinic, etc., alter the environment in such a way as to retard growth and development in a greater or lesser degree. The interfering agent may act just once as in the case of rubella or X-radiation, or be chronic in nature as in the case of syphilis or nutritional deficiences.

Nutritional/...

Nutritional deficiencies, however, are rarely powerful enough to cause malformations. Thus a severe diabetic may be sterile; treated with insulin, she may conceive though abort; or if she has viable offspring, there is likely to be a higher incidence of congenital malformations amongst them. Or the genetic constitution may be such, that the best environment we are able to provide to date, cannot save the foetus. For example, a hetrozygous individual with brachyphalangy is viable (one dominant factor in the germ cell); yet a homozygote cannot survive (two dominants). So we see again, both genetic or environmental upsets may cause the same type of malformation. The stage of embryonic development, or activity, at which the organism is attacked, tends to determine the nature and extent of the malformation. Thus rubella may produce cataract, microcephaly, or congenital morbus cordis, depending on which structure, at the time of infection, is hardest hit. Unfortunately, today, many external factors and many genetic factors causing anomalies are unknown or ill-understood.

Common misapprehension is to regard congenital as hereditary. While some hereditary disease may be congenital, they are not invariably so. A child may be born with congenital syphilis, for example, but does not inherit it, inasmuch as the disease is not based on genetic factors, but on infection acquired from the mother in utero. The spirochaetes pass from affected organs inside the mother, through the placenta, and infect the child antenatally, so that syphilis is manifested at birth, or later

in /.....

in childhood. In the latter case, the process is still congenital, being deducible as such by various methods. Obviously in such cases the division between congenital and postnatal disease is very fine, and rests upon the demonstration, in one way or another, of the particular morbid process, at birth. With better diagnostic methods, in future we shall probably find more cases to be of congenital origin, which are now regarded as post-natal.

In syphilis, the father cannot directly pass on the disease to the foetus, without first infecting the mother; the sperm cells are not affected genetically. Even though the disease may rarely reappear in a child in the third generation, it is acquired by infection from a congenitally syphlitic mother. Thus a congenital disease may be "transmitted" through three generations, without actually being hereditary. Of course independant infection may occur in the third generation.

In congenital syphilis, the mother harbours the disease in either manifest or latent manner. The father may also have a latent infection, becoming so spontaneously, or as a result of insufficient treatment; or he may actually have been cured, thus appearing to be normal at the time of his child's birth.

Just as in the past, infants used not infrequently to contract syphilis from wet nurses, so, today many European infants contract the disease from handling by infected Bantu servants; and such cases are sometimes mistakenly regarded as being of congenital origin. However, the history, search for a primary chancre (easily overlooked in an infant), and

clinical and serological studies of the affected child, its parents and all contacts, will provide the correct answer. Of course, older children, usually above the age of 10 years may occasionally acquire the disease by sexual contact (Smith, 1949), and the fact that syphilis of congenital origin may only become manifest later in childhood, tends to confuse the issue. Hence it behoves the investigator very carefully to evaluate his findings before coming to a conclusion regarding the aetiology of syphilis in a child.

A mother suffering from primary syphilis has about 90% chance of transmitting the infection, so that abortion will take place, or a diseased foetus be delivered. Syphilis is, however, not a common cause of early abortion (Whipple & Danhorn, 1938), In late pregnancy, however, maternal infection may be consistent with the birth of a child who appears to be normal, only to manifest the disease later on. Generally speaking, the less active the disease in the mother, the more likely is the foetus to have the malady in a milder form, if not to escape it altogether. However, latent syphilis in the mother is no guarantee against infection in her child, and although there is a tendency for the disease to manifest itself in lesser and lesser degree with each successive pregnancy, this is not invariably so. The classic sequence of events is that of abortions, stillbirths, syphilitic and then normal children, but an infected woman may give birth to a syphilitic child after first producing a normal one. In fact, syphilitic children have been born 15 to 20 years after the mother originally became infected. Early treatment of the mother in

a/....

pregnancy reduces the risk of transmitting the disease.

It is important to note that a child with congenital syphilis may have a negative serological reaction, because it has not yet had time to develop allergy or sensitivity to the infection. On the other hand, a congenitally positive test may result from maternal antibodies being transferred into the foetal circulation in the absence of any foetal infection. Diagnosis is made on radiological and other grounds. After 6 months, the tests are extremely reliable in congenital syphilis. Cases responding to anti-leutic theraphy may yet continue to have a positive serology for several months. Repeatedly doubtful reactions in childhood, in the absence of previous theraphy, are almost invariably due to causes other than syphilis. (e.g. malaria), because serological reversal cannot occur except over a very long period.

These observations about congenital syphilis are dealt with at some length, as they serve so well to illustrate the difficulties encountered in separating effects produced by Nature and Nurture. Here we have a disease, which is congenital; and in which the acquired type may be mistaken for the congenital form; which may be "familial", affecting several sibs; which may "skip" several members; where the parents may appear outwardly normal while passing on the disease; where a positive serological reaction may be "inherited" at birth from the mother; where "pleiotropic" and "lethal" action may be demonstrated in different sibs; and where the disease, "concealed" at birth, may show up later in childhood. And yet, in this disease where the sins of the fathers are visited upon the children, heredity plays no part.

(2) GENERAL SURVEY OF CONGENITAL MALFORMATIONS.

Mall (1917) is reported by Gates (1946) to have studied 1,000 pathological embryos, and to have discovered that they aborted in the first half of pregnancy, while, nearly all embryos with slighter malformations also aborted before the middle of pregnancy, relatively few reaching full term. Landtman (1948) found 19.5% of the mothers of malformed children had had previous abortions as against 7.5% in the control group without malformed children. He also observed that ante-partum haemorrhage occurred more often in pregnancies resulting in the birth of deformed children. The incidence of this disorder was 20.5% and 4.3% respectively in the two groups. Worcester et al., (1950) also found a higher rate of threatened abortion amongst mothers of deformed children. They consider investigation is needed to determine whether prenatal bleeding is a cause or effect of malformation.

Primogeniture, multiple births etc.

Macklin (1938) investigated further 1420 reports of congenital malformations, and found heredity to be the most important aetiological factor. Among 72 pairs of twins, in 32 pairs, both twins were affected and the sex distribution of the other 40 pairs indicated that they were mostly DZ (dizygotic) Types. In 311 families, there were 2 cases of malformations per family, and in 80% of these, the two

anomalies/....

anomalies were identical. The evidence here, is therefore very strongly in favour of hereditary factors. McFarland and Meade (1932) support these observations by their work with MZ (monozygotic, "identical") twins.

Stillbirth:

Murphy (1940) surveyed 130, 132 births in Philadelphia over a 5 year period (1929-1933):

Malformations 1476 - 1.13% .

7,478 Stillborn : 222 cases (2.97%) (had congenital malformations.

122,654 live born : 668 cases (0.54%) (had congenital malformations.

130,132 total births.

Malformation in stillborn were thus 5.6 times more frequent than in liveborn. About 25% of the congenital malformations were in stillborn. One in 213 of liveborn of this series showed congenital anomalies (0.5%)

Many causes of neonatal deaths are the same as for stillbirths, and it is found, that where the stillbirth rate is high, the neonatal mortality is also high (Baird 1945). Congenital abnormality as a cause of neonatal mortality varies to some extent with the stillbirth rate, since it has been shown that as the stillbirth rate falls, the death rate from congenital malformation increases. Presumably this is due to a greater number of infants with anomalies being born alive instead of dead.

Murphy also found that :- Malformations in Negroes were half the rate in whites in spite of their low economic level. (Miller, 1950, also found a lower incidence of malformation in Negroes.) There was no higher rate of malformations amongst illegitimate births.

In families/....

In families with a malformed child, the birth of a second is 25 times more frequent than in the general population.

Murphy stated that the mothers of malformed children were not unhealthy, but older mothers appeared more likely to produce a malformed child. Landtman (1948) also found that the mean age of the mothers with malformed children was significantly higher than the maternal age of controls where there were no malformed progeny. Worcester et al (1950) found that the mothers of defective infants, and the neonatal mortality of normal infants showed the same association with advanced maternal age. From their data, however, these workers were unable to establish a relationship between age of the mother and the incidence of congenital malformations, except in the case of mongolism.

Malformations were slightly more frequent in the lower socio-economic groups according to Murphy but there appeared to be no relation to chronic illness, or syphilis of the parents at time of conception.

Types of Malformations:

In 6.? per cent of cases, a congenital malfortion was found in the family of one or both parents. In families with 2 malformed children, the defect was identical in 50 per cent of cases (Murphy).

Murphy's widespread survey disclosed that of all types of congenital malformations, 60% were in the central nervous system, chiefly:-

Hydrocephalus (with or wihout spina bifida),
Meningocoele,
Craniorachischisis,
Encephalocoele,
Anencephaly,
Microcephaly,
Mongolism.

Worcester et al (1950) found polyhydramnios to occur in 10% of pregnancies which resulted in a malformed infant. Sixty per cent of pregnancies with polyhydramnios were found to result in anencephaly.

ALIMENTARY SYSTEM: 46.9% of malformations of the gastrointestinal tract were pyloric stenosis. (Murphy).

pyloric stenosis 46.9%
atresia of oesophagus, smallgut, or anus 24.7%

SKIN -MUSCLE-SKELETAL SYSTEM: The distribution of different types of anomalies within this system were (according to Murphy):

Cleft palate and hare-lip :	44.7%
Gastrocshisis (abdomen not closed):	13.6%
Malformations of extremities :	11.7%
Hernia or absence of diaphragm :	6.7%
Dislocation of hips:	3.6%

Other Factors:

Murphy's survey was comprehensive and included observations on diet, use of tea, coffee by mother, menstrual irregularities, pelvic inflammation in the maternal parent, and many other factors. He found that, "in families containing two malformed siblings, the subsequent defective child is more likely to be born later in the family than it is to be the next child in order of birth to the first defective sibling. In families possessing congenitally malformed children and in which miscarriages, premature births and stillbirths occur, the latter are usually likely

to occur/....

to occur close to the time that the malformed child is born rather than very early or very late in the reproductive life of the mother. Many mothers did not conceive after the birth of their defective offspring; none of this group was under observation for as long as five years. Every woman who was followed for that length of time experienced, during or after that period, one or more subsequent conceptions. This observation suggests that any fear of giving birth to a subsequent malformed offspring failed to prevent conception after a five year period had elapsed. The normally developed siblings exhibited no unusual morbidity or mortality."

Murphy (1940) also found that very few of the mothers with congenitally deformed offspring had used contraceptive vaginal douches. There was also no unusual frequency of placenta praevia, nor did season of year appear to affect the incidence of anomalies. (These investigations were done from 1929 to 1933, i.e. before the widespread rubella epedemics). Worcester et al (1950) found a certain seasonal relationship for malformed infants whose defects required presumably more than one month for development. Such defective infants showed higher birth incidence during the third and fourth quarters of the year. Conception and organogenesis is therefore related (in U.S.A.) to times when respiratory diseases are common. Certain malformations appeared to affect one sex more than the other.

As regards the mothers of congenitally deformed children, Murphy found their diets to be significantly lacking in adequate amounts of calcium, phosphorus,

iron/....

iron and vitamins B, C and D. Landtman (1948), in his series of cases in England, did not find vitamin deficiency to be a significant factor in the production of congenital malformations. Worcester et al (1950) found twinning to occur with approximately twice the expected frequency in stillbirths as compared with ordinary births.

During pregnancy, the most commonly observed physiological abnormalities, according to Murphy, were polyhydramnios and abnormality of foetal movement. Of all the malformed individuals studied, 90% were either stillborn, or died within the first year of life. Although it has long been known that children may be born underweight after toxaemias of pregnancy, Landtman (1948), and Worcester and co-workers (1950) found the toxaemias to cause no greater incidence of abnormalities than in healthy controls. Worcester et al (1950) found 21 per cent of mothers who gave birth to infants with multiple anomalies, suffered from chronic illness, as compared to 9.9 per cent of mothers in the total series. They did not find maternal heart disease to be an important factor in the aetiology of congenital defect, but hyperemesis seemed to be related to a higher incidence of anomalies.

Murphy also found wide differences between the ages of the parents to be of no significance, nor did he find any correlation between the incidence of congenital anomalies, and the occupation of the father. It is interesting to speculate about the possibly increased incidence of congenital anoma-

lies in the future descendants of radiologists. Cantarow and Trumpar (1944) give figures which show as unusually large proportion of stillbirths occurring in the children of fathers exposed to lead. In 9.5 per cent of cases of congenital cardiac disease with adequate records, the father's occupation involved continued exposure to lead, as in the case of painters, or workers in battery plants. This evidence is suggestive, but not conclusive.

The vast majority of mothers had uneventful pregnancies, so that maternal morbidity only affects the incidence of congenital anomalies in a minority of cases. Genetic factors are actually the most important aetiological agents, and, although in the succeeding sections of this work much space is devoted to rubella as an aetiological factor, it is important to retain a correct sense of proportion in regard to its frequency as a natal crippler. For instance, in late years, it has been assessed that, in cases of congenital morbus cordis, only about 1 per cent of cases can be traced to rubella (Dogramaci & Green, 1947).

On the other hand, the seriousness of congenital malformations as a cause of neonatal death can be realised from figures provided by the United States Bureau of Census (Children's Bureau, 1941.)

TABLE I.

COMMON CAUSES OF DEATH IN THE FIRST MONTH OF LIFE - 1941

TOTAL NUMBER OF DEATHS - 69,559

CAUSE	NUMBER OF DEATHS	PER CENT OF TOTAL
1. Premature Birth	32,278	46
2. Injury at Birth	10,662	15
3. Congenital Malformations	7,947	12
4. Respiratory Diseases	3,444	5
5. Gastro-enteric Diseases	1,412	2
Deaths represented in this group	55,793	80

On the above figures, the actual percentage of neonatal deaths caused by congenital malformations should be upwards of 12 per cent because many of the prematures failing to survive the first month of life, probably had serious congenital anomalies as well. Prematures are also more susceptible to the effects of birth injury. Spence and Miller (1939) point out however, that in England, at least in one-third of the total cases of infantile deaths, the causes of mortality as recorded on death certificates are inaccurate; and in the United States some similar error must obtain. Nevertheless, if congenital anomalies could be eliminated, much wastage of life and suffering could be spared.

In fact, Miller (1950) found an even higher incidence. Miller gives figures obtained from an investigation made upon the incidence of congenitally determined defects and diseases in the neonatal popu-

lation/....

lation at the University of Kansas Medical Centre. Histories of all infants weighing 1000 gm. or more and born from 1944 to 1948 inclusively with congenital defects or disease, were reviewed. Out of 4095 consecutive births including stillbirths, 89 or 2.2 per cent were found to have either congenital malformations or diseased states caused by maternal syphilis, diabetes or iso-immunisation. *Twenty per cent of the stillborn infants, 30.8 per cent of the neonatal deaths and 1.3 per cent of the surviving infants were either congenitally defective, or had some disease related to prenatal conditions in the mother. Most of these 89 infants had some congenital defect.* There were only 23 of these who had either congenital syphilis, erythoblastosis foetalis or were born to a diabetic mother; the remaining 66 had congenital defects. A further analysis revealed that the incidences of congenitally determined diseases and defects were both higher in premature infants than in full term infants, viz. 7 per cent in premature infants as against 1.6 per cent in full term children. It was also found that more white infants had prenatally determined diseases than did Negro infants, largely because there were more white infants who had erythoblastosis foetalis. The incidence of congenital malformations was about the same in both races, although 16 of the 36 Negro infants with anomalies had supernumerary fingers. If only severe malformations were taken into account, then white infants had a higher incidence of these. There was a high incidence of CNS defects which corroborates the findings elsewhere.

Congenital abnormalities associated with diabetes mellitus in the mother were according to Warkany, (1947) and other investigators, as follows:

Harelip, agenesis of gall bladder, septate uterus and vagina, agenesis of left femur and fibula, syndactylism, double ureter, hydro-ureter, hydronephrosis, cor biventriculare, hypoplasia of aorta, bicuspid pulmonary valve, anencephalus, agenesis of kidneys, ureters and bladder, and persistent pupillary membrane. One or many of the above defects were found in 7 out of 19 autopsies on children born to diabetic mothers. Barns (1941) also lists congenital heart disease, deformity of the arm, and abnormal vascular supply to the lower limbs as occurring in 3 children of 21 diabetic mothers.

CHAPTER XIII.

TERATOLOGY (Continued)

PATHOGENESIS OF POST-RUBELLA CONGENITAL MALFORMATIONS.

H. Spemann (1938) and others working on amphibian embryos showed that sublethal noxa, such as cyanides, alcohol, heat, cold, ultraviolet light, and alkaloids applied to the developing embryo may produce structural anomalies due to interference with cells which are rapidly dividing. Not all parts of the embryo are growing at the same rate, and hence the ill effects of noxious agents would appear to depend on the stage of embryonic development. Those cell masses which are proliferating most rapidly, are electronegative relative to those parts where protoplasmic activity is at lower ebb. Susceptibility to poisons can be shown to be directly related to the extent of metabolic activity, cellular proliferation, and electronegativity. Such active regions are the first to succumb to poisons in high concentration, although with low concentrations, they may be the quickest to become "acclimatised" (Lancet 1947).

In mammals, the effects of X-Rays, trypan blue (Gillman, 1948), and other noxaeare being studied. The evidence seems to point to the fact that the type of induced anomaly is related to the stage of development at the time of injury, rather than to the nature of the noxious agent itself.

The mode in which the rubella agent induces pathological lesions in the foetus has not been elucidated. Is it transplacental invasion by the virus itself of embryonic tissues? Is it transplacental passage of toxins? Or is it disturbed maternal metabo-

lism/....

lism consequent on infection of placenta or maternal tissues?

There is established in the human embryo at the end of the second embryonal week, a completely closed blood circulation with a heart, two aortae, an umbilical artery anastomosing in the chorion with two umbilical veins. At this stage, when the developing organism is only 1.3 millimetres long, there is already a barrier formed between the mother and embryo, where an exchange of substances takes place. Mobile germs such as *Borrelia recurrentis*, *Eberthella typhosus*, and *Plasmodium malariae* may penetrate the placenta with only transitory or slight epithelial lesions. Other mobile organisms such as *Treponema pallidum*, however, cause severe placental changes. Some immobile organisms like the tubercle bacilli, pyogenic cocci and leprosy bacilli, can by epithelial destruction pass through the chorion into the foetal circulation. Filtrable virus , especially chicken pox has long been known to be transmitted to the newborn, and hence may imply passage of the organism through the placenta. A case of congenital rubella has even been reported. Presumably the small size of virus particles is a factor in their possible transplacental passage by some process of absorption with ultra-filtration, and differences in permeability may be related to the molecular size of different viruses. (Werthemann, 1948).

Goodpasture (1942) inoculated the virus of herpes simplex and vaccinia into the chorio-allantoic membrane of the chick embryo. Widely disseminated....

areas/....

areas of focal necrosis within the embryo were subsequently noted, whereas the same viruses implanted into adult hens produced no effects at all. Similar experiments performed on chickens produced only mild lesions. Experimentally, the virus is found to affect tissue much more when the latter is in an active state of proliferation, and this result is consistent with the findings in rubella. Gallagher and Woolpert (1940) demonstrated that mammalian tissues (rabbit) were much more susceptible to virus infection in the embryonic than in the adult state.

On this basis, the inference is, that when the rubella virus attacks the embryo after the organogenetic period, the disease in the embryo resembles that in adults, modified of course, by the peculiar environmental circumstances obtaining in the embryo. During the organogenetic period structural defects may originate due to arrested or impaired development. For example, measles may be congenital; even a case of rubella in an otherwise normal infant has been reported at birth; smallpox contracted by a pregnant woman after the fourth month of gestation, produces pock-marks in the child, visible at birth; syphilis contracted by a mother in pregnancy may cause, in the child, congenital lesions resembling adult lues. The fact that cataract and deaf-mutism do not commonly occur together after foetal rubella is also significant in view of the fact that the eye and ear do not begin to develop in the embryo at the same time.

Brown (1944) discusses the question of post-rubella defects occurring through the virus attacking the adrenal gland. He produces evidence in favour of

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the embryonic adrenal cortex controlling the development of the brain, and probably also of the heart and other structures. It has long been known that anencephalic monsters are born with abnormally small adrenals, (Boyd 1944), and according to Brown, major congenital defects are associated with only one constant locus of abnormality, viz. a hypoplastic adrenal cortex. A normal embryo, on the other hand, has a very marked adrenal cortex, and the gland itself is larger than the kidney. Furthermore, post-rubella infants show many signs suggestive of adrenal hypofunction, namely, retinal pigmentation, anorexia, asthenia, susceptibility to infection, and persistent thymus. Other symptoms possibly related to hypo-adrenalism are, arrested development and prematurity, immaturity, pyloric stenosis, glaucoma and mongolism. It should be noted, however, that the embryonic adrenal gland does not function along the physiological lines of later life (Swan, 1949[b]).

Mesodermal elements and ectodermal elements would seem to be particularly susceptible to the action of rubella virus. Apparently not only cell-proliferation, but also cell differentiation, are factors concerned. The lens and cochlea are frequently involved, as is the mesoderm of the cardiac anlage. Gregg observed a dry, scaly, eczematous condition of the face, scalp, and limbs, very resistant to treatment. Hypospadias also occurred. (The distal part of the urethra is of ectodermal origin.) Dental defects also probably originate in ectodermal anlages; but high, arched palate, large anterior fontanelle, spina bifida occulta, bifid

sternum/....

sternum, fusion of radius and ulna, talipes equino-varus appear to be mesodermal in origin. The fact that cell differentiation is occurring, appears to be important. In microphthalmus, both ectodermal and mesodermal structures appear to be affected, but are they affected concurrently, or is the anomalous development of the one dependant on the arrest of the other? In other words, are some of the deformities not the result of interference with secondary or tertiary organiser action?

The high incidence of cardiac lesions after maternal rubella, and the occasional demonstration of sclerotic lesions in the kidneys, (Swan, 1944) suggests that the rubella agent has a strong affinity for vascular tissue. Involvement of the lens with cataract formation, has been ascribed to secondary effects following damage to the hyaloid artery. Gregg's original observations, that the worst cases of maternal rubella tended to show the worst foetal abnormalities, has not been substantiated in the light of recent work.

Are the cardiac lesions associated with maternal rubella, the result of a foetal endocarditis? Farber and Hubbard (1933) point out that cardiac malformations may be divided into two groups. The first, comprising severe disturbances of structure, is caused by a primary abnormal development. The second group consists of stenoses or atresias of ostiums in otherwise normal hearts, and may be produced by endomyocarditis in the embryo. Gruenwald (1947) has said that microscopic study of the..

latter/...

latter group has sometimes supported the theory of inflammation followed by fibrositis and calcification.

Abnormalities of the blood vessels are in general relatively frequent. The inferior venae cavae and many retroperitoneal veins are subject to considerable anatomical variation. The complex pattern of the embryonic veins rather invites variation in development, but hereditary anomalies of veins are recorded. Gruenwald (1947) also discounts the theory that abnormal renal vein vessels cause dystopia of the kidneys, because it is now known that permanent renal vessels only develop after the kidneys have reached their final location. In early chick embryos, as a result of anoxia, riboflavine deficiency and other causes, abnormalities of the extra-embryonic vessels appear as forerunners of complex malformation syndromes. (Byerly, 1926).

Abnormalities of the blood and blood-forming tissues may be primary, on a genetic basis, or secondary to other defects, where the anaemia is compensated for by excessive extramedullary blood formation. In chondrodrystrophy where there is insufficient space in the skeleton for marrow, abnormal blood-forming tissues are found.

Ingalls (1948) noted that in 12 out of 77 cases of congenital encephalo-ophthalmic dysplasia there were, in addition to the eye and cerebral defects, also single or multiple haemangiomata in the skin, and in 1 fatal case, gelatinous masses of haematomatous tissue were found at the base of the brain. A significant correlation was found to

exist/....

exist between the ocular and other lesions, and maternal toxaemia and placental haemorrhages. These maternal disturbances occurred during the second trimester of pregnancy, or a little later. At this period, under normal conditions, the differentiation of the primary vitreous is completed, and its sheath disappears. This suggested that this process of involution is assisted by foetal anoxia resulting from maternal toxaemia, or placental haemorrhages at such a time. If this hypothesis is correct, it might also explain the occurrence of ordinary cutaneous haemangiomata, and also of the rare Lindau's Disease, where there is retinal and cerebral angiomatosis. The same theory of arrested development of particular tissues leading to aberrant growth, is applied in explanation of the multiple deformities in the ocular lens, heart and brain that occurs in the developing foetus after maternal rubella; only the different distribution and character of the defects may be due to the noxious agent operating at an earlier period of development, namely the first trimester of pregnancy. The multiple defects of mongolism, occurring also at an early stage of foetal life, are also explained by the same theory of arrested development of the tissues due to vascular faults, and subsequent failure of oxygen supplies. In mongolism, congenital encephalo-ophthalmic dysplasia, and post-rubella congenital defects, is postulated a common basic defect, which may be caused by different agents (e.g. bleeding, toxaemia, infections, multiple or premature births), and which may produce different patterns of

defects/...

defects according to the stage of development, the severity and site of the lesions, and the secondary changes. Genetic factors apparently play no significant part in the production of such anomalies. Worcester et al (1950) found that 39.4 per cent of mothers who gave birth to congenitally deformed children, had haemoglobin levels below 75 per cent, thereby also suggesting an anoxic aetiological factor.

Several interesting questions have arisen. In the first place, it is a remarkable fact that the unusual type of cataract following rubella has never been noticed before Gregg's memorable investigations. There are two likely alternative explanations for this. According to the first hypothesis, German measles had been so infrequent in years prior to 1941, as to allow a vast non-immune population of susceptibles to arise, whilst wartime conditions facilitated spread of infection. Thus it was that considerable numbers of women were attacked in early pregnancy, giving rise to an abnormally high incidence of that special type of cataract hitherto unrecognised. This theory is the most probable, but other writers postulate an unusual virus strain as the producer of such syndromes of congenital disease. In support of this, they also describe the prevalence of sore throats in Australia coincident with the rubella epidemics. They also refer to Fox and Bortin's cases (1946), where there was apparently a lower incidence of congenital abnormality following rubella. However, the sore throat epidemics in Australia appear to have been an infection where the organism *Haemophilus influenzae* predominated, as established by cultures

(Swan/....

(Swan et al 1943), and such cases were quite unrelated to rubella. One female in Swan's series who contracted such a throat condition early in pregnancy incidentally had a normal child. Meanwhile from all parts of the world evidence has collected to show that rubella apparently affects the incidence of congenital abnormality in a fairly uniform manner. Fox and Bortin's results are possibly the nature of "flukes"; nor can errors of diagnosis be excluded, as the series was very small, (12 cases). Workers in Sweden (H. Grönvall et Selander, 1948) also found that the incidence of congenital anomalies after rubella appeared to be lower in Sweden than in Australia, and Atlee (1937) states that school Medical Officers have recognised two types of rash in rubella, namely a macular rose rash and a punctate scarlatiniform eruption. However, the same cases properly followed, often exhibit a change from the one type of rash to the other on successive days, thus indicating a single infection with a pleomorphic eruption (Wesselhoeft, 1946).

At first, doubts were even expressed as to the identity of that febrile illness in pregnancy which lead to cataract and other deformities, but the evidence now is quite conclusive that the Australian exanthem was in fact rubella, and that rubella has since been demonstrated time and again to have definite teratogeneous effects. By retrospective investigation, Beswick et al (1949) established the fact that maternal rubella caused congenital abnormalities even before the Australian epidemic in 1940. They quote 3 cases where the mothers had rubella in 1936,

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and 1930. All the children of these pregnancies were deaf, and had various other stigmata associated with post-rubella children, thus indicating that the connection between maternal rubella and congenital defect in the offspring is not new. L'Etang (1947) referred to a case of congenital deaf-mutism in a male aged 65 years whose "mother always insisted it was due to the fact that during pregnancy she suffered from German measles." Gronvall and Selander's statement that rubella has a lesser teratogenous effect in Sweden than in Australia, may be based on the lower incidence of the disease in Sweden, and hence frequent non-recognition of the condition. Gerard-Lefebvre and Merlen (1948) state that rubella in pregnancy is rare in France, and very mild in type. Candiotti (1949) makes the observation that rubella is more prevalent amongst Anglo-Saxon races and comparatively rare in France. Such a lessened incidence of the exanthem would provide lesser opportunities for post-rubella congenital defects to be recognised, and to be correlated with the maternal infection.

The very low virulence of the rubella virus appears to be a factor in the production of congenital anomalies. Elsewhere (Chap. XII(2)) reference has been made to the fact, that as the stillbirth rate falls, the neonatal mortality rate from congenital deformities increases, presumably because more infants with anomalies are born alive instead of dead (Baird 1945). A more virulent organism such as the measles virus will probably kill the foetus, and lead to an abortion, whereas a less virulent organism such

as/....

such as the rubella virus infects the foetus more mildly, permitting it to live, but disorganising its development, thereby producing malformations. Occasionally only, is the infection lethal and abortion is induced in the case of rubella.

To establish whether post-rubella defects in the embryo are caused by actual virus infection, attempts should be made to inoculate the virus into susceptible pregnant animals and to note the effect on the offspring (Swan, 1949[b]). In this connection the work of Habel (1942) is important. He demonstrated that it was possible to infect rhesus monkeys *(Macaca mulatto)* by throat washings from human cases in the eruptive stage of rubella. Such monkeys should offer excellent material for experimental study. At the same time possibly, work could be done on the physiology of the placenta and the role that it plays in infections, and its status as regards disturbed metabolism in the foetus. Attempts should also be made to obtain autopsies on all cases of abortions, miscarriages and stillbirths following on maternal rubella.

Swan et al (1946) attempted to prove that the post-rubella syndrome was the result of actual intra-uterine virus infection, by showing that children suffering from the syndrome are immune to natural infection. In a follow-up study of 49 patients whose mothers had had rubella during pregnancy, 9 had contracted whooping cough, 8 measles, and 2 mumps. Only one child had contracted rubella,

and she was free from congenital defects. This series was, however, small, and as Swan (1949[b]) suggests, the crucial experiment would be to demonstrate that children congenitally deformed as a result of maternal rubella in pregnancy, and not having suffered from a postnatal natural infection, are immune to the disease according to the technique of Anderson (1948), whereby infective washings are sprayed into the subject's oro-pharynx.

With regard to the question of transplacental transmission, some possibilities arise. The amniotic fluid appears to subserve metabolic and physiological functions apart from being a cushion or shock-absorber (Clement Smith, 1945). Congenital anomalies in newborn rats have been produced by injecting the mother rats with trypan blue. Mohn and Witebsky (1948) claim that Rh antigens are detectable in most samples of amniotic fluid.

Gillman et al (1948) point out that the congenital cardiac defects after rubella of pregnancy are usually patent foramen ovale or patient ductus arteriosus. The fact that these physiological, (for the foetus) structures persist after birth, suggests that rubella is bound up in some way with the embryo's metabolism. They have shown that the injection of trypan blue into pregnant rats produces abnormalities in the offspring, although the dye cannot be demonstrated in the tissues of such offspring. Either it is changed into a form not recognisable, or it does not pass the placental barrier to any great extent. In actual fact, it was only found in the yolk-sacs of

the/.....

the affected young. These workers were prompted to use trypan blue, by its binding effect on plasma proteins, anticipating thereby to interfere with the metabolism of the developing embryo. That their hypothesis may be correct, is suggested by the appearance in the pups of treated female rats, of a whole series of abnormalities ranging from eye, ear, skull defects, tail defects, umbilical hernia, imperforate anus, arm dislocation, hip dislocations, meningocoele, to commoner defects such as hydrocephalus, and spina bifida.

Their dosage of the dye could with fair nicety be regulated to increase the incidence of congenital anomalies in rats, and constitute a warning to all those who lightly introduce all manner of foreign substances into the bodies of women during the gestation period, especially by injection. Timing of the injections affected the incidence of abnormalities, but a most significant feature was the fact that preconception injections of trypan blue increased the incidence of malformations in the offspring. Injection of the dye 16 days before conception, was followed by birth of pups with jaundice developing in the first three days of neonatal life. Rats injected the day before conception, showed a 25 per cent incidence of abnormal offspring; rats injected 7 days before conception and 7 days after conception yielded as much as 80 per cent incidence of abnormal pups. Such evidence may shed light on the reported cases of congenitally malformed children born from mothers who were attacked by rubella preconceptionally.

These/....

These authors say, "we have devoted considerable attention to the structural and biochemical changes in our trypan blue treated rats. Striking changes may be detected. Severe anaemia, increased sedimentation of the erythrocytes, hyalinisation of the glomeruli of the kidney, fatty changes in the liver cells and a remarkable concentration and peculiar modification of the round cells in the portal tracts of the liver; gross enlargement of the adrenal, associated frequently with splenic and lymph gland enlargement were constant findings. Such morphological disturbances merely served to demonstrate the extent of the changes at the chemical level.

"It is in this setting that the rat becomes pregnant, that the fertilised ovum is transported along the tube to the uterus to implant itself and there to embark on the first stage of a perverted life track".

The period of greatest vulnerability to trypan blue in the rat and to rubella in the human, appears to coincide with active differentiation of the somites as well as chorionic attachment to the decidua with contact between its villi and the maternal blood, i.e. when nutrition of the foetus becomes highly dependant on the mother's placental metabolism. There is however, more to the problem than this, as Swan and Tostevan have indicated. In rubella, for example, one eye may be seriously deformed, while the other is apparently normal. However, the apparently normal eye, while not showing any changes at the morphological level, may yet have undergone change at

a bio-chemical level. An analagous condition occurs in chick embryos where there is often a temporary lag in the development of the left eye. When the head is turned to the side, and the left eye is further from the egg-shell than the right eye, it receives less oxygen by diffusion than the right eye which is directly underneath the shell. Such a set-up may predispose one eye to injury more so than the other (Cairns, 1941). So also, might a difference in the embryonic blood supply to each eye.

Moreover, in the rat experiments, (Gillman et al., 1948), some of the offspring may appear perfectly normal, others may be born under apparently similar conditions, grossly deformed, a fact particularly astonishing in the case of the rat, where litters of 8 or 10 are produced at a time. That all of these seemingly normal offspring did not entirely escape injury, however, seemed to be borne out by the fact that some of them were less fertile, or less hardy, or did not survive long, or themselves produced litters exhibiting high mortality rates, or jaundice in an abnormally high percentage of cases. These workers therefore suggest that such evidence of persistence of disorder in the second generation may shed light on hitherto unexplored factors causing puzzling discrepancies in genetic statistics.

In the light of the trypan blue experiments, and in the light of virological knowledge, certain other interesting possibilities arise:-

(1) The virus may attack the embryo earlier than the mother, owing to possibly increased susceptibility of embryonic tissues;

(2)/.....

(2) The virus may take time to pass the placental barrier, and hence may affect the embryo AFTER the mother;

(3) The virus may enter the mother preconceptually, and remain dormant in the maternal tissues, to attack the embryo at a later date. Cases have been recorded, which suggest that such actually happens (see Chapter XXII).

The importance of metabolic and other extrinsic factors in the aetiology of congenital malformations is further developed in the discussion on mongolian idiocy (see Chapter XIX). Miller (1950) points out, that statistics show an increase in the frequency of pyloric stenosis with increasing age in the mother. However, there is high incidence of consanguinity amongst the parents strongly suggesting recessive inheritance. Therefore, in the case of pyloric stenosis, there appears to be a connection between the genetic constitution of the foetus and variable intra-uterine environment, provided by mothers of different ages. The penetrance of the child's genotype is low where it develops in a younger, higher when in an older mother. Similarly, it is not impossible that such definite environmental teratogenous factors as X-Ray (and even rubella), may produce effects varying with the particular genetic constitution of the foetus.

Post-rubella syndromes vary in different cases in a puzzling way. In the laboratory too, typical and atypical malformations may also occur, and the results produced are dependant on which of the mechanisms were involved, at which time and place. Another factor pointed out by Gruenwald (1947) is the reparative power possessed by the living organism

even/.....

even in the embryo. Defective parts may even be partially restituted, (if the set up is not against such a process), with the result that an atypical defect comes to light. Gruenwald quotes replacement of the extirpated lens in amphibia. The new lens is not formed from the superficial ectoderm (cornea) but from the upper portion of the iris which is normally not concerned with lens formation.

CHAPTER XIV.

TERATOLOGY (Continued)

GENERAL SURVEY OF POST RUBELLA CONGENITAL DEFECTS.

1. INCIDENCE OF DIFFERENT ABNORMALITIES AFTER MATERNAL RUBELLA.

Swan et al (1946) summarised the anomalies found in Australia amongst 120 cases as shown below. In 68 out of 118 mothers, the infection had been diagnosed as German measles by medical practitioners.

ANOMALY	NO. OF CASES.	
Microcephaly	62	
Heart disease	52	
Deaf mutism	48	(one child deaf only)
Cataract	18	
Mental deficiency	5	
Strabissmus	4	
Inguinal hernia	3	
Cryptorchism	4	
Spina bifida occulta	3	
High arched palate	3	
Mongolism	2	
Speech defect	2	
Epilepsy	2	
Cleft palate (soft)	2	
Pyloric stenosis	2	
Buphthalmus	1	
Hypospadias	1	
Hydrocoele	1	
Bifid sternum	1	
Spastic diplegia	1	
Bilateral optic atrophy	1	
Lack of closure choroidal fissure of the eye	1	
Naevus	1	
Horner's syndrome	1	
Hemiparesis	1	
Unilateral hernia	1	
Obliteration bile ducts	1	
Azygos lobe lung	1	
Fusion upper end radius and ulna	1	
Talipes equinus	1	
TOTAL NUMBER OF CASES:	120	

Conte et al (1945) analysed (by a questionnaire method) 135 cases of congenital anomalies where there was a definite history of virus infection occurring during pregnancy. All were rubella except 2 cases, one of...

influenza/...

influenza and one of mumps respectively. Except for 3 cases, the rubella occurred before the third month of pregnancy and the incidence of defects was as follows:-

80% had unilateral or bilateral cataracts
62% had mental deficiency
57% had heart disease
54% had cataracts plus heart disease
38.2% had multiple anomalies

Abel and van Dellen (1949) inserted a request in a health column of an American publication for replies from mothers who had German measles. Of the 90 odd replies received, 82 were regarded as acceptable. As there were 2 sets of twins in the series, 84 children were under consideration. The defects found in order of frequency were :

Congenital heart disease	19
congenital cataracts	17
deafness	14
mental deficiency	7
malformed teeth	5

Gastro-intestinal, spinal and skeletal defects occurred in lesser numbers.

It must be emphasised that all the above information was obtained retrospectively.

Swan (1949[a]) in a recent, excellent and exhaustive review of the subject of post-rubella deformities, lists a considerable number of miscellaneous defects found after pregnancy. complicated by rubella. Many of these may well have been coincidental, but they are all recorded with references (J.Obstet. and Gynaec. Brit. Emp., 56: p.360 : 1949).

Skeletal/....

Skeletal system:

Large size anterior fontanelle,	5 cases
deformed face,	1 case
malformed ear lobe,	1 case
malformed concha,	1 case
atresia of auditory canal,	1 case
widely curved maxillary arch with gross narrowing of mandibular arch,	1 case
absence of zygomatic arch,	1 case
high arched palate,	4 cases
peculiarly long trunk,	1 case
spina bifida occulta,	3 cases
spina bifida,	1 case
bifid sternum,	1 case
malformed rib,	1 case
fusion of upper ends of radius and ulna,	1 case
Madelung's deformity,	1 case
arachnodactyly,	2 cases
dislocation of hip joint,	1 case
talipes valgus,	3 cases
talipes equinovarus	2 cases
talipes varus,	1 case
displacement of fourth toes,	1 case

Muscular System:

Amyotonia,	1 case
poor muscular tone	2 cases
poor muscular co-ordination	2 cases

Nervous System:

Agenesis of corpus callosum,	1 case
hydrocephalus,	2 cases
epilepsy,	2 cases
spastic diplegia,	1 case
Horner's syndrome	1 case

Genito-urinary tract:

Cryptorchidism,	6 cases
hydrocoele,	1 case
bilobed kidney,	1 case
bicornuate uterus,	1 case
hypospadias,	4 cases

Hernia:

Umbilical hernia,	4 cases
inguinal hernia,	4 cases

Respiratory system:

The anomalies were limited to 1 case of azygous lobe of a lung.

Digestive system:

Pyloric stenosis,	4 cases
obliteration of bile ducts	1 case

Palate:/....

Palate:

Cleft of soft palate,	2 cases
completely cleft palate,	5 cases

Skin:

Naevus was noted in 5 cases. Dermatitis was noted "in a few cases".

Blood Diseases:

Anaemia	4 cases
purpura	1 case

In the United States, Miller et al (1949) apart from finding cataract and the usual eye defects after rubella, also list the following ocular anomalies amongst children whose mothers had rubella actually diagnosed during pregnancy by a doctor:

Glaucoma (5th - 8th week of pregnancy),
Agenesis of optic centres of brain (9th - 12th week),
Bilateral hemianopsia (13th week or after),
Retrolental fibroplasia (13th week or after).

In such cases where rubella had actually been diagnosed clinically during gestation, they also found recorded in addition to the usual rubella anomalies:-

Hypogonadism Umbilical hernia Hypertrophy left ear Hypertrophy left breast	(5th - 8th week of pregnancy
Hypoplasia maxilla with failure to erupt second right upper molar Malformations of hands and feet	(9th - 12th week)

Where maternal rubella had been diagnosed retrospectively by history, in addition to anomalies previously noted, the following unusual defects were found, mostly in association with the "rubella syndrome":

Clubfeet/.....

Clubfeet
chorio-retinitis
chorio-retinal atrophy
strabismus
webbed fingers
anomaly of 4th rib
cretinism
mongolism
micrognathia
contracted Achilles tendon (bilateral)
congenital pes equino-valgus
meningocoele
hydro-ureters

Lande (1950) also by retrospective investigations, found in addition to the usual "post-rubella defects",

Large deformed ears,
spasticity of extremities,
hypotonia of extremities with hyperactivity or absence of deep reflexes,
convulsions, jerking spells and petit mal.

McLorinan (1949) mentions the possibility of a relationship between rubella in pregnancy and hydatidiform mole.

2. INCIDENCE OF CONGENITAL DEFECTS ACCORDING TO THE STAGE OF PREGNANCY WHEN RUBELLA WAS CONTRACTED.

Swan, Tostevan and Black (1946), in their 1942-1946 summary, give the following figures, as regards all anomalies in South Australia :-

TABLE II : Defects Correlated to Maternal Rubella.

Month of Pregnancy	No. of cases	No. of children abnormal
Month preceding conception	2	0
1st month after conception	20	19
2nd do.	42	40
3rd do.	23	21
4th do.	8	7
5th do.	7	4
6th do.	6	3
7th do.	5	2
8th do.	3	2
9th do.	2	1
TOTAL	118	

For first trimester = ± 94 per cent.

The following table was compiled by Aycock & Ingalls (1946).

TABLE III.

Series of one hundred cases congenital defects following maternal rubella.									
Month of pregnancy:	1	2	3	4	5	6	7	8	9
Carruthers (1945)	2	8	6	3		1			
Swan et al (1943)	12	19	10	2					
Erikson (1944)	7	4							
Reese (1944)	3								
Rones (1944)	1	1	2						
Green & Dogramaci (1946)	2	2	1						
Albaugh (1945)	2	4	3						
Krause (1945)	1	4							
TOTALS :	30	42	22	5		1			

(Green and Dogramaci (1946):- Paper published in 1947; see Dogramaci and Green (1947))

Incidence : 94% in first 3 months of pregnancy.

According to investigations done up to this time, it appeared that rubella contracted in early pregnancy provided an almost 100% incidence of congenital anomalies, (actually 94% : see table above).

From reports of infectious disease made to the Health Authorities in Milwaukee, (where rubella is a notifiable disease), Fox and Bortin found 152 married women with a history of rubella, 11 of whom contracted the exanthem during pregnancy with the following results:

First 2 months : 5 women :	1 hydrocephalic still-born foetus 1 hydrocephalic "blue baby", later becoming normal spontaneously.
Between 2nd & 4th months : 4 women :	no congenital defects.
After 4th month: 2 women :	no congenital defects.

Aycock and Ingalls (1946) applied the same method in Massachusetts. Out of 1300 cases reported to the authorities they found 4 instances of rubella in pregnancy:

TABLE IV.

Case	Length of pregnancy before rubella	Result
1	2nd month	normal baby.
2	2nd month	mental retardation.
3	4th month	normal baby
4	9th month (12 days antepartum)	normal baby

Both these series add up to a total of 11 cases of rubella in the first 3 months of pregnancy. Out of the 11, there are 3 abnormal infants:

1 spontaneously subsiding hydrocephalus
1 hydrocephalic stillborn
1 mentally retarded.

Three/....

Three abnormals out of 11 equals a 27% morbidity rate. Fox and Bortin do not consider the "spontaneously subsiding hydrocephalus" as an abnormality. Aycock and Ingalls further criticise the figures on the following grounds. They, themselves, collected 7 cases, 2 of spontaneous abortion, and 5 of congenital defects. Of the latter cases, only one had been reported to the Health authorities, thereby indicating that the figures cannot be accurate in respect of cases notified.

TABLE V.

Case	Lengths of pregnancy before rubella	Defect	Reported to Health Authorities
1	2nd month	Deafness	No
2	2nd month	Mental retardation	No
3	2nd month	Heart disease	No
4	1st month	Cleft palate	Yes
5	2nd month	Cataract, heart disease, deafness	No

Summarising, we find, that the incidence of congenital anomalies following rubella varies from 80% in Australia, to 27% in the United States on the basis of the above figures. However, Wesselhoeft (1947[b]) points out that the figures given previously in relation to trimester of pregnancy do not reflect the true position, because of the relatively small number of normal infants born to mothers who had rubella in the last trimester. Actually a larger number of normal babies would have been expected, if susceptibility to teratological effects of rubella diminishes with stage of pregnancy. One might be able to explain such an apparent anomaly however, by

the/....

the fact that many of the mothers whose children were abnormal, may have looked back into their pregnancy to search for a cause. Wesselhoeft's unified figures are as follows:-

TABLE VI.

RELATION BETWEEN STAGE OF PREGNANCY AT ONSET OF RUBELLA AND BIRTH OF DEFECTIVE AND NORMAL CHILDREN.

Months	Stage of pregnancy	Infants with congenital defects		Normal Children		TOTAL
0 - 1		30		2		32
1 - 2		88		2		90
	First 2 months		118		4	
2 - 3		59		5		64
	First Trimester		177		9	
3 - 4		28		4		32
4 - 5		3		5		8
5 - 6		2		7		9
	Second Trimester		33		16	
6 - 7				4		4
7 - 8		1		2		3
8 - 9				2		2
	Last 5 months		6		20	
	Third Trimester		1		8	
		211		33		244

Conte et al (1945) analysed 136 cases of congenital anomalies in which there was a definite history of virus infection occurring during pregnancy.

All were rubella, except 2 cases, one of influenza, and one of mumps respectively. Rubella occurred in all others before the 3rd month of pregnancy, except for 3 cases in which infection occurred in the 4th, 5th and 6th months.

These authors remark on the difficulty in obtaining adequate controls, but they arrived at the following conclusions from another questionnaire sent to the mothers of 120 congenitally malformed children, namely that 4.2% gave a history of rubella during pregnancy, a percentage figure ten times the actu al case rate of maternal rubella for the childbearing age

group in the population at large. Twenty cases of maternal rubella without congenital malformations in the infant are included in the survey of Conte and his co-workers -

in 4 cases, rubella occurred in the third month
and
in 16 cases, rubella occurred after the first trimester.

Conte adds 5 cases of maternal rubella from his own files, following response to questionnaires. Congenital defects, ocular, cardiac or mental occurred in all cases. Four of these mothers had had rubella during the first trimester and the fifth had had the infection in the seventh month.

Questionnaires sent by Ober and co-workers (1947) to women between 17 and 49 years of age who had rubella in 1943 as reported to the Department of Public Health, Boston, revealed that 54 out of some 3,000 women had contracted the exanthem during pregnancy. Out of these 54 -

8 infants were born with abnormalities;
9 abortions or stillbirths occurred.

Eleven out of 17 abnormal pregnancies occurred in women who contracted rubella in the first trimester. Some 22 of the group of 54 pregnant women suffered from the disease in the first trimester, the 11 abnormal pregnancies out of the total of 22 represents an incidence of 50% lost or defective.

The same workers sent another questionnaire and found that of 9 pregnancies complicated by rubella, only 3 produced normal infants. Eight out of the 9 women contracted rubella in the first trimester.

Abel & van Dellen (1949) reiterate that an important issue is not what percentage of congenital defects are the result of rubella, but rather what percentage of mothers with rubella in pregnancy give rise to infants with congenital defects, particularly in view of the scant data available of women having had rubella in early pregnancy and subsequently giving birth to normal children. These workers received 82 replies concerning 84 babies (two sets of twins included) in response to a request made (through the medium of a syndicated health column) to all women having had rubella during pregnancy.

The limitations of this method are realised, as for example some reports depend on the patient's memory and the accuracy of diagnosis in retrospect is not certain. Furthermore the proportion of normal to abnormal children as shown in their figures is probably not strictly accurate, because some mothers, with normal offspring, either do not remember having had rubella or were not sufficiently impressed with the significance of the disease, to reply. Actually the parent of a defective child is much more likely to respond, than the parent of a normal child.

Abel and van Dellen found amongst the 84 babies whose mothers had had rubella during gestation, the following figures:-

Stillbirths 3 (all these mothers had had rubella in the first trimester).

Of the 81 living children :

25 were normal
56 were abnormal (36 with a single defect.
20 with multiple defects,
18 cases of which arose from maternal disease in the first trimester.)

In 44 of the malformed children, the mothers had had rubella in the first trimester (78.6%).

In 8 of the malformed children, the mothers had had rubella in the second trimester (14.3%).

In 1 questionable case (cerebral palsy), rubella was acquired in the last trimester, but was probably not related to the defect. (1.8%).

In 3 cases the period of gestation was unknown (5.3%)

In summary, 87% of babies born of mothers having rubella during the first trimester of pregnancy were abnormal, 42% of those born in the second trimester were abnormal, and probably none in the third trimester was abnormal. These authors further state that "At least the high percentage of congenital anomalies following maternal rubella is disturbing enough to warrant consideration of therapeutic curettage in these cases".

Miller (1950) unified the figures of Fox and Bortin (1946), Aycock and Ingalls (1946), Ober et al (1947) and Patrick (1948).

TABLE VII.

INCIDENCE OF DEFECTIVE INFANTS FOLLOWING MATERNAL RUBELLA

	Cases of Rubella	Defective Infants	
		No.	%
Total	331	68	20
First Trimester	110	41	37

These unified 4 studies involve a total population of 32,000 individuals. About 40% of foetuses

whose/...

whose mothers contracted rubella in the first trimester of pregnancy, were born with congenital defects. Abortions and stillbirths are not included in these figures, and the figures themselves are only offered as an approximation of the actual incidence in view of the factors to be set down presently.

Swan (1949[a]) unified 39 studies from all parts of the world including Swiss and Scandinavian countries. Out of a grand total of 558 cases with congenital anomalies, in 519, the mother had contracted rubella in the first four months of pregnancy, an approximate incidence of 93%.

Swan et al, Wesselhoeft (1946), Miller (1949) and other workers have drawn attention to the difficulties met with in attempting to assess rubella as a teratogenous agent:

(1) The uncertainty of diagnosis. The infection is sometimes misdiagnosed even in the acute stage.

(2) The mildness of the infection, and its ubiquity.

(3) The inability to accurately determine the onset of pregnancy.

(4) Greater interest in reporting abnormalities after maternal rubella as opposed to lack of anomalies.

(5) Inadequacy of retospective histories in hospital records.

(6) Inaccuracy of retrospective histories obtained from parents. Miller et al (1949) reported five cases of cataract whose mothers had contracted rubella 13 or more weeks after pregnancy had begun. This throws doubt on the historical method as a reliable method of assessing at what stage of pregnancy in-

fection/...

fection occurred. They found only two children with defects out of fourteen, whose mothers were diagnosed as having had rubella on examination by a medico, as compared with 8 children with defects out of 13 mothers whose rubella was diagnosed by history in retrospect.

Sixteen children and infants who showed congenital malformations resembling the "post-rubella syndrome" were studied by Lande (1950) at the Dixon and Lincoln State Hospitals, Illonois. On admission, a careful history was taken, but it was realised that the mothers had great difficulty in remembering details of their health during pregnancy. Only 2 mothers, at the time of the children's admission, gave a history of rubella in the first trimester of pregnancy. Even questionnaires, which were sent to the remaining mothers, gave no results. Personal interviews were then arranged, and the mothers were asked to remember all details of the early months of pregnancy, and to discuss them with, and inquire from husbands, parents and friends. This method produced more positive conclusions and showed up a remarkable discrepancy between results in the questionnaire method and the personal interview method. Therefore it is inferred that the results of questionnaires are liable to considerable error.

(7) Definition of "rubella syndrome". Nystagmus, glaucoma, buphthalmus, strabismus, inguinal hernia, cryptorchidism, hypogonadism, and hypospadias do not occur sufficiently commonly after maternal rubella to be included under the name of the "syndrome". Even

doubtful,/...

doubtful, especially if occurring singly, are mongolism, cretinism, hydrocephalus, meningocoele, etc.

(8) Certain anomalies which have come to be associated with rubella, may, no doubt, occur in children who have had no known foetal infection, and in such cases, retrospective historical study may be sometimes misleading. Reference to prevailing epidemics may assist in the study. It should be remember, too, that any couple have one chance in 200 of producing a congenitally defective infant (Murphy, 1947), so any sample of infants if big enough, is bound to include defective individuals.

Absence of Congenital Defects following Rubella in Pregnancy.

Prendergast (1946) reported 4 cases where normal children had been born after the mothers had contracted rubella in the first trimester of pregnancy.

Swan (1949[a]) unified 180 cases collected from 10 sources in the literature, where normal children had been born after maternal rubella. The duration of pregnancy at the time of infection was as follows: first month, 11 cases, second month 26, third month 31, fourth month 23, fifth month 28, sixth month 20, seventh month 16, eighth month 7, ninth month 8, month indeterminate 10. The previous remarks regarding accuracy apply to these figures, particularly the statement that there is greater interest in reporting anomalies after maternal rubella as opposed to lack of anomalies.

The present writer would like to quote the following case of maternal rubella actually diagnosed

by/....

by doctors and communicated to him by Dr. P. Oosterhagen of Pretoria.

> A woman aged 36 years, the wife of a radiographer at the Pretoria Hospital, contracted rubella "just before she was quite three months pregnant", according to her own statement. Her doctor, who was aware of the possible teratogenous effect on the foetus, called in his partner, who also confirmed the diagnosis. This was the patient's third pregnancy, and it was allowed to go to full term. A healthy male child was born, which, at the time of writing, is one year old and has no demonstrable defect at all.

How can the absence of congenital defects be explained after a pregnancy complicated by rubella where the diagnosis appeared beyond dispute, and where the infection had occurred early? Swan (1949[b]) suggests that either the virus failed to penetrate the placental barrier or that it attacked the embryo at a period designated by Stockard as a "moment of indifference", that is, when no rapid growth is taking place. Gillman's work on rats (1948) suggests that a metabolic factor may be involved, and in this connection the inherent health of the placenta as a functioning organ is to be considered. Miller (1950) refers to a possible underlying genetic set-up which in some way may become manifest as a result of the virus infection. Some mechanical factor may be implicated, as suggested by the occurrence of unilateral cataract in some cases of post-rubella children.

3. THE PROGRESS OF POST RUBELLA CHILDREN.

(i) Discovery of additional anomalies.

Forty-nine of the original post-rubella defective children were re-examined by Swan et al (1946). Nine had died in the interim, one was autopsied, and additional anomalies, viz. right cryptorchism, and ...

hydrocoele/...

hydrococle were discovered. Out of 17 cases, previously considered normal, 10 showed abnormalities on subsequent examination, viz:

Heart disease	5	(4 showing only abnormal radiological signs, e.g. globular heart, with increased transverse diameter of heart, or increased vascular markings in lungs.
Mongolism	1	
Azygos lobe, right lung (probably chance abnormality)	1	
Left-sided Horner's syndrome	1	
Fusion upper and lower ends of Radius	1	(probably not a chance abnormality; associated with heart disease as well.
Microcephaly	5	(slight degree only)

Of cases orginally diagnosed as abnormal:

(1) in 14 cases, the original findings were confirmed.

(2) in 1 case of microcephaly
1 case of congenital heart disease (signs had disappeared, and no abnormalities were now detected.

1 case, originally diagnosed as cardiac disease, now doubtful.

(3) Additional deformities were detected in 12 cases :

2 definite and 1 doubtful deaf mutism
1 definite cardiac; 1 doubtful cardiac
3 highly arched palate
1 mental deficiency with bifid lower half sternum
1 bilateral optic atrophy, with gross visual defect and epilepsy.
1 microcephaly
1 cryptorchism and left inguinal hernia
1 definite spina bifida occulta, and 1 doubtful case plus bilateral cryptorchism and left inguinal hernia.

The whole story of post-rubella defects has not yet been written. Post-rubella children should

be/.....

be re-examined periodically at puberty, adulthood, and various other stages of their lives. It is conceivable that more defects may become apparent later, and others previously deemed normal may later evidence abnormalities.

(ii) Parity of Mothers and Social implications:

Swan et al (1946) investigated the parity of the mothers concerned, with the following results:-

28 were first children
11 were 2nd children
12 were 3rd children
1 was a 4th child

(Of mothers having subsequent children 19 cases, only one had a congenital defect, namely, talipes valgus.)

In the follow-up, out of 92 cases, 58 had no subsequent pregnancies between 1940 and 1946, probably because of (1) the fear of repetition of defects in future progeny, (a fear now shown to be practically unfounded, as the possibility of contracting rubella a second time, and during pregnancy is minimal.) (2) The time of these mothers was taken up fully in tending to defective or retarded children.

Clayton-Jones (1947) inquired into 9 cases of post-rubella deformities and found that 5 of the mothers concerned were under, and 4 were over, 24 years when the affected child was born. All but one child were the first children in the family. The young age of these mothers is no doubt due to the fact that rubella is rarely found after young adulthood in the population at large.

Beswick et al (1949) describe a very interesting and quite illuminating case of a mother who had rubella during the third week of pregnancy during

1930. She gave birth to unlike-sexed twins, who each had bilateral cataracts, congenital heart disease, deafness, microcephaly, and mental retardation followed by epilepsy.

A woman whose child suffers from post-rubella congenital malformation may be reassured with a fair degree of certainty that any subsequent children will not be born deformed. The unfortunate children with post-rubella defects are social problems in proportion to the severity and number of their defects. In the worse cases instruction in special schools is necessary, but where possible, contact with the family should not be broken especially in pre-school years. Nor should guidance and psychological instruction be omitted in the case of all the members of such unfortunate families. This question is further elaborated in Chapter XVI, in the section of deaf-mutism.

(iii) Weakness, poor feeding and weight.

Out of 78 cases originally reported by Gregg, 15 died, several from bronchopneumonia. In 3, death occurred in 24 hours after a sudden rise in temperature. In 130 cases reported by the New South Wales Committee (1945) the average birth-weight was 5 pounds, 15 ounces.

The 1946 follow-up (Swan et al) showed that 20 out of 49 cases were difficult feeders. Most of these difficulties disappeared after the first few months of birth. (All of these, with one exception, had congenital abnormalities.

Clayton-Jones (1947) remarked on the fact that feeding difficulties often persisted beyond ....

infancy/....

infancy, and that in 12 cases the average birth-weight was 5 pounds 15¾ ounces.

Lande (1950) also emphasises the high grade of feeding difficulties and retardation of growth found in some of his post-rubella children in Illonois, U.S.A. Although some of these children did well, they did not appear to put on weight. This disturbance of nutrition is attributed to a central defect. This writer states, "there is almost no other disease entity in which such severe dystrophies are seen. Body weights of 20 and 25 pounds at 5 years of age are not unusual in this group of children."

Swan et al (1946) give the following weight tables of post-rubella children.

Abnormal Babies.		Normal Babies.	
2 weighed	2 – 3 lbs.	2 weighed	4 – 5 lbs.
5 "	3 – 4 lbs.	1 "	5 – 6 lbs.
14 "	4 – 5 lbs.	3 "	6 – 7 lbs.
22 "	5 – 6 lbs.	6 "	7 – 8 lbs.
29 "	6 – 7 lbs.	3 "	8 – 9 lbs.
14 "	7 – 8 lbs.	1 "	9 – 10 lbs.
8 "	8 – 9 lbs.	3 "	?
6 "	?		

Of those weighing less than 4 pounds –

7 showed microcephaly
5 showed "eye defect"
5 showed cardiac defect and other abnormalities distributed, e.g.

Deaf-mutism,
high arched palate,
spina bifida occulta,
bifid sternum,
inguinal hernia,
cryptorchism.

Lande (1950) found that amongst 7 post-rubella defective children one weighed 20 pounds at 5 years, one wieghed 35 pounds at 6 years, one weighed 20 pounds at 5½ years, one weighed 28 pounds at 6 years, and one

weighed/....

weighed 27½ pounds at 6 years. All of these dystrophic children had bilateral cataract and severe mental deficiency, but the hearing of one appeared to be normal. Three of those cases appeared to have congenital cardiac disease.

Hopkins (1949) gives figures which show that the average weight of post-rubella children studied by her, increased according to the lateness of the stage of pregnancy when rubella was contracted.

(iv) Motor Function.

The standard for control of micturition and defaecation was arbitrarily fixed at 2 years by Swan and co-workers (1946). Of the post-rubella children examined they found;

25 conformed, but 4 were abnormal children.
20 did not conform - only 1 was free from abnormalities.

Ages varied from 2 years to 3½ years.
One examined at 39 months still had no control.

Taking fifteen months as the average age at which a normal child can properly walk, Clayton-Jones (1947) found that in a small series of 8 cases, 5 were late, and 3 were grossly delayed in walking (twenty months, or later).

(v) Liability to Infectious Diseases.

Swan et al (1946) followed up 49 patients comprising their first and second series and found that:

8	contracted	chickenpox	(From these figures
8	"	morbilli	(it would appear
2	"	mumps	(that such children
9	"	whooping Cough	(are more susceptible to infection (than other children.

Every/....

Every effort should be made to protect such children, if suffering from severe defects, from pertussis and measles, in view of the extra strain which may be placed upon the heart or the possibility of cerebral hemorrhage following whooping cough, or aggravation of any ocular condition by measles. Immunisation against whooping cough, particularly, should be instituted, and should any of the more serious exanthemata arise, use should be made of all suitable antibiotics and treatment to prevent aggravation of already existing pathological conditions.

Only one case in the above series of 49, contracted rubella, and she was free from congenital defects. At the time of examination however, these children were relatively young, and may not have come into contact with rubella, which after all, is not so common in early childhood as the other infections above listed. Also to be considered is the fact that these children grew up after the rubella pandemic had abated. The significance of immunity to rubella in post-rubella defective children is discussed under the section on pathogenesis (Chapter XIII).

CHAPTER XV.

CONGENITAL CARDIAC DISEASE.

1. CARDIAC EMBRYOLOGY.

The primitive heart consists of three chambers, an auricular, a ventricular and an aortic bulb which become divided longitudinally by formation of septa, while undergoing at the same time a process of spiral twisting. The cardiac septa are normally closed by the end of the 7th week. The bulbus cordis is absorbed into the ventricles, and in the right ventricle forms the infundibulum. Associated with its maldevelopment, are defects of the aortic cusps, aortic, sub-aortic, or pulmonary stenosis, and fusion of the pulmonary valves. Defective development of the interauricular septum causes patent foramen ovale, persistent foramen secundum, or completely absent septum (cor triloculare). Deviation of the septum to the right causes pulmonary stenosis, deviation to the left causes dextroposition of the aorta. During foetal life, the ductus arteriosus is patent and performs the important physiological function of short-circuiting the lungs and delivering oxygenated blood into the systemic circulation of the foetus. Congenital cardiac defects are sometimes associated with anomalies outside of the cardiovascular system.

2. CONGENITAL CARDIAC DISEASE : GENERAL SURVEY.

The incidence of congenital heart disease declines with advancing age because many individuals with severe malformations die during the first month or .....

second/.....

second decade of life. Congenital heart disease causes more deaths than any other congenital defect in the first year of life. According to the United States Bureau of Census (Lyon, 1945) approximately 50 per cent of deaths from congenital defects are due to cardiac lesions. Worcester et al.,(1950) found that 32 per cent of malformed neonatal deaths had defects referable to the cardiovascular system.

Stein and Barber (1945) report congenital cardiac disease in a mother, son and daughter, and they emphasize that high mortality prevents transmission.

Evans (1933) found the frequency of *congenital stenosis.* or atresia of the aortic arch to be about one in 1000.

Koletsky (1941) found 18 cases in 3300 consecutive autopsies (i.e. 0.54 per cent) of congenital bicuspid aortic valves, which therefore can be looked upon as a relatively common cardiac anomaly. The same investigator found 8 cases of acquired bicuspid aortic valves in 3,500 autopsies. The ages ranged between 13 and 74 years, and these cases probably were rheumatic in origin. Koletsky (1941[a]) also found congenital bicuspid pulmonary valves present in 8 cases out of 3,500 autopsies (0.22 per cent). In some cases, the pulmonary valves have evidenced 4 cusps. Incidentally, bicuspid pulmonary valves are of little or no clinical importance.

Muir and Brown (1935) describe aortic stenosis in brother and sister sibs, also in 2 brothers of another sibship, patent ductus arteriosus in 2 sisters, dextrocardia in father, 2 sons, and a daughter.

Congenital/....

Congenital pulmonary stenosis with closed cardiac septa is rare. Maud Abbott (1932) found amongst 1,000 collected cases of congenital heart disease, there were only 9 instances of pulmonary stenosis with closed auricular and ventricular septa.

Congenital defects of the Pericardium are very uncommon, viz: 2 in 13,000 autopsy reports according to Verse (1909). The defect appears almost invariably in the left side and in a proportion of such cases, there is a common cavity containing the heart and left lung. Seventy-seven per cent of the subjects were males. Pericardial defects are not incompatible with normal life, and sometimes the pericardium may be completely absent. There appears to be no evidence to substantiate that such defects are inherited, although Gates cites Von Scheuer and Zepperlin who concluded from skiagraphs, that heart shape is inherited.

Ectopia cordis, if thoracic, is usually fatal. George (1945) found this type usually to be associated with hare-lip, cleft palate, club-foot, or hernia.

Right posterior aortic arch, usually symptomless, occurred in 0.35 per cent of cases examined fluoroscopically (Eisen 1944). The two children of one case, and the other of another were investigated with negative results. To date there is no evidence of genetic factors in the aetiology. Hughes and Rumore (1944) described 2 cases of anomalous pulmonary veins.

Maladie de Roger is perhaps the commonest congenital cardiac, defect and is relatively benign. Perry (1931) found that 35 per cent of 119 schoolchildren with congenital hearts, possessed this defect. ...

In *Tetralogy of Fallot*, , there is R. ventricular hypertrophy, patent interventricular septum, pulmonary stenosis, and dextro-position of the aorta. This syndrome was found in 85 per cent of cynotic cases of congenital morbus cordis reaching adulthood. L. Miller (1936) indicates that pulmonary stenosis and patent foramen ovale are the commonest congenital lesions associated with cyanosis. H.C. Miller (1949) records this condition as occurring in children whose mothers had had rubella during early pregnancy.

Patent foramen ovale was found in 17 per cent of 500 hearts. (Seib, 1934).

According to Bauer (1945) paroxysmal tachycardia and auricular fibrillation are recorded in families.

Gross (1941) denies that there is any proved case of foetal endocarditis but Plaut and Sharnoff (1935), Plaut (1939) and others (Gruenwald, 1947; Stadler et al., 1950) describe apparently definite cases of prenatal origin occurring late in pregnancy. As only a few early embryos are examined by serial section it is not surprising that direct evidence of embryonic endocarditis is not found in early phases. Foetal myocarditis is described by Stoloff (1928), and Farber and Hubbard (1933). The last named point out, that of two groups into which congenital abnormalities of the heart can be divided, the one comprising gross departures from the normal developmental pattern is not likely to be due to endocarditis. The other group includes hearts with normal septums and anatomical relationships, exhibiting valvular atresia, which may have been caused by inflammatory processes.

3. DIAGNOSIS OF CONGENITAL MORBUS CORDIS.

Because of the vastness of the subject, only a few general observations can be essayed in this work. Cases of congenital morbus cordis may present no clinical features at all, and even radiological evidence may be lacking, especially in early infant life. Whereas many children are born with transient murmurs which have no pathological significance, so also, the absence of a murmur in an infant does not exclude congenital heart disease. Bruits and other clinical signs may manifest themselves at a later stage; at birth they may be physiological, and associated with temporary patency of the ductus arteriosus, or interauricular septum. Cyanosis at birth or in the neonatal period, may be due to several causes:

(1) Asphyxia associated with maternal analgesic drugs, Caesarean section, aspiration of amniotic fluid, etc.

(2) Prolonged, difficult labour, intracranial head injury.

(3) Prematurity, general asthenia.

(4) Atelectasis

(5) Aspiration pneumonia.

(6) Congenital obstruction of the respiratory tract.

(7) Erythroblastosis foetalis

(8) Metabolic disturbances in the mother, e.g. diabetes mellitus.

(9) Diaphragmatic hernia

(10) Spontaneous pneumothorax.

(11) Inborn metabolic defects, e.g. methaemoglobinaemia.

Although good physique is not incompatible with congenital morbus cordis, many afflicted infants are

puny/.....

puny and underdeveloped, and some are bad feeders. Insufficient oxygenation may contribute to this state of affairs. In a minority of cases, the bad feeding may be due to deglutition difficulty, where the oesophagus is constricted by a double aortic arch, or a persistent right aortic arch (Neuhauser, 1947). Chest deformity in cases with enlarged hearts, occurs later in childhood.

Maude Abbott's three groups of congenital cardiac disease, acyanotic, potentially cyanotic, and cyanotic, form a useful basis for clinical classification. Cases which are potentially cyanotic often become cyanotic on straining or crying, or when shocked or fatigued. These cases, together with those of the cyanotic group, are prone to develop respiratory infections on account of the associated pulmonary congestion. Pulmonary congestion is evidenced on X-ray by increased peribronchial markings often of the "drooping moustache" type. It may be difficult to distinguish between a pulmonary infection and congestive cardiac failure, a frequent end result, but the size of the liver is helpful in arriving at a decision (Taussig, 1947).

Many of the children cyanosed during early life, tend to become less cyanotic with advancing age. Cyanosis of the head and upper extremities is very uncommon and may be associated with patency of the ductus arteriosus complicated by other cardiac lesions. Pulmonary stenosis rarely exists as an isolated lesion. The most typical cyanotic types are seen in Fallot's tetralogy, where a squatting posture is so often adopted as to be most suggestive of the condition (Taussig, 1947). Cyanosis is often associated with polycythemia and clubbing of /....

bing of the fingers. Young children and infants are apt to suffer from attacks of paroxysmal dyspnoea, sometimes so severe, that consciousness may be lost.

In general, bruits associated with congenital disease of the heart are harsh and loud, situated at the base and conducted out of the cardiac area. Cases of patent ductus arteriosus sometimes do not develop the machinery murmur until a few years after birth, and the diagnosis of this condition should be accepted with great reserve in the absence of the typically continuous to and fro murmur. A venous hum may be confused with a machinery murmur but is differentiated by turning the child's head to one side during auscultatory examination. In uncomplicated patency of the ductus arteriosus, the shunt is from left to right and cyanosis is absent. The presence of cyanosis suggests a diminished blood flow to the lungs, which flow would further be lessened by obliteration of the ductus (Gibson, 1950).

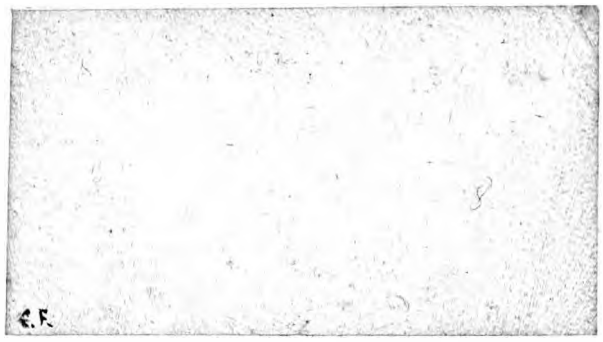
Although there may be no obvious disability resulting from congenital morbus cordis, as for instance in patent ductus or patent interventricular septum, there remains an ever present danger of subacute bacterial endocarditis. Patent interauricular septum is not uncommonly associated with mitral stenosis (Lutembacher's syndrome), and hence the latter condition should be kept in mind whenever signs of mitral stenosis are clinically apparent, and especially if stunting of growth is associated.

Before arriving at a decision in a case of congenital cardiac disease, in addition to the usual examination, the body should be inspected for evidence of

abnormal/.....



Merging of discrete rash into scarlatiniform rubella rash.



Typical rose type eruption in rubella.



Rash in Tick Bite Fever
with typical tick bite.
Note dusky colour of eruption.

abnormal collateral circulation, the neck veins for reflux pulsation, and the blood pressure should be taken in each upper limb separately, and in the lower limb. In the case of young children, a narrow cuff should be used for taking blood pressure readings with a sphygmomanometer.

Clinical diagnosis should be confirmed by other adjuvant procedures. Radiography should include fluoroscopy to determine size and shape of heart, presence of "hilar dance", pulmonary congestion, abnormal vascular markings on the ribs, distortion of oesophagus on barium swallow, and angiography. Also to be done are electrocardiographic studies, cardiac catheterisation, circulation time studies, and exercise tests measuring the oxygen consumption per litre ventilated. Measurement of oxygen content, capacity and percentage saturation of arterial blood, red cell count, haemoglobin content and haematocrit are useful procedures (Blalock, 1946). Diagnosis of double aortic arch depends on the demonstration of compression of the trachea and oesophagus at the level of the aortic arch. Radiography in such cases may be assisted by bronchoscopy (Gibson, 1950). These patients evidence stridor, beginning usually after birth, wheezing, metallic cough, dysphagia and repeated respiratory infections. Otherwise there are no signs referable to the heart.

4. POST-RUBELLA CARDIAC DISEASE.

In the original Australian series, the post-rubella children evidenced harsh systolic murmurs over the precordium, usually loudest at the base of the heart,

or/.....

or pulmonic area, and there was absence of cyanosis. (Swan, 1944). Swan, Tostevan, and Black (1946) in their follow up 2 years later, found mothers who described transient cyanotic attacks related to excitement, pyelitis, or whooping cough. Out of 7 cases having had cyanotic attacks in early infancy, only two were found to have permanent heart disease.

Dogramaci and Green (1947) surveyed the records of 434 children at the Childrens Hospital, Boston, suffering from congenital heart disease, with the following results:-

TABLE VIII.

DATA IN FIVE CASES OF CONGENITAL HEART DISEASE RELATED TO RUBELLA.

(Dogramaci and Green)

Stage of pregnancy when rubella occurred	Presence of Cataracts	Nature of Cardiac Defect	Physical signs	X-Ray findings
1 month	+ (Bilateral)	Tetrad of Fallot (operation by Dr. Blalock)	Typical Cyanosis	
3 months	+ (Bilateral)	Uncertain	Rough systolic murmur over praecordium	Globular heart
2½ months	+ (Left eye)	I.V. Septal defect	Harsh to and fro murmurs in pulmonic area with grade 2 murmur over apex : I.V. Septal defect	Globular heart with broad base".
1 month	0	Patent ductus arteriosus	"Typical"	"Typical"
2 months (exposure to rubella: susceptible)	0	Pulmonary stenosis I.V. Septal defect	Cyanosis	-
3 months	+ (Bilateral)	Patent ductus: E.C.G. showed R axis deviation	Cyanosis Prematurity.	-

The/....

The above records, out of 434 children suffering from congenital heart disease, indicate 5 cases where the aetiology was related to rubella (about 1.2 per cent); and one case, associated with congenital morbus cordis, where there was only exposure to infection. Note also, the presence of cyanosis in these case records, contrasting with earlier reports.

Conte et al (1945) being also on the qui vive, surveyed all congenital anomalies and found, out of 120, there were 4 cases of congenital morbus cordis following maternal rubella, i.e. an incidence of about 4 per cent. This higher figure is arrived at probably, because:-

(i) ALL Congenital defects were studied.

(ii) A detailed questionnaire was posted directly to the 120 mothers together with a stamped, self-addressed envelope. Sixty-one mothers replied, and the remainder were assumed not to have had rubella.

The results yielded four cases out of the 120, showing congenital morbus cordis.

In the cases of transient cardiac disease, previously mentioned, Swan et al., (1946), the radiological findings were :-

(i) Globular heart with small aorta

(ii) Waist of heart convex with increased pulmonary vascular markings. Possibly a congenital defect.

(iii) Transverse diameter increased, with increased pulmonary vessel markings.

(iv) Left border convex without aorta being visible.

(v) Slight enlargement with filling of waist. (The second pulmonic sound clicking and rough.)

(vi) "Waist of heart filled in. Pulmonary vessels pronounced. No aorta visible. Size of heart within normal limits".

There/....

There was no *clinical* evidence of heart disease in these cases, except possibly in (v). It has been emphasized, that where only radiological evidence is available about possible heart disease, the diagnosis should be accepted with reserve, and the subjects followed up periodically. It is clear, however, that only a very small percentage of cases with congenital morbus cordis originate from prenatal rubella infection. Swan et al (1946), and the New South Wales Director General of Public Health Committee of (1945) mention cases which have negative clinical findings during life and positive cardiac lesions on radiological or post-mortem examination.

To determine the relationship between the time of onset of rubella and the occurrence of congenital heart disease in infants born subsequently, Swan (1949a) analysed 185 recorded cases of post-rubella cardiac disease. He found that the cases were virtually confined to the first four months of pregnancy, with the highest incidence in the first and second months.

Aycock and Ingalls (1946) extracted from combined authors an average period of 5 - 10 weeks pregnancy for cardiac defects.

The so-called "critical" embryological period in cardiac development is from the fifth to the eighth week of intrauterine existence. During this period the cardiac septa are developing, and torsion of the great vessels occurs. Swan (1944) autopsied 3 affected children and found the ductus arteriosus widely patent; also there was variable patency of the foramen ovale. One child had an interventricular septal defect. ....

Miller et al., (1949), in their study extending over the United States found that the incidence of post-rubella congenital cardiac anomalies was about twice as high when the maternal infection was diagnosed retrospectively from history as when it was made personally by an examining doctor. It is emphasized that the recorded incidence of cardiac defects varies according to the extent of investigation, X-Rays, operative confirmation, etc. They mention three autopsies performed on such children. One showed an interventricular defect, another had a patent ductus, while the third had aortic coarctation associated with patent ductus. Three of the five cyanotic children for whom data were given, were diagnosed as cases of Fallot's tetralogy on the basis of clinical and radiological studies.

The majority of cases of post-rubella cardiac disease however, falls into the acyanotic group (Swan 1949[a]). Miller et al., (1949), Albaugh (1945), Goar and Potts (1946), Friedman and Cohen (1947) also give instances of the cyanotic types. In the last named case, the mother had suffered from a rash in the second month of pregnancy, which probably was rubella. When bruits occurred, in the majority of cases, they were systolic in time and harsh or rough in character, less commonly of the "machinery" type and usually situated basally with maximum intensity over the pulmonary area (Swan, 1949[a]). The latter author cites that sometimes the murmurs were audible all over the precordium, that they were occasionally apical or accompanied by a thrill or clinical evidence of cardiac enlargement. The ....

commonest/....

commonest cases were those of patent ductus arteriosus, and patent interventricular septum. Hopkins (1946) mentions a possible case of bicuspid aortic valve with regurgitation.

Swan et al., (1946) noted that post-rubella congenital morbus cordis occurred more often in association with cataract than with deaf-mutism. Cardiac disease was also observed as the sole abnormality in some cases. The following case, which was seen in Johannesburg, is here recorded :-

> A woman, a premigravida developed a blotchy rash over the whole body about the end of July, 1943 when she was 8 to 10 weeks pregnant. According to her own statement she was "smothered in the rash". The face and extremities were also involved. The rash only lasted a few days, during which time she was ill and confined to bed. She was also suffering from "morning sickness" at the time, but she cannot remember whether she had enlarged glands in the neck or behind the ears. The doctor was called to see her at a time when the rash was disappearing, and he was not sure whether the case was one of rubella, or a mild attack of measles during the convalescent stage. The child was subsequently born near term and cyanosis was present at birth, especially noticeable in the face, around the mouth more particularly, and in the extremities. He also had a persistent cardiac bruit. The cyanosis has persisted, and is aggravated by exercise. The child is now 7 years old, and is able to perform mild physical exertion such as riding a tricycle; but he then becomes more cyanotic. He has been seen by several specialists, who consider the diagnosis to rest between that of Eisenmenger's complex and Fallot's tetralogy. The child is normal in all other respects.

In retrospect, it is difficult to establish the identity of the above rash, but the diagnosis of rubella is considered to be most likely, more especially in view of the fact that rubella was prevalent at that time. The sole abnormality in this case was congenital morbus cordis, which was also the only anomaly to be found in some of Swan's post-rubella cases.

The/....

The PATHOGENESIS of congenital morbus cordis is still being investigated. In the case of post-rubella congenital cardiac defects, the aetiology is touched upon in Chapter XIII. Does foetal endomyocarditis occur by actual invasion of the rubella virus itself? The following workers provide evidence to show that pre-natal infection of the cardiac tissues may occur late in pregnancy: Stoloff (1928), Farber and Hubbard (1933) Plaut and Scharnoff (1935), Plaut (1939), Gruenwald (1947), Stadler et al (1950). Virus infection of embryonic tissue may occur during organogenesis, but all evidence of inflammatory reaction would be effaced by the reparative powers of embryonic tissue and its peculiar response to injury under the influence of evocators, organisers, etc.

On the other hand, disturbed metabolism of the maternal tissues may influence the environment of the developing embryo in such a way as to disturb normal development.

Dogramaci and Green (1947) investigated records of 1,387 women with various virus and exanthematous diseases. Seventeen of these were pregnant, and of these, 6 were in the first half of gestation :

TABLE IX./....

TABLE IX.

OFFSPRING OF MOTHERS WITH VIRUS AND OTHER EXANTHEMATOUS DISEASES OF EARLY PREGNANCY.

(Dogramaci and Green)

Disease	Stage of Pregnancy	Birth at term (T) or Premature (P)	Abnormalities	Remarks
Mumps	2 months	T	0	Bilateral submax and L parotid glands
Rubeola	3 months	T	Obstruction R. lacrimal duct.	Mild
Scarlatina	1½ months	T	0	Treated with sulphadiazine 5 days
Scarlatina	2 months	T	0	Also had bronchial asthma
Scarlatina	2 months	P (?)	0	Treated with sulphadiazine 5 days
Scarlatina (exposure to Rubeola) Did not develop rubeola? because of gamma globulin	4½ months	T	0	Gamma globulin, sulphadiazine 5 days

We see therefore that mumps, measles and scarlet fever during early pregnancy do not constantly produce offspring with anomalies.

A case is here reported, where measles infection occurring early in pregnancy was followed by the birth of a child with congenital defects of the heart:-

A woman/....

A woman aged 26 years developed a blotchy rash. At the time she was unaware of the fact that she was pregnant, as her period was just overdue and this irregularity happened occasionally. The rash and illness was diagnosed by an experienced and capable medical practitioner to be typical measles. The patient soon realised that she was pregnant as well. The expected date of delivery was the 5th July, 1943, but she went over the period and when labour commenced, it lasted for two days. A Caesarean section was performed on the 23rd July, because of arrested progress due to transverse lie of the foetal head. The child, a male, weighed 9 pounds 2 ounces and had persistent cyanosis from birth. There was also a basal systolic murmur. At five months, the child developed bronchitis and was seriously ill, being treated in a nursing home and requiring prolonged oxygen administration on account of dyspnoea and cyanosis. After that he recovered, and developed normally, but was slow to sit up. At one year, he began to get attacks of unconsciousness which necessitated oxygen administration and coramine injections. He was never really able to walk, as his legs appeared to be weak, although there was no obvious deformity. He died at the age of nineteen months. There was never any indication of mental backwardness or deafness, and deglutition was normal. The cardiac condition was regarded to be most likely a case of Fallot's tetralogy. There was no history of congenital cardiac disease in the families of both parents. The mother has since had a miscarriage and a living child quite normal.

Dogramaci and Green (1947) further studied 434 patients with congenital cardiac disease. They found that in 9 cases there was a history of virus infection in the mother during the first trimester of pregnancy:

? Infectious factors	9 cases of virus infection in first trimester (Four of the cases were rubella)
	8 cases of non-exanthematous bacterial infection during pregnancy.
	2 cases of acute rheumatic fever in first trimester.
	1 case of chorea, first trimester
	2 cases of maternal syphilis
	1 case of ptomaine poisoning, first month of pregnancy, was seriously ill one week: child suffering from ? Eisenmenger syndrome.

? Meta-bolic factors	4 cases of allergy during early pregnancy. 5 cases of severe trauma, first trimester. 1 case of thyrotoxicosis, developing 2 months prior to conception and requiring subtotal thyroidectomy in second month pregnancy. 1 case of low basal metabolic rate throughout pregnancy requiring thyroid administration. 3 cases of paternal exposure to lead.

Lamy and Schweisguth (1948) studied 230 children with cardiac malformations. Apart from 2 cases where rubella had probably occurred in early pregnancy, in 9 other cases infections diseases developed during the first trimester, including 1 case of mumps, 2 of pertussis, and 2 of *B. coli* pyuria. In 3 cases the onset of pregnancy was marked by uterine hemorrhage. One patient suffered severe abdominal trauma due to a fall, and one other attempted abortion by taking quinine. There was 1 case of drug intoxication by Stovarsol, and 1 of severe food deficiency. The significance of all the above data however, is minimised by lack of information regarding the incidence of the various above-listed pathological conditions in non-pregnant females of the same age and circumstances in the population at large.

While the embryonic cardiovascular system is being integrated, so are other systems developing as well, which fact helps to explain the frequent occurrence of associated and multiple defects. Lamy and Schweisguth (1948) who studied 230 children with cardiac malformations found that 14 per cent of them had additional anomalies. Mongolism was the commonest, occuring in 9 cases (4 per cent). Dogramaci and Green (1947) found the incidence of concomitant mongolism to be 5.8 per cent. Heredity was shown to be a very important factor, as 10 per cent

of 680 cases of congenital cardiac anomalies reported having congenital heart defects or other anomalies in other members of the family. In 4 per cent, other siblings were involved, and in one case, identical twins had apparently similar cardiac anomalies. Lamy and Schweisguth (1948) found histories of congenital defects in the family in 7.8 per cent of cases. In 2 cases, brother and sister suffered from Roger's disease, and in one family, mother and daughter had a patent ductus. Cases of other concomitant malformations were found in 7 per cent, while parental consanguinity was found in 2,6 per cent of cases as against 0.6 per cent and 1.0 per cent in the general population.

Lamy and Schweisguth also found, apart from mongolism, other malformations such as congenital cataract, clubfoot, cleft lip, spina bifida, various skeletal anomalies, deaf mutism, angiomata and malformations of the digestive and urinary tracts. Many of these cases of multiple anomalies are doubtless of genetic origin, but Lamy and Schweisguth found in their series, discordance in two sets of twins apparently definitely uniovular. In the first set of twins, one showed a typical interventricular defect, while the other had an apparently normal heart. In the other set, one had congenital dilatation of the pulmonary artery, while the other had no signs of cardiac anomalies. The discordance in these two sets of twins pleads against a genotypic origin for the cardiac defects in these two special cases, but

of course/...

of course it is not impossible that each twin who appeared normal, might have had cardiac defects which were not recognizable by the diagnostic methods employed.

In summing up, it is safe to say, that while maternal rubella in early pregnancy in many cases causes congenital cardiac disease in the child, other virus and bacterial infections and pathological states during gestation, cannot at this stage be definitely implicated as aetiological factors. Heredity seems to play a big part in the aetiology of congenital cardiac defects in general, but study of these (and other anomalies) will be greatly assisted by culling of adequate data to act as controls for purposes of comparison.

TREATMENT. Taussig (1947) summarizes the general medical care which should be extended to a child suffering from a congenitally defective heart. The child should be encouraged to attend regular classes and its education should not be neglected. Diphtheria and pertussis immunisations should be performed at the usual age. Operations may be performed as needed, because anaesthesia is well tolerated, and tonsillectomy if indicated should be done to guard against subacute bacterial endocorditis. The teeth should be well cared for, and extraction performed if necessary, provided prophylactic chemotherapy be instituted before and after extraction.

These patients as a rule withstand intercurrent illnesses remarkably well under the circumstances,..

but/....

but many cases develop pulmonary infections which demand antibiotics such as penicillin, aureomycin, chloramphenicol, and sulpha-drugs, depending on the nature of the infecting organism or organisms. Whenever septicaemia or bacteriaemia is suspected, appropriate chemotherapy should be given. The presence of subacute bacterial endocarditis is no bar to operative treatment such as ligation of a patent ductus, and indeed, operative closure in such cases will result in cure, but is better performed before the onset of endocarditis (Gilchrist, 1947). Pre-operative and post-operative administration of penicillin is essential for success, as well as anti-coagulant therapy.

Patients with cyanosis should be guarded against extreme fatigue and especially dehydration, because thromboses are prone to occur at all ages. Especially common, are the cerebral types which may be followed by convulsions or hemiplegia. The treatment is venesection, oxygen therapy, intravenous fluids and heparin. Extremely cyanosed, anoxaemic patients may be more comfortable at sea level than at higher altitudes, and such cases should not travel by air unless supplementary oxygen is available, especially at heights exceeding 12,000 feet.

Cardiac failure may ensue due to an ever increasing load placed upon the heart by the malformation or by intercurrent illness, superimposed infection of the myocardium, surgical operation or excessively rapid heart action. Pulmonary congestion is often a com-

posite/.....

posite of infection and decompensation, both of which conditions should receive appropriate treatment. Early signs of cardiac failure in infancy are a greatly increased respiratory rate and engorgement of the liver. In adults, the early signs are râles at the lung bases and odoema of the extremities. Treatment is by rest, venesection, oxygen therapy, diuretics and digitalis. Attacks of poroxysmal dyspnoea are alleviated by administration of morphine and oxygen. The dose of digitalis should be regulated by body weight and in acutely ill patients administered parenterally. With improvement in the patient, maintenance can be carried out by oral therapy, if necessary for many months, although over a period of years, the infant or child usually outgrows the need for the drug.

A few moderate cases of Fallot's tetralogy are consistent with a fair degree of longevity (Taussig, 1947) but severe cases are benefited by anastomosis of the subclavian, carotid or innominate artery to one of the larger pulmonary arteries. The best time for operation is between two and twelve years, and should not be done unless the pulmonary artery is of small size, and congestion of the lung fields, clinically and radiologically is absent (Blalock, 1946). The position of the aortic arch must however, be determined before the chest is entered (Gibson, 1950). Aortic coarctation can be operated upon, as well as abnormalities of the aortic arch causing obstruction to the oesophagus and trachea (Gross, 1946). In recent years operative attempts have been made to relieve stenosis of valves,

but/.....

but time will help to decide upon the efficacy of such procedures.

Although the immediate results of surgery in Fallot's tetralogy are highly gratifying, we do not yet know whether the artificially created anastomotic channels will grow as the child grows. Furthermore, by surgery, there is added to an already deformed heart, the new burden of pumping more blood to the lungs (Potts, 1950). After all operative procedures, adequate hydration must be maintained to militate against thromboses. (Taussig, 1947).

The use of anti-coagulants such as heparin has greatly facilitated operative work on the blood vessels.

CHAPTER XVI.

DEAF MUTISM

(1) GENERAL SURVEY.

DEAF-MUTISM results from congenital deafness, or complete loss of hearing before the age of 7 years. The dumbness is secondary to defective hearing and in most congenital cases, the organ of Corti is undeveloped. (Otosclerosis occurs later in life, and the auditory nerve is intact.) Congenital deaf-mutism may actually be "acquired" in utero (e.g. as in syphilis, rubella), so all congenital deaf-mutism is not necessarily hereditary in origin. As many deaf-mutes are educated in special schools, they often meet and marry deaf partners. From a eugenic point of view this may be better than marrying into normal families and so spreading the affliction, where the latter is of genetic origin.

Deaf-mutes occasionally exhibit retinitis pigmentosa, and more often feeble-mindedness and sterility. Hypogenitalism and infantilism are sometimes found in recessive types. One family is quoted by Gates (1946), where deaf-mutism is combined with heterochromia iridis, Horner's syndrome and strabismus.

Otitis media may cause deafness, and according to Bauer (1945) susceptibility to otitis media may be inherited, being sometimes familial. The deafness, if occurring early, may be associated with mutism.

Gates (1946) also cites Lindborg, who believes that hereditary deaf-mutism is due to one Mendelian recessive character, as against Plates's two factors.

Love/.....

Love (1920) described a family with five affected generations, descended from a common ancestor, and postulates a recessive mode of inheritance.

Kraatz (1925) studied many pedigrees statistically, and came to the conclusion that deaf-mutism cannot be due to a single dominant, recessive or sex-linked character, but that the statistics pointed to the operation of two recessive factors. However, on the basis of two factors, Deaf x Deaf may give all normal children in some families so that lack of penetrance is a more probable explanation. Persons who are heterozygous for "deafness" can hear perfectly well on the audiometer, so the condition is recessive.

Tinkle (1933) also believes that 2 recessive genes are concerned with the production of hereditary deaf-mutism, but suggests that a third pair of genes control the development of the middle and internal ears.

Switzerland has the highest incidence of deaf-mutism in the world, namely 0.12 per cent as against 0.023 per cent, in Germany for instance (Gates 1946). Hanhart is cited as saying that 60 per cent of deafness in Switzerland is "sporadic", being related to cretinism. In Sweden, where there are few cretins, the ratio of congenital to acquired deafness is estimated as 100 : 67. Murray and Wilson (1945) show a relationship between deaf-mutism and goitre and cretinism. In 3 goitrous districts in Oxfordshire with low water and soil iodine content, there were 28 deaf-mutes in a population of 36,635, whereas in 3 non-goitrous areas, there were only 5 deaf-mutes in 38,910. Some of the deaf-mutes have enlarged thyroids, and belong to goitrous families, but unlike in goitre, both sexes are equally

affected/....

affected.

Also cited, (Gates, 1946) are Muller and Hanhart, who describe another type of labrynthine deaf-mutism with morphological changes in the ductus and sacculus, apparently inherited as a dominant, and occuring at such an early age as to cause deaf-mutism. One such pedigree, had 11 cases in 4 generations, showing dominant inheritance with 10 sibs out of 19 affected. Other instances are quoted. In one family, the child was normal, both parents deaf, and grandparents were carrying different forms of deaf-mutism in a recessive state. In another family, the father had white hairs in the beard and was not deaf. His 5 children were all deaf-mutes. Two of these who mated with other deaf-mutes had normal progeny. The 5 children had pigmentary anomalies with white patches on hair and skin, pigmentation on the body, persistent lanugo on the back and mongoloid features. There were 19 deaf-mutes in 4 generations, and 8 cases (6 of them deaf-mutes), of pigmentary anomaly. Apparently the latter was dominant and the former recessive, with different genes for deaf-mutism in the progenitors.

In the late years, maternal rubella has been found to affect the foetus, producing congenital deafness. Maternal rubella, however, plays a relatively insignificant role in the etiology of deafness in general.

(2) DIAGNOSIS.

That the diagnosis of deaf-mutism in infancy is a difficult matter, is common knowledge to all paediatricians. The deaf baby gurgles and coos in a normal fashion and is not mute. In fact "deaf and

dumb"/....

dumb" children are rare, The surest sign of deafness in infancy, is delay in the development of speech. If the parents are suspicious of such a defect, the suspicion is generally well-founded. In any child over the age of eighteen months, where there is no normal speech development and no imbecility, impairment of hearing must be first excluded. Strange to relate, parents often interpret baby sounds as various words of speech and will not admit any early speech difficulty until the age of 3 or 4 years, when abnormal behaviour patterns are manifested. The children adopt a self-willed, intractable, aggressive attitude and cry repetitiously in a sharp, strident way. Unfortunately, it is very unusual for audiometery to be successfully employed for diagnostic purposes under the age of 5 years, although there is now a promising technique being investigated, which uses the principle of the conditioned reflex and which will no doubt eventually accurately measure auditory acuity in children after 10 months of age (Bakwin, 1950). Actually for accurate diagnosis audiometry is essential, because regional deafness may easily be missed when the clock, watch, tuning fork or voice is used. When there is an impairment in the mid-high range, then it is difficult to distinguish differences in consonants of words such as bed, led, said, dead, etc.

In the usual case of congenital deaf-mutism the child is "bird-witted", very intelligent and dexterous. It spontaneously develops lip-reading technique, and because it may sometimes say "mum", or "dad", the parents come to believe that the child can hear, and is being solely neurotic and over-apprehensive. Speech

may be/.....

may be defective by omission of sounds or syllables corresponding to the presence of "islands" of deafness, and in most cases the condition is inherited as a Mendelian recessive. With both parents having normal hearing, the chance of their child being born deaf, is one in four, with deafness in the family (Crooks, 1947). These children with impaired hearing in both ears often possess "residual hearing" for loud noises, such as that of an aeroplane, especially if such noises are accompanied by gross vibration. Occasionally, however, because of speechlessness, they are treated for aphasia, thereby wasting valuable time. The tympanum and external ear appear normal.

Arnold Gesell (1946) in his usual systematised fashion has listed signs suggestive of deafness in infants and young children, under the developmental system in which they are most likely to appear:-

1. *HEARING AND COMPREHENSION OF SPEECH.*

General indifference to sound.
Lack of response to spoken word.
Response to noises as opposed to voice.

2. *VOCALISATION AND SOUND PRODUCTION.*

Monotonal quality.
Indistinctness.
Lessened laughter.
Meagre experimental sound play and squealing.
Vocal play for vibratory sensation.
Head banging, foot stamping for vibratory sensation.
Yelling, screeching to express pleasure, annoyance or need.

3. *VISUAL ATTENTION AND RECIPROCAL COMPREHENSION.*

Augmented visual vigilance and attentiveness,
Alertness to gestures and movements,
Marked imitativeness in play,
Vehemence of gestures.

(Note that at 6 months of age, the deaf child becomes progressively quieter, but more visually attentive.)

(4) SOCIAL/.....

(4) *SOCIAL RAPPORT AND ADAPTATION.*

Subnormal rapport in vocal nursery games.
Intensified preoccupation with things rather than persons,
Inquiring, sometimes confused or thwarted facial expression,
Puzzled and unhappy episodes in social situations,
Suspicious alertness, alternating with co-operation.
Markedly reactive to praise and affection.

(5) *EMOTIONAL BEHAVIOUR.*

Tantrums to call attention to self or need.
Tensions, tantrums, resistances due to lack of comprehension,
Frequent obstinancies, teasing tendencies,
Irritability at not making self understood,
Explosions due to self-vexation.
Impulsive and avalanche initiatives.

Deafness in early infancy, may result from meningitis, influenza, scarlet fever, whooping cough and measles, and may be mistakenly regarded as being of congenital origin if not carefully investigated. Both ears are usually affected, and after meningitis, resultant deafness is generally complete. Mumps may cause a meningo-encephalitis, which attacks the labyrinth of one or both ears, usually one, making it deaf. Congenital syphilis may also cause deafness by catarrhal otitis, associated with "snuffles".

The writer attempted in 1948 to analyse the records of the St. Vincent's School for the Deaf, Johannesburg, but unfortunately details of admitted cases were very meagre. Out of 170 children, 138 were classified as congenitally deaf, while in 42 cases, the cause of deafness was given as "post-infective" or acquired:-

Acquired/....

Deafness Acquired.	No. of Cases
Meningitis	25
Mastoid, abscess in ear, "ear trouble"	4
Measles	4
Whooping cough	1
Chicken pox	1
Tetanus	1
Encephalitis	1
"Nerve deafness"	4
"Progressive deafness"	1

Of the 138 congenitally deaf children, the pre-natal histories obtained from the mother's on the child's admission were inadequate and no mention was made of rubella during the pregnancy. Figures obtained by Hughson et al (1939) in Pennsylvania also show a vast preponderance of congenital cases over acquired, in an institution for deaf children.

Sensory Aphasia: Congenital aphasia occurs in children and of course, such children are not improved by mechanical hearing aids. There are several types of aphasia.

Auditory-verbal agnosia (Inability to appreciate the meaning of words, though hearing them clearly), is a condition quite easily passing for deaf-mutism. Such children are alert, often over-active, purposeful, investigative, but retiring and unsocial. They respond to unusual noises, but are inattentive to speech. The basis may be organic or functional, the prognosis being usually better, with treatment, in the latter type of case. Without treatment, all such cases show apparent mental retardation.

In *Syntactical Aphasia* the main disability is to appreciate the correct relationship of one word to another, although hearing is quite clear. Such children produce "jargon" speech, simulating mental defectiveness

or/.....

or deaf mutism. Their hearing is of course, intact. In *Amnesic Aphasia*, normal hearing and comprehension is present, but the right word cannot be recalled. The child can explain what he is seeing, but not name it. The condition is tinged with emotional disturbance.

Motor Aphasia: The child with motor speech delay (Broca's aphasia), in contrast to the word-deaf child, evidences considerable understanding of speech, and does not exhibit that striking auditory inattention. He tends to concentrate more on doing things. Rudimentary conversation is laboriously attempted and failure is inclined to cause emotional disturbances and frustration. Mild cases may clear up spontaneously, or speech is developed in lisping or baby fashion.

In the diagnosis of deafness, and the aphasias, local condition must be excluded, e.g. cleft palate etc. and anatomical defects such as those following cerebral tumour, encephalitis, meningitis, diphtheria, the prognosis varying according to the nature of the lesion. Some children acquiring jargon or unintelligible speech due to bad training and environmental conditions, improve in nursery schools; in others there is an anatomical defect of the ear, brain or cerebellum. Audiometry, when practicable, is invaluable.

DEAFNESS Involving the Auditory Apparatus. Where the auditory apparatus is implicated, and acuities are low, the voice may be low, monotonous, metallic and words are poorly enunciated, and badly understood. When high or low frequency sounds are not properly appreciated, speech is correspondingly affected by omission of sounds and syllables. The individual with conduction deafness hears his voice magnified by bone conduction in his own

skull/....

skull and hence his voice tends to be low. The perception deaf individual, in whom the inner ear is affected, speaks very loudly because he cannot hear his own voice and inflection is bad for the same reason. Individuals with nerve type deafness often hear sounds in the lower range reasonably well, but may not hear well enough in the middle and upper registers to distinguish many speech sounds. It appears that the number of children with all types of deafness who can be helped to use their residual hearing is considerably greater than was formerly believed to be the case. Total hearing loss appears not to exceed 5 per cent of cases as determined in a Pennsylvania School for Deaf (Hughson et al (1939).

(3) DEAF MUTISM FOLLOWING MATERNAL RUBELLA. In the original Australian series of cases showing mostly ocular conditions, subsequent anomalies were anticipated, in children apparently otherwise normal at the time, and sure enough they occurred, amongst them being deaf mutism, such being difficult of diagnosis at 18 months or even 2 years.

Of Swan, Tostevan and Black's original 7 cases of deaf-mutism, (Swan,1944) five were female and 2 were males. Martin (1945) and Hopkins (1949) also found a higher preponderance in females. Two of the original cases had congenital heart disease as well. Generally speaking they were not totally deaf, but could hear shrill notes such as train-whistles, but rarely the spoken word. Speech, as expected, was either absent, or limited to a few words, such as "Mum" and "Dad". In no case was there a history of hereditary deaf-mutism, but in one case there was a family history of adult ....

deafness. The impression was gained that bone conduction was much better than air conduction for high notes. The external canals and tympanic membranes were not abnormal and one child improved much with lip-reading instruction and battery-aid, commencing at 2½ years of age.

Swan et al (1946) commented on the fact that deafness may be complete or partial, involving the middle or inner ears. If complete, the mutism is secondary. If incomplete, speech may be delayed or imperfect owing to "small islands of deafness". The autopsy findings in one case showed no differentiation, in both ears, of primitive cells to form the organs of Corti.

Werthemann (1948) confirms that histologically there is no differentiation of the primitive cells of Cortis organ. He also states that the accoustic nerve and spiral ganglion are well developed, and the basilar membrane and bony spiral lamina are easily identifiable. Vascularisation of the striae vasculares is somewhat poor and the tectorial membrane is rudimentary, being surrounded by nucleated flat cells. Reissner's membrane is not evident, but the middle and external ear remain normal.

The severity of the rubella attack appeared to have no relation to the severity of the damage to hearing. (Carruthers, 1945; Clayton-Jones 1947). Most of the children examined by Carruthers gave some evidence of hearing over the tone range from 512 to 2048. Nine patients were given caloric labrynthine tests, with results that showed little deviation from normal, except that there was no vomiting, even though nystagmus was induced. Welch (1945) drew attention to the fact

that/....

that in Australia the highest incidence of deaf mutes born in any year since 1930, occurred in 1938, and of these, 34 cases gave a history of German measles in the mother in first 2 to 4 months of pregnancy. The history of 13 others was doubtful. The following figures were supplied from the admissions made to a school for deaf and blind in Queensland and are published by Welch:

Year	No. of cases	Year	No. of cases
1930	9	1936	4
1931	5	1937	6
1932	3	1938	47
1933	4	1939	5
1934	7	1940	3
1935	7	1941	2

TOTAL 102.

Clayton-Jones (1947) who investigated post-rubella deaf children, found that all were born between August and February. These months seem related to the periods of prevalence of rubella (March - July), allowing of course for the added period of gestation.

Vickery (1945) studied the children of mothers who had rubella in the first 3 months of pregnancy. Of these 21 children, only two had congenital cataract, and most of them showed failure to thrive, difficulty in management, and not one could put sentences together. Eleven were undersized and underweight, and 13 showed cardiac lesions with murmurs, praecordial bulging, and on X-Ray examination, left ventricular dilatation. In one case, the patent ductus was successfully ligated by operation. This child's physique and development improved considerably, and the murmur subsided.

Vickery said that most of the 21 deaf children had general nervous instability. They would lie awake for hours during the night, especially during the first

2 years/.....

2 years of life. They were unable to concentrate, and showed a peculiar fleeting, prying interest, in things. Not one of these cases was totally deaf, but all had impairment of hearing to the extent that they could not comprehend what was spoken to them. During the 4th year of life, the concentrating powers of most of them had greatly improved, and many were learning to coöperate with hands and eyes, although hearing and speech were still much retarded. Dr. Vickery regarded the future outlook as being reasonably good for those whose physique had not been greatly retarded by their cardiac lesions, and it seemed that they might be taught some useful manual trade. He even felt that many would learn to speak. Carruthers urged that speech should be encouraged as early as possible, and Bakwin (1950) states that hearing aids should be used as early as possible in all cases where deafness is not total. Apparently some children are able to use these aids at 2 or 3 years of age, if the intelligence is not affected, although 6 or 7 years is the usual period. Modern instruments give a gain of 40 to 50 decibels.

Hopkins (1949) investigated statistically 92 post-rubella deaf children and compared them with 61 deaf children whose mothers had not had rubella during pregnancy. Both groups were also compared with their respective sibs. From the data obtained, she concluded that the arrest in development of the rubella deafened children was not due to the deafness *per se* but to the general after effects of the virus infection on the organism as a whole.

Clayton-Jones (1947) found that deaf children with a maternal history of rubella commonly had bilateral

incomplete/...

incomplete inner-ear deafness usually fairly uniform throughout the frequency range. The audiograms showed no evidence of islands of hearing and the deafness was fairly equal in degree in both ears. Hopkins (1949) in a larger series of post-rubella deaf children found that 53 were profoundly deaf, and 38 were partially deaf.

Patrick (1948) graded 34 cases of post-rubella congenital deafness according to severity and found that in 27 the degree of deafness was so bad as to "require education by methods used for deaf children without naturally acquired speech or language". Two cases fell within the grade where even with "the help of a favourable position in class, individual hearing aids, or tuition in lip reading, fail to make satisfactory progress in ordinary classes in ordinary schools". One case fell within the grade, where with the above quoted assistance, could make satisfactory progress in ordinary classes in ordinary schools. Only 4 cases in the series, had such slight disturbance in hearing as not to require assistance at school and could make satisfactory progress.

Clayton-Jones (1947) found that in 36 post-rubella deaf children, difficulty in feeding was commonly reported, and examination showed a tendency to deformity of the jaw, pigeon-chest and atonic musculature; but the intelligence of these children seemed normal and no cataract or definite heart lesion was detected in any case. These cases, were investigated in institutions for deaf-children. In 13 cases, the maternal rubella had been diagnosed by a medical practitioner.

Hopkins (1949) investigated 92 post-rubella deaf children. Ten children born of mothers with rubella during the first 2 months of pregnancy had congenital ocular defects including cataracts, unilateral or bilateral. None of the children born of mothers having rubella during the third month of pregnancy had any reported ocular defects. A total of 30 post-rubella deaf children out of 92, born of mothers who had rubella during the first "trimester of pregnancy, were also reported to have congenital conditions", which however, were not always accurately described. Four of the investigated children out of the whole series were mentally defective, and 2 had spastic paralysis; 2 were treated for congenitally dislocated hips; 1 had umbilical hernia; one had obstruction in the penis; 1 had hypospadias, and 1 had a pilonidal dimple. A number of children had several defects other than deafness, but for a total of 53 children the only reported defect was deafness (out of 92 cases.)

Miller et al (1949) found an apparently lower incidence of congenital deafness after maternal rubella in the United States as compared with Australia. They attribute this discrepancy possibly to the fact that reports were obtained from specialists whose interest may have been restricted; also to the difficulty in diagnosing deafness and mental deficiency in infants. Clayton-Jones (1947), investigated 19 cases and found that the deafness was recognized in 3 cases before the first year of life but in the remaining cases, was only recognised from 1 to 4½ years after birth.

Stage/.....

Stage of Pregnancy when rubella was contracted.

Of the 18 cases of deaf-mutism reported by Carruthers (1945) the mother had contracted rubella -

in the	first	month	of gestation,	..... 2 cases
	second	"	"	.....10 cases
	third	"	"	..... 4 cases
	fourth	"	"	..... 1 case
	sixth	"	"	..... 1 case

In Queensland, Winterbotham (1946), investigating 34 congenital deaf-mutes, found that the mothers had suffered from German measles in all instances, at some stage during the first four months of gestation. In 11 of the children a cardiac condition was also present.

In England, Martin (1945),(1946) reported on 36 cases of congenital deafness in which there was a history of maternal rubella at some stage during the first 4 months of pregnancy.

Analysing the combined work of several authors. Aycock and Ingalls (1946) give an average figure of 9 weeks for deaf-mutism. For combined cataract and deafness, the maternal rubella occurred in the first month in 1 case, and in the second month in another case.

Hopkins (1949) found that out of 92 post-rubella deaf children, in 10 cases with congenital ocular defects, the mother had contracted rubella during the first 2 months of pregnancy.

Swan and co-workers (1946) noted that deaf-mutism and cataract did not commonly occur together. They found in fact, that deaf-mutism occurred three times more frequently than cataract. Several theories were advanced. One was that the "cochlea anlage might be more vulnerable to virus infection for a greater

period/.....

period of time". Another theory was that there was a higher mortality rate amongst cataract cases, causing early elimination from statistical reckoning. Swan (1949[a]) gives a table of 24 cases collected from the world literature, where deaf-mutism occurred concomitantly with cataract. The maternal rubella infection had in all cases occurred within the first 2 months of pregnancy (13 in the first month and 11 in the second month.) The same author gives another table relating to 226 cases of congenital deaf-mutism irrespective of whether there were concomitant defects or not. These cases were virtually confined to children whose mothers had contracted rubella during the first 4 months of pregnancy and the highest incidence of cases was in the second and third months.

Aycock and Ingalls (1946) further extracted the following average periods of pregnancy, for post-rubella anomalies (cf. p.272):

For cataract	6 weeks
For deafness	9 weeks
For cardiac abnormalities	5 - 10 weeks
For deformed teeth..	6 - 9 weeks

They quoted Carruthers, ".... in the first 6 weeks, foetal damage may be widespread, and include the eyes, both divisions of the ears, the heart, and perhaps many other parts. After the sixth week, the eyes may escape, the heart may be spared, and the semi-circular canals may become normally developed; but the cochlea is still likely to be damaged".

Clayton-Jones (1947), who investigated post-rubella deaf children, found in no case a history of maternal infection after the first four months of pregnancy. Nor did he find an obvious tendency to

premature/.....

premature birth amongst such children. His census was very small, however, (20 cases) and Hopkins (1949) in a larger census found a definite tendency to premature births, especially where the maternal infection had occurred in the first month of pregnancy.

Handling of post-rubella deaf children.

Unfortunately, so many post-rubella deaf children are mentally defective, but congenital deafness, may produce as we have seen, a pattern suggestive of feeble-mindedness. The ordinary intelligence tests are not effective, and the most satisfactory of these are performance tests such as picture completion tests, form-board tests, block designs and suchlike manipulations. The Goodenough "Draw a Man" test is fairly good at 4 - 5 years (Silver, 1950; Gesell, 1940) but the Pintner-Paterson (1923) and Pintner non-language tests are regarded as the most reliable for the deaf.

It is again to be emphasized that whenever a child does not commence talking at the expected age, or whenever its speech is unintelligible, or when simple words appear meaningless to him, a careful investigation of the auditory powers should be instituted. It should also be borne in mind that a deaf child often gives some kind of "bluff" response, whether he hears or not.

The congenitally deaf have great difficulty in learning to read or write. Some never acquire these abilities, and school progress is correspondingly painfully slow. Many deaf children have, however, attained academic success in spite of their handicap.

There is no consistent personality pattern

amongst deaf children, and these unfortunates vary much in behaviour depending on parental attitudes, home environment, and ability to adjust socially. When loss of hearing amounts to 15 decibels or more, difficulties tend to appear in adjustment (Bakwin, 1950). Bakwin further notes that an important factor tending to make a child feel rejected, is the likelihood of his being sent to an institution, especially if his normal siblings remain at home. Schooling for deaf children should ideally begin very early, even at 2 or 3 years in Nursery groups, and the early use of mechanical aids is advised. Of course, parental embarrassment and feelings of guilt need to be contended with, and guidance or reassurance is necessary. During the early years, the deaf child adjusts well in the house, and learns with great facility except where language is concerned, and in this respect, the parents should be guided as to how best to help the child. Because there is so often some residual hearing, it is important to expose these infants from very early to a constant flow of language, just as if the child were normal in hearing capabilities. Bakwin (1950) cites that the mother should talk close to the child's ear, and objects should be named and then pointed to. The speaker's head should be steady, in a good light, on a level with the child's face, and speech should be a little more slow than usual.

Matching one thing to another is employed in education and the child's attention should be drawn to various other sounds of everyday life, such as motor horns, church bells, etc. Apart from speech difficulties, the deaf child of normal intelligence, is not at a great/...

a great disadvantage but actual teaching of speech is best left to trained individuals. For reading instruction, books should be simple at first, so as not to discourage the handicapped child. If the child is bright, the ability to read is a wonderful asset, and fortunately only a few post-rubella children are blind as well as deaf.

The deaf child, like most handicapped children, should be loved, but not spoilt or felt sorry for. Punishment should never be administered for default unless it is perfectly clear that the child is disobedient through sheer "naughtiness", and not through lack of understanding on account of his deafness. Full acceptance of the child in the family, by the family, is ideal. Unfortunately, economic and other necessities force many deaf children into institutions. At St. Vincent's School for Deaf in Johannesburg, it has been the experience that deaf children who are so often frustrated and "difficult" at home, become easy to handle in the institution, and learn readily.

CHAPTER XVII.

C A T A R A C T.

AND OTHER OCULAR DEFECTS.

(1) EMBRYOLOGY OF THE EYE, AND PARALLEL DEVELOPMENT OF OTHER SYSTEMS.

In embryos as far back as the eight somite stage (about fourth week), an optic area can be identified on each side of the wall of the forebrain (Arey, 1946). At 14 somites, when the neural groove is still incompletely closed, the optic areas become easily identifiable as hemispheric swellings. Before the embryo is 4 millemitres long, the *optic vesicles* are attached to the primitive brain by *optic stalks* along which the optic nerve later grows. The lens is formed by a thickening of overlying surface ectoderm. Contemporaneously in the fourth week, the accoustic ganglia are appearing, the neural crest becomes a continuous band, a primitive paired blood vessel system is forming, and the heart tubes are fusing into an S-shaped bend. From the fifth to the tenth week, the heart and blood vessel system undergoes tremendous development, and about the ninth week, the internal and external ear parts assume final from. From the sixth to the ninth week, the teeth anlages develop from labio-dental laminae to primitive enamel organs and dental papillae. From seven to eight weeks the cerebral hemispheres are markedly distinguishable, and the cerebral cortex acquires typical cells. The lens vesicle becomes detached at six weeks, retinal pigment appears, the vitreous body is present, and the chorioid fissure is closing. The early appearance of

eye/.....

eye anlages helps to explain the high incidence of ocular defects found amohgst all congenital anomalies, and why so many eye malformations are associated with defects of the central nervous and other systems.

(2) GENERAL SURVEY.

It would appear that most cataracts, congenital and even senile, are based on genetic factors. Inheritance is usually dominant, sometimes recessive and very rarely sex-linked. Post-rubella cataract, is ofcourse, a notable exception, but comprises only a small minority of cataract cases. In some families, cataract appears during childhood in some members, and in late life (senile type) in other members. Senile cataract may occur in identical senile twins.

The crystalline lens is a living structure, the transparency of which is related to various biological processes, involving osmosis as well as calcium, potassium amino-acids, proteins and glutathione metabolism. The lens capsule, or envelope, is normally permeable to electrolytes and small colloids of low molecular weight. A decrease in permeability allows proteins to escape, and precipitation of lens proteins induces opacity. Campbell (1936) states that sugar excess, vitamin deficiency, disturbed calcium metabolism or loss of cystine from the lens substance are all probable aetiological factors. In rats, tryptophane deficiency, or a diet of galactose may produce cataract, and hence tends to support the above statement.

Cataract inherited in sublethal and sex-linked fashion is described, and Gates (1946) citing Danforth, gives a pedigree where lamellar cataract together with

deformed/.....

deformed retina presented as a dominant in 9 cases in 3 generations. The original male progenitor had several normal children by a normal first wife. The second wife, also normal, bore one child with cataract from which the descent arose. The probability is, that this child represented a mutation, although recessive factors carried by other children cannot be excluded, particularly when it is seen that there are six affected sibs in the fourth generation.

Gates quotes figures showing that 13 per cent of pupils in blind schools are cataract cases, and should not have children, especially where inheritance is by the dominant mode. Five blind progenitors produced a total of 68 congenitally blind descendants in 3 or 4 generations.

In all hereditary eye diseases, many isolated cases occur in a family history. Such are probably mutations, recessive Mendelian "outcrops". In some pedigrees, too, anticipation appears to be operative, because members in succeeding generations are attacked earlier and earlier (Vinsonhaler & Cosgrove, 1936). Julius Bauer (1945) in "Constitution and Disease", draws attention to what appears to be, in certain cases, a constitutional weakness of ectodermal structures as evidenced by cataract, neurodermatitis and other rare skin diseases.

The especial liability of the eye to be affected in congenital disease (e.g. after maternal rubella) appears to be related in some degree, to its initial rapid development. (Gruenwald, 1947). Apparently no type of teratogenic agent will fail to produce eye ....

defects/....

defects under certain conditions. Lande (1950) studied retrospectively 16 children in an institution showing the post-rubella type of syndrome. In 7 of these, a history of maternal rubella was found, but in 5 cases a common cold, and in 1 case virus influenza, during the first trimester were the aetiological factors regarded as being operative. The ocular defects associated with the common cold and influenza appeared to differ from those in post-rubella patients. Buphthalmus, complete agenesia of the eyeballs, optic atrophy and residual chorioretinitis or abnormal pigmentation of the retina were seen in addition to cataracts.

Toxoplosmosis by prenatal infection from the mother may cause a chorio-retinitis. Congenital syphilis may also very rarely cause iritis or chorio-retinitis in early infancy.

Retrolental fibroplasia, is an eye condition which presents a grey, seemingly opaque or opaque tissue in the anterior part of the vitreous immediately behind the lens. Occasionally blood vessels and sometimes even haemorrhages are seen in this tissue (Post, 1950).

Since Terry (1942) first described this condition, more cases have been reported from all over the world. The present writer has traced two cases in South Africa through the National Council for the Blind (1950). In the one case the child was born prematurely, and in the other, the child might have been born prematurely. Reese (1949) states that the condition may occur in full time infants (though mostly in infants born prematurely); and it is found in one or more of twins or triplets in from 10 to 15 per cent of cases. Twenty five per cent of cases of retrolental

fibroplasia/...

fibroplasia have associated elevated skin haemangiomas, often multiple and widespread, present at birth. According to Reese, the condition is congenital and he found vaginal bleeding in the mothers during pregnancy in about 30 to 33 per cent of cases. Ingalls (1948) suggests foetal anoxia as an aetiological factor in cases of a similar nature. Owens and Owens (1949) maintain that the disease develops post-natally and that vitamin E deficiency may be implicated. The writer considers it possible that the cause may be found in a combination of factors involving the mother before the child's birth, and the environment post-natally, and a better comprehension of the aetiology may help to elucidate the pathogenesis of post-rubella congenital cataract.

(3) EYE DEFECTS FOLLOWING MATERNAL RUBELLA.

(a) Incidence. Cataract is the fourth commonest congenital anomaly following maternal rubella, as found by Swan and his co-workers, although other workers find a higher incidence (Conte et al, 1945). Bardram et alter (1947) cited 8 cases of maternal rubella followed by congenital defects in infants. Five mothers had rubella between the 3rd and 4th weeks of pregnancy. One foetus was still-born after 6 months. There was a high incidence of ocular anomalies in this series:

Cataract -	Bilateral	5 cases
	unilateral	2 cases
Microphthalmus		3 cases
Pigmentary degeneration of retina		3 cases
Incomplete iris coloboma		1 case
Morbus cordis		5 cases
Peculiarly long trunk		1 case
Long fingers and toes		1 case

Of/.....

Of 204 cases of post-rubella cataract collected by Swan (1949[a]), in 150 the defect was binocular, and in 54, monocular. Of 35 unilateral cases, in 21 the cataract was left-sided and in 14 it was right-sided.

Microphthalmus is a frequent concomitant of post-rubella congenital cataract. Gregg noted it in approximately two-thirds of his cases. Swan et al (1943), Reese (1944) and Albaugh (1945) emphasise the shallowness usually found in the anterior chamber. Reese (1944) and Krause (1945) noted a sluggish pupillary reaction to light, while Albaugh (1945), and Goar and Potts (1946) obtained a brisk reflex. Subluxation of cataractous lenses was occasionally noted (Swan 1949[a]), as was also strabismus, optic atrophy, anterior uveitis, and nasolacrimal stenosis.

In U.S.A., Miller et al (1949) found recorded in children whose mothers had had rubella actually diagnosed by direct medical examination during pregnancy, agenesis of optic centres of brain (rubella 9th - 12th week of pregnancy), bilateral hemianopsia and retrolental fibroplasia each occurring singly as separate defects (rubella in 13th week or after). Glaucoma was found to be associated with cataract, microcephaly, and mental deficiency in 2 out of 3 cases. Where the maternal infection had been diagnosed in retrospect by history, amongst the usual ocular anomalies recorded, were the following:

> Chorio-retinal atrophy associated with cataracts, deafness and cardiac anomaly (maternal infection in first 4 weeks of pregnancy); chorio-retinitis associated with deafness and microcephaly (rubella in 9th to 12 week).

Of the/....

Of the post-rubella ocular lesions occurring in the absence of cataract, probably the most important of these was buphthalmos. (Swan et al 1943; The New South Wales Committee, 1945; Prendergast, 1946). Pigmentary changes of the retina, strabismus, and microphthalmos sometimes occurred (Swan, 1949[a]) and more rarely corneal opacity, naso-lacrimal stenosis, nystagmus, amaurosis, amblyopia, atrophy of iris, optic atrophy, doubtful coloboma, and vitreous opacities (Swan 1949[a]).

(b) Stage of pregnancy when rubella incurred: Out of 16 cases of cataract reviewed by Swan et al (1946), the following information was disclosed:-

Cataract - 16 cases (1st month : 9 cases) (2nd month : 6 cases) (3rd month : 1 case)

Aycock and Ingalls (1946) extracted from the combined work of several authors, the fact that the average period for cataract development was 6 weeks of pregnancy. Swan (1949[a]) collected 108 cases of post-rubella cataract from 26 different sources in the literature, and found that cases of cataract are virtually limited to infants whose mothers had suffered from German measles in the first 3 months of pregnancy, and that the highest incidence was in the first month (nearly 50 per cent of the cases). Cases of cataract occurring concomitantly with deaf-mutism were found by the same writer to be confined to the first 2 months of gestation (24 cases).

Miller et al (1949) found in U.S.A. that of 89 children whose mothers had had rubella during the first trimester of pregnancy, 51 showed cataract formation. The highest incidence occurred in those

cases/.....

cases in which the disease was present between the fifth and eighth week.

(c) Diagnosis. Cataract as a congenital anomaly following rubella is usually bilateral, and subtotal in type. There is associated nystagmus, and often sluggish pupillary reaction to light. Dilatation with atropine is difficult. Light perception is apparently quite obvious. The nystagmus tends to be absent in young babies, but very common in older or untreated cases, generally developing after the first three months of life. The eyeballs jerk in coarse, purposeless movements, "searchlight" in type, but without fixation. Gregg emphasised that a guarded prognosis should be given as to the future mental status of children with bilateral cataract in view of the very great tendency for such cases to show associated mental defects.

The iris is often atrophic in appearance. (Krause, 1945; New South Wales Director General of Public Health, Committee 1945). The nuclear portion of the lens is most affected and the cataract does not correspond to any previously known type.

Behind the crystalline lens, there is opaque, vascularised tissue, on which vessels tend to radiate from a central point. In appearance, the lens is a flat white disc with radiating lines visible. The peripheral zone appears clear, if the pupil is properly dilated. Swan et al (1943) say the cataract "resembles a minute white starfish". The lens is small and tends to move while being needled.

Histological examination done by Swan et al (1943) showed the peripheral part of the lens to be ...

degenerated/...

degenerated or necrosed, with vacuoles interspersed throughout. The central core was amorphous in appearance. Cordes and Barber (1946) found a somewhat similar histological appearance in the eye of an embryo, where the maternal rubella infection had occurred in the fifth week. Cordes (1949) examined the eyes of a 11 week old embryo, with a history of rubella in the last part of the second month of gestation, and found shallow anterior chambers as well as cataract formation. Most of the primary and secondary lens fibres showed degeneration with formation of globules and homogeneous masses of dark staining fluid. Nuclei of the primary lens fibres showed pyknosis and fragmentation. Cordes also reports on the eyes of embryos where rubella had been contracted just before the second month of gestation, just before the third month, and about the third month respectively. Macroscopic and histological examination in these cases disclosed no abnormalities of the eyes at all.

For proper examination a general anaesthetic is necessary. Some of the autopsied children were found to have enlargement of thymus, and if such findings can be accepted as a contributory cause of death, then anaesthesia apart from any concomitant weakness or cardiac disease, is risky. The cardiac lesion of course, may not be obvious.

Discission. Gregg and Swan found discission difficult, because of the small cornea, and shallow anterior chamber. They felt that breaking up the whole cataract was called for, rather than needling. Dr. A. Robbin quoted by Albaugh (1945) removed such a cataract by a

suction/.....

suction method and and was able to observe the fundus immediately after operation. He found it not to differ from that of a child with the ordinary type of cataract. Morlet (1949) examined 60 post rubella children in a follow-up study in Western Australia, and in 36 cases unmistakable choroido-retinal changes were present. Therefore 60 per cent of "rubella children" examined in Western Australia, had abnormal fundi. Morlet noted also that in no single case so far, had loss of visual acuity attributable to retinal changes been found. Gamble (1946) describes a membraenous type of cataract. Ehrlich (1948) cites a few cases all over the age of 6 months where on needling, only a thin membrane was found, which divided readily.

Atropine dilatation, of the pupil is difficult (Swan et al, 1943; Swan et al, 1946) and infants are prone to develop constitutional effects from its local use, perhaps because of the weakened state of the infant, and because drops from an ordinary dropper contain a fairly large amount of atropine relative to the small bulk of the child. (Albaugh, 1945). Albaugh therefore used neo-synephrine with apparently much better results.

On dilatation, two main types of post-rubella opacity were observed:

(1) The type, with a marked contrast between the large pearly central area and the small, clear, periphery, giving a red reflex. Between the clear periphery and the opacity, was an intermediate zone, smoky in appearance of lesser density than the central opacity.

(2) Type of cataract with more uniform density throughout, extending to all but the most superficial layers of cells.

The/.....

The ordinary type of congenital cataract in children is of two main types.

In the lamellar type, the opacity is situated in the peripheral part, the central core containing punctate opacities. Outside this is another clearer concentric ring. This type is not present at birth, but occurs early in childhood, and is probably of congenital origin. Parsons (1936) notes that lamellar cataract is almost invariably associated with defective enamel in certain of the permanent teeth. The teeth have an eroded appearance with transverse lines across them, the incisors and canines being most affected, and differ essentially from the condition found in congenital syphilis. Parson says, "when the pupil is dilated, a grey discoid opacity is seen, surrounded by a perfectly transparent marginal area .... occasionally two concentric rings are seen." Sometimes "riders" or radiating spokes are detectable on the peripheral edge of the opacity, penetrating slightly into the clear area. The condition tends to be bilateral, though more advanced in one eye than in the other.

Parsons (1936) says that, experimentally, lamellar cataract has been produced in offspring of rats, whose mothers had been fed on a diet lacking in vitamin A., fat and phosphorus. That this condition is a deficiency disease, is shown by the fact that such cataracts are curable by giving the affected offspring a normal diet. In the young, there is cataract but no rachitic changes. In their mothers, fed on vitamin A deficient diets, there are rachitic changes. Warkany and Schraffenberger (1946) found eye changes in the young of mother rats fed on vitamin A deficient dietary.

"Open/.....

"Open eyes", an abnormality, folded retina, coloboma, eversion of the retina were sometimes found; also, rudimentary iris and ciliary body, or fusion of cornea with lids. The lens, however, was essentially normal, the most constant defect being the presence of a retro-lental membrane of fibrous tissue around the hyaloid vascularisation, with replacement of the vitreous. Abortion was frequent, and there were also associated thoracic and abdominal anomalies. Cohtrol rats of a similar strain on normal diets produced normal offspring.

The anterior capsular kind of ordinary congenital cataract, cortical or nuclear in type, consists of a small spherical opacity in the centre of the lens, surrounded by a clear cortex. Fusiform, or spindle-shaped types occur, occasionally with branching coral-like processes. This form has a tendency to be familial. Discoid cataract is also of genetic origin, occurring in families, and showing up as a somewhat ill-defined disc-like opacity just behind the nucleus in the posterior cortex. The punctate-type, self-descriptive, varies in form; and there is a total type. Many of these, the "ordinary" type of congenital cataract, are associated with other congenital stigmata, e.g. nystagmus, coloboma etc., and most are stationary, requiring rarely urgent interference.

Traneshetti (1947) describes a "digito-ocular phenomenon" found chiefly in children with congenital cataracts and relates it to the occurrence of phosphenes because it is not found in patients with faulty light projection. It does not develop in cases of incomplete cataract where some vision is retained. The

afflicted/....

afflicted children, vary somewhat in their behaviour. Sometimes they push their fingers into both orbits, sometimes only into one. Some children touch the globe with one finger; others with several fingers. One of his cases, showed an antero-posterior movement of the head. Franeschetti, who had observed this phenomenon in several cases since 1931, afterwards related it also to two cases of congenital cataract where the mother had had "rubeola" (German measles, translation from the French) during the first trimester of pregnancy. He too, suggested early operation on such cataracts, because nystagmus does not develop until a few months after birth.

In ordinary congenital cataract, all that is necessary, is to pierce the capsule, thus permitting aqueous to enter into contact with the lens material. In the post-rubella type, the lens substance may be required to be broken up to obviate glaucoma (Smith, 1948). In some cases, at operation, the whole opaque disc was displaced into the anterior chamber, with subsequent relatively rapid absorption. Swan et al describe attempts to lift the cataract out at operation. Early operation was recommended in bilateral cases, although delay was considered justifiable in unilateral cases if the patient's condition was not considered suitable for surgical intervention. Correcting lenses are probably advisable post-operatively. Even with early operation in bilateral cases, there is great danger of the eyes remaining with amblyopia and strabismus. Perera (1948) believes that early operation is advisable before the sixth month of life, preferably during the 2nd and 3rd

month.

A description was given of the follow-up on two cases of post rubella cataract (Swan et al., 1946).

(a) A child was admitted with doubtful glaucoma at the age of three years, 9 months, spontaneously subsiding. There were keratic precipitates in the eye. The cataract was of the Morgagni type, i.e. a solidified nucleus in the fluid semi-opaque cortex, gravitating downwards and shifting with movements of the head. At five years and one month, the cataract had disappeared spontaneously, thus explaining the original inflammatory attack. The keratic precipitates had also vanished, but bilateral nystagmus was still present, and no fundal detail was distinguishable. In the opposite eye, the fundus was clearly visible, and evidenced irregular pigment in the macular region with white choroidal spots in the vicinity.

(b) One case with bilateral cataracts had been treated by discission, commencing at 3 months of age. At three years and 7 months the child was able to differentiate colour easily, and name objects correctly.

Adams (1945) noted that progressive increase in the size of the cataracts sometimes took place. Ehrlich (1948) described the case of a baby girl born 4 weeks prematurely with congenital cataract and deafness. The mother had had rubella in the first month of pregnancy. Both lenses commenced to show absorption after the age of 10 months, more so in the right eye. Discission was delayed until 3 years and complete success was attained in the right eye, while the left is still under treatment. Ehrlich cites 4 other cases of possibly spontaneous absorption of congenital cataract, in three of which the mother had had rubella during the early part of pregnancy. Morlet (1949) tracked, in Western Australia, 82 post rubella congenitally defective children in a follow-up study. All the children, but two, were deaf, and none were completely blind.

CHAPTER XVIII.

DENTAL ABNORMALITIES.

Out of 8 children of the original Australian series classified as normal when originally examined, 2 later exhibited dental defects. Most of the defects were related to rubella in the early half of pregnancy, and especially in the first 6 to 9 weeks, (Evans 1944). Evans (1947), found 30 of 67 post-rubella children to be suffering from major congenital dental anomalies excluding caries. If caries and restricted arch formation be taken into account then 46 of the children exhibited anomalies. All but 5 of these showed other congenital anomalies as well.

The dental laminae are first detectable in the 6th week of embryonic life, and dental papillae appear in 9 weeks; calcification commences in the 20th week. On this basis, cases were divided into groups A, B and C, shown below. Evans (1944) investigated 34 cases, where the mothers had had rubella in pregnancy, and found 23 exhibiting congenital dental anomalies, 18 of major nature. Each group of teeth has its own critical period of development, and the time of German measles infection could possibly be determined to a certain extent on the basis of developmental anomalies of the teeth.

TABLE/.....

T A B L E X. (Evans, 1944).

Post-Rubella Congenital Defects.

Retarded Dentition	Total No. Cases	No. of Children affected	Eruption grading of affected Children			Average age in months at eruption of 1st tooth in both affected infants and normal infants
			+++	++	+	
Group A (Rubella before 6th week pregnancy)	9	5	1	1	3	11.5 (9)[x]
Group B. (Rubella between 6 to 9 weeks)	12	9	2	2	5	11.8 (9)
Group C. (Rubella after 9 weeks)	13	2	0	0	2	7.6 (13)

Eruption grading is based on the time of appearance of 1st and subsequent teeth (6 - 9 months for first tooth) and varies from most retarded +++ to to least retarded +. [x](The number of cases on which figures are based are in parenthesis.)

(1) Retarded Eruption was the most significant abnormality. Evans notes that retarded eruption is also seen in syphilis, rickets, idiocy and cretinism. It was surmised that later follow-up would show retardation of permanent teeth, although retarded dentition does not appear to be of great clinical significance. Contrary to the findings of the New South Wales Commitee (1945), a further 53 cases investigated by Evans in 1947 further confirmed these results. Retarded eruption of decidious teeth seemed to have a

much/....

much higher incidence in the early pregnancy groups.

In 4 out of the 67 children, however, there was *premature eruption* of the permanent dentition, incisor or molar teeth after the 3rd year and before the 5th birthday. In all of these cases, the mothers had had rubella prior to the second month of pregnancy, and these 4 children had other serious concomitant anomalies, deaf-mutism or microcephaly.

(2) Hypoplasia, either mild, or marked may occur. Pitts is cited for the incidence of hypoplasia in decidious dentition of normal infants as about 0.4 per cent. In Evans' series of 34 cases, the incidence was approximately 23.5 per cent. In a later series (Evans 1947), with 33 additional cases, the incidence was 20 per cent. The hypoplasia was not general, being mainly localised to 1 or 2 pairs (in one case 3 pairs). In all but 2 cases the hypoplasia was mild. Four cases of hypoplasia occurred in group A cases (rubella before the 6th week of pregnancy and hence before the appearance of the dental anlages), and are tentatively explained by persistence of virus in the tissues. The present writer feels that it is difficult to fix by history the time of conception and hence length of pregnancy. The hypoplastic teeth are not more susceptible to dental caries, according to Evans. The virus of rubella is suspected of affecting the connective tissue cells, causing tissue collapse.

(3) Abnormal Tooth Form: Seven out of 34 had defective tooth form. (With one exception, all mothers had had rubella in first 2 months of pregnancy). (Evans 1944).

In/....

In all cases the incisor edges were affected, "sharklike". In two cases incisor edge lacked magnitude being pointed, and one case showed "marked labial convexity in lower anteriors, the incisor edge representing the arc of a circle, instead of a straight line". In one case, the incisor edge was rounded instead of straight. One case showed abnormality of biting edge of upper incisors. Both central incisors had extremely rounded edges.

Other anomalies: 3 out of Evans' augmented series of 67 children (1947) showed absence, confirmed by radiography, of upper or lower lateral incisors. Six out of 34 showed evidence of restricted arch formation, which did not differ very significantly from children whose foetal life was normal (Evans, 1944). Sex appeared to have no influence on the incidence of congenital dental anomalies in general. (Evans 1947).

(4) Dental Caries: Kronfeld (1939) is quoted as saying "there is strong evidence that the tendency towards dental caries or an immunity to the disease may be transmitted from parent to child according to the laws of familial inheritance". Apparently environmental factors play a contributing role. Four out of 34 showed dental caries, a higher incidence than for a similar group of the population at large. However, the small number of cases invalidated accurate conclusions. The result is merely suggestive.

Evans in his later survey (1947), which recorded 67 children (including the original 34), further substantiated his original findings. Of the 67 children, 14 were found to be suffering from early

caries, "a proportion considerably higher than that occurring in a similar age group independantly selected from a cross-section of the community. This proportion was also higher than that recorded by the same author in his original series of 34.

The dental caries appeared to be related to the period of pregnancy at which rubella, occurred. Only one case of caries was noted in Group A where maternal rubella was contracted before the 6th week of pregnancy, although other dental anomalies were seen. As the fibrillar network of early tooth formation is laid down before the 10th week, it is precisely during this period (6 - 9th week - Group B) that maternal rubella induces the highest incidence of dental caries in the offspring. The later pregnancy groups were relatively free from caries. Weinmann J.P. (cited by Grüenwald, 1947[a]) postulates that inhibition of enamel matrix deposition causes hypoplasia of enamel and if maturation be affected, then hypocalcification results. These abnormalities may result from hereditary or intrinsic causes. Hereditary varieties affect all teeth uniformly, whereas extrinsic causes produce enamel defects in the parts which were developing while the noxae were operative.

Clayton Jones (1947) in a small series of 7 cases investigated, found no evidence of delay in the eruption of the second teeth and no abnormal tendency to caries. His series was very small. Hopkins (1949) calculated in post-rubella deaf children, the average age at which these children got their

first tooth. She obtained control figures included below in rubella deafened children.

TABLE XI.

Eruption of Teeth in Post-Rubella Deafened Children.

Rubella deafened children: Month of pregnancy in which mother had rubella.	Age Month
First	11:6
Second	9:4
Third	8.2
Sibs of rubella-deafened children	6.6
Hereditarily deaf children	7:3
Sibs of hereditarily deaf children ...	6.7

CHAPTER XIX

MONGOLISM : AETIOLOGY, PATHOGENESIS, AND ITS RELATION TO RUBELLA.

Mongolism in a sense, should be considered a symptom, and not a specific condition based on one aetiological factor. This condition, is here discussed at some length, because it appears to result from an interaction between intrinsic genetic and extrinsic factors, the exact nature of which interaction, if better understood, would lead to opening up a whole continent of exploration in the genesis of malformations.

1. GENERAL SURVEY.

The term, "mongolian", is applied to a type of idiocy purely in a descriptive morphological sense, but has no genetic implications as regards true mongolian characters occurring in people of that race or racial descent. Mongolian idiocy may occur in any race of any colour, and true Mongolians are not exempt from the condition, although in them diagnosis is rendered more difficult.

Mongolian idiocy was first recognised by Langdon-Down in 1866. Brushfield (1924) found a high incidence of strabismus amongst those affected, but he did not find the "mongolian spot" in any of his cases. High gums, webbed fingers, and other abnormalities were frequently noted. Brushfield (1925) found an oblique plantar arch to be an almost constant feature. In 34 per cent of his 179 cases ill-health was present in the mother. Macklin (1929[a]) found in 68 foetuses

with/.....

with malformation especially anencephaly, 13 (20 per cent) exhibited simian creases which are so commonly found in mongolism. Benda (1939) states that only one-third of mongolian idiots have an epicanthal fold at birth. Growth is found to be at a slow normal level in the first 9 years of life, but early cessation of growth in height occurs, and after puberty, dystrophia adiposo-genitalis is frequently encountered. The skull is not microcephalic at birth, but it grows so slowly as to eventually be small relative to the child's age. Brachycephaly also occurs, due to early arrest in development at the base of the skull. Benda contends that the mongolian facies results from disturbance becoming apparent during foetal life. Gates cites Muralt (1942) who examined 22 Mongolian idiots, and found:-

> abnormal corneal refraction, oblique eyelid axes in all cases;
>
> in 14 cases;
>
> was partially astigmatic and poor, and all except three had cataract.

According to Gates (1946) mongolian idiocy is probably a mutation with recessive inheritance, at least so in most cases. Bleyer (1934) deduced from the soft elastic folds in the neck, and the tiny nipples set on a flat surface with a minimum of areola, that the condition is a degressive mutation.

Schlapp (1925) regards mongolism as a chemical phenomenon, and found cases in Jews and Negroes. In South Africa, cases are known amongst the Bantu.

Davidoff, (1928) described the brains of 10 mongoloid idiots. They all had, in common, a small

cerebellum and brainstem. The convolutional patterns were embryonic in type, being large, coarse and simple. There was a paucity of ganglion cells, in the third cortical layer when examined histologically. Findings can be summarised under three headings.

1) Agenesis (cell paucity with few gyrations)
2) Aplasia (small size, especially cerebellum and brain-stem)
3) Paragenesis (frequent occurrence of anomalies)

Gates quotes Schroder (1939) who made a genealogical study in 50 families where mongolism had appeared. He found a slight increase in feeble-mindedness, as well as single malformations and slight anomalies in the relatives, especially the sibs. A comprehensive statistical study disclosed that no general correlation exists between mongolism and malformations, but in pedigrees with mongolism, slight morphological aberrations are more common. He feels that some complicated genetic factor is concerned in the inheritance of the condition. He found more premature births and higher child mortality in families with mongolism. MZ (monozyotic twins) showed 88 per cent concordance. Twenty-five per cent of all the sibs of mongoloids showed aberration of intellect, but feeble-mindedness was no more frequent than in other families. There was, however, a high familial incidence of strabismus, attached ear lobes, primitive ear muscles, and polydactyly. He regards the condition as a polymeric recessive with genetical relations to feeblemindedness, associated too, with ovarian deficiency, hypogenitalism, and hormone derangement, whereby he explains the greater incidence of miscarriages and premature

births/.....

births amongst mongoloids.

Macklin (1929[a]), from a wide survey of the literature, extracted evidence that neither syphilis, nor advanced maternal age, uterine exhaustion, great relative differences between ages of both parents, mental or physical suffering of mother during pregnancy had any aetiological significance. She found it to be inherited, but not due to a single pair of recessive factors. In all of 275 cases she found the parents to be normal. She also recorded 22 cases, where two mongols occurred in the same sibship. Penrose (1934) added 7 more. There is also a record of 2 mongoloids having a total of 3 normal children by a normal spouse. The maternal age at their birth was 39 years and 40 years respectively, and various components of mongolism were seen in relatives (Halperin 1940).

From evidence such as the above, a recessive inheritance is indicated, and yet in a total of 2491 families, 2526 mongoloids were born, that is more than one to a family. Fantham (1925) found 9 cases among 32 children in a family of 3 generations, where rapid breeding was an associated occurrence, though not a proved aetiological one. Two sisters each bore mongoloid children, but transmission also occurred through the father. Lipizky & Boshes (1942) report the following cases:-

Two brothers married, and each had a mongoloid child. In both, there had been one previous normal child, and there was a history of miscarriage, premature birth, or stillbirth, (recessive inheritance). Cited are 2 sisters, each giving birth to a mongoloid.

Gates cites Waardenburg, who postulates as an aetiological factor, chromosomal aberrations such as loss of a chromosome segment. This view is based on:-

1) infrequent occurrence of mongolism.

2) combination of dominant and recessive characters.

3) tendency to further abnormalities and congenital defects in sibs.

AGE OF PARENT: In spite of Macklin's conclusion (supra), Penrose (1935) confirmed, statistically, that in general, mongols are born to elderly parents. He felt that mongolism was a recessive condition, with a high threshold value more likely to be attained, when the mother is older. He actually visited 150 families, and recorded the parental age at the birth of each child in a family with at least one mongoloid. He concluded that maternal age, but not paternal, was significant. Engler (1944) surveyed 113 cases of mongolism over 20 years, in a hospital. In 70 per cent the mother was over 35 years, but there were several young mothers. He also found that the majority of mongoloids were the last born in rather large families. In at least 12.7 per cent of his cases, a mongoloid was born following a curettage or the use of an abortefacient.

S. Wright (1926) showed that the age of guinea pig dams significantly affected the incidence of white coat colour and polydactyly in the offspring; but the age of the sire was unimportant.

Gates summarises his survey of mongolian idiocy as follows: "It appears that all the evidence except the usual occurrence of a single case in a family, leads to the conclusion that mongolism is a simple. . .

Mendelian/.....

Mendelian recessive, although the age of the mother may lower the threshold of expression." Many single cases might be due to family limitation after a mongol appears. Maternal age or multiparity may induce placenta praevia which may also be a possible aetiological factor.

Schuttleworth (1909) found 350 single cases, and Schlapp (1925) discovered 500. The low penetrance may have some relation to extrinsic factors. Hanhart, (1941) found 285 cases in 24 different stocks, and regards the condition as an irregular dominant, the father transmitting as often as the mother. He also found the average maternal age to be 35.5 years. Clinodactyly (deflection of the fingers), and other finger defects were frequent. He gained the impression that one of the parents usually shows finger deformities and other defects. In 105 pedigrees, a brother and sister each produced a mongolian idiot. The use of the term "dominant" is criticised on account of the rarity of reproduction in mongols.

C.E. Benda (1946) on the other hand, who did much work on the same subject, has contrary views: "my own material of more than 350 families, accumulated evidence that hereditary factors are of no importance." He noted that mongolism occurs amongst all social classes, and he feels that feeble-mindedness occurring in a family, as well as mongolian idiocy, is but a chance association. He considers that, since many a mongoloid child studied by him has had 10 - 13 siblings, yet in no such family has multiple incidence of mongolism occurred. This is at variance with Mendelian concepts, where one would expect increased

incidence/....

incidence of an inherited character in proportion to the number of offspring. Consanguinity, too, he states, has never been shown to result in increased incidence of mongolism as compared with the population at large. Yet he does not deny that hereditary factors play some part. There would appear to exist, however, some other factor in the mother upon which the mongoloid tendency is superimposed.

Benda also draws attention to cases of mongolism in dizygotic twins. Mutation, in such cases, at any rate, is out of question because of its rarity. Gillman's recent work with trypan blue, rather tends to confirm that mongolism in dizygotic twins is related to a disturbed metabolic state existing in the mother at the time of conception. Ingalls (1947) also remarks on a changed environment at time of implantation, as being able to affect two ova, even if not monozygotic.

Benda (1946) noticed also an increased tendency to miscarriages in a female who has produced a mongoloid child, and he wonders "if some of these miscarriages are not abortions of mongoloid babies." Other investigators certainly have detected mongoloid characteristics in foetuses. The present writer has on more than one occasion successfully diagnosed mongolian idiocy in premature infants born just after the seventh month of gestation. Macklin (1929a) found in 68 foetuses with malformations, especially anencaphaly, 20 per cent. exhibited simian creases so commonly seen in mongolism. Benda (1946) has drawn charts to show, that in families with a mongoloid child at the end of the childbearing period, the age of the mother, at the time when the..

normal children were born, was higher than in other families, i.e. childbearing commenced at a higher age than in the control group. Eighty four per cent of sibs related to a mongoloid child were born before it, and 16 per cent after it. Quoting the same author:

"mothers who gave birth to a mongoloid child had a period in their lives when they had children at, or even above, the average for all mothers. Then something happened: as a result, a mongoloid child was born, and from that point on, these mothers produced at a rate which was much below average. The imbalance between the number of children born before and afterwards suggests that the birth of a mongoloid child indicates the development of a pathological condition of the mother, which bears a definite relationship to her ability to have children. The decrease in fecundity in the mother, after a mongoloid child is not complete, as a small number of children are born afterwards. The condition of the mother is not irreversible, and yet the material shows that the birth of a mongoloid child marks a turning point which is followed by a decided diminution in the number of children born subsequently."

One might ask, however, whether the diminution in rate of child-bearing after a mongoloid child does not reflect the mother's fears of repetition of the condition, or increased preoccupation with an abnormal child precluding the care of other children.

Benda's reply is threefold:

1) The mongoloid baby is liked, is "cute", not distasteful.

2) Mongolism in many cases is not recognised until several years have elapsed, during which time the mothers might have become pregnant again.

3) Control investigation on mothers who produced spastic paralytic children, hydrocephalic infants, etc., indicated that although many are first children, the majority of parents continue to have many more children afterwards.

In families of more than five children, according to Benda, the mongoloid is almost always among the last three children. On the other hand, where the mongoloid was the first or second child, an unusually long time existed before the first, or between the two

children./...

children.

This author doubts the advisability of saving a foetus in an unexpected pregnancy where abortion is threatened, and where the woman is near the menopause.

Congenital cardiac anomalies, also, are commonly associated with mongolism. The incidence, on clinical evidence is 20 per cent; on pathological evidence, higher (Hill, 1908-9). Maud Abbott (1936) stresses as a "feature of extraordinary interest .... the frequent combination of mongolian-idiocy with ostium primum". There may be various valvular and other anomalies, including patent ductus arteriosus, pulmonary stenosis, and aortic stenosis.

In mongoloids, the genitalia are underdeveloped, especially in males. Normal sexual maturity is rare. Possibly a relationship exists between the hypogonadism and the poorly developed adrenal cortex found in the cases. It is also interesting to note that there is a relationship between anencephaly, microcephaly, and the adrenal cortex, though most likely all these anomalies are secondary to another primary factor. Only very rarely are there concomitant anomalies of other endocrines, e.g. absent thymus, persistent thymus, pituitary dwarfirm, pituitary enlargement, and absence of thyroid. Benda (1946) concluded that there is a constant pathological condition of the pituitary as shown by deformities or abnormalities of the intracellular secretary granules; "Mongolism is the congenital type of hypopituitarism." Ingalls (1947) quotes deformities such as ectropion, blepharitis, myotonia, and hydrocephalus as not originating in any particular stage of development. Those malformations which can

be/.....

be correlated with embryological growth are: narrow, oblique palpebral fissures, malformed ears, small size of pharynx, slit nostrils, defective and abnormally high palate, interventricular septal defects, spina bifida, syndactyly of fingers and toes, small undeveloped testes, hypospadias and atresia ani. Ingalls (1947) autopsied 13 cases, and found no characteristic gross or microscopic changes in the endocrine glands. In one instance only, was the sella turcica and its contained hypophysis unequivocally small; one infant aged 1½ months had marked hypoplasia of the cerebellum, pons, and medulla, with a suprasellar tumour located just posterior to the hypophyseal stalk. Are the above autopsy findings not secondary to some intrinsically primary genetic set-up? Bauer (1945) develops a theme showing how an intrinsic genetic constitution merely employs the endocrine system as a means to express end results; the endocrines are not primarily at fault. Two other infants in the series of 13, died of leukaemia, one at 8 weeks, (acute myeloid leukaemia), and one at 19 months with acute lymphatic leukaemia. This may also be an illustration of hidden genetic factors at work.

2) MONGOLISM AND RUBELLA: Up to the Australian Survey in 1946, mongolism was associated with maternal disease as follows :

Disease	No. of cases.
Rubella	4
Mumps	2
Pustular rash of obscure origin	1

Out of the above 7 cases, all but one were associated with infection in second half of pregnancy.

15 cases/.....

Fifteen cases of mongolism were surveyed retrospectively in the Adelaide Children's Hospital, but gave a negative history of any maternal infection during pregnancy. According to Swan, Tostevan and Black, "at the moment, there are no grounds for believing that rubella or any other infection during pregnancy, plays any part in the aetiology of mongolism".

Aycock and Ingalls, quote data in a survey by Ingalls and Davies (1947) of 50 mothers giving birth to mongolian idiots, 5 gave a history of some intercurrent disease, not necessarily rubella, during gestation: the intercurrent infections which all occurred in the second month of pregnancy, were rubella, "flu", mumps, mastoidectomy and pleurisy (3rd month).

This information contrasts sharply with that collected by Swan, Tostevan and Black, who found 6 out of their series of 7, to be associated with mongolism in the <u>second</u> half of pregnancy. The following information was also noted from hospital records in the series of 50, as being possibly of potential value:-

3 cases - ("Sick throughout entire 9 months"
(Sick all 9 months, nausea and vomiting,
(pain in right side,
(Haemorrhaged before delivery.

"continually vomiting".

"Grippe," during 6 month ..... 1 case
Afebrile rash, last trimester 1 case
Alcoholism ..... 1 case

Cholecystectomy, between 2nd pregnancy (normal) and a 3rd (stillborn), followed by a 4th pregnancy (mongolian) : <u>1 case</u>

a 8-gravida had a 9th (miscarriage at 3 months), followed by a 10th (mongolian), "pink staining" at time of period - 2nd month ..... : <u>1 case</u>

Summarising/.....

Summarising, in this series of 50 cases on mongolism, "there were 5 instances when a specific, relatively incisive maternal illness was present at the 8th week of gestation, and five others in which a more chronic maternal disorder included the 8th week of foetal life."

Attention was drawn to the localisation of the maternal disease to a specific stage of pregnancy, and to such concomitant defects, other than primary mongolian stigmata (e.g. 12 cases with deformed little finger). These defects included:

Imperforate anus	–	3 cases
Webbed fingers	–	1 case
Webbed toes	–	1 case
Cleft palate	–	1 case

These deformities may possibly, in some way, be connected with the embryological formation of the structures concerned, e.g. "membranous imperforate anus results from a persistence of the anal membrane, and arrest at about the 8th week. The limb-buds are visible on the 4th week, by the 6th week, there is crude differentiation of the limbs into their 3 divisions; phalangeal ossification occurs in the 8th week. Cleft palate is related to non-union of the palatal processes, such union normally occurring in the eighth week". (Ladd & Gross, 1934).

Ingalls & Davis (1947) later increase to 7 the number of cases of mongolism following intercurrent disease in the mother. (In 1 case the maternal disease was rubella). They correlate the disease with the second month of pregnancy and remark on the fact that mongolism is often associated with cleft-palate, syndactyly, imperforate anus, etc. which are also

localised/....

localised to the same period of pregnancy. They state that, "since there are 40 weeks to a normal pregnancy, there is only one chance in forty for a given illness to occur in any particular week - if the phenomenon is only a chance one." They provide the following table:-

TABLE XII: MATERNAL MORBIDITY AND MONGOLISM.

Age of mother	Intercurrent Disease	Stage of Pregnancy.
25 years	Influenza	2 months
34 "	Rubella	2 months
39 "	Mumps	2 months
* 43 " (?)	Mastoiditis	2 months
39 "	Pleurisy (in bed 3 weeks)	2 months
** 25 "	"Grippe"	2 months
*** 30 "	Acute purulent otitis media and sinusitis (with vomiting)	2 months

* Mother had pneumonia at birth of child and died.

** On a diet the first month of pregnancy, the patient lost 15 lbs.

*** Sinusitis occurred just prior to otitis. Mother was admitted to Hospital because of vomiting, necessitating intravenous administration of fluids.

Levy & Perry (1948) performed a controlled study and could find no definite evidence in favour of non-specific infections such as "flu" and "grippe" being causal factors in mongolism.

Patrick (1948) investigated, by means of a questionnaire method, 7822 out of a total of 21,509 children born in Queensland during 1941. Altogether there were 262 cases where the mothers were certain that they had contracted rubella during that particular

pregnancy/....

pregnancy and 129 of the children were examined clinically. Amongst these were 2 cases of mongolism.

In the series of 5 cases with anomalies investigated by Conte, McCammon & Christie (1945) in America, where rubella had been contracted during gestation, there was 1 case of mongolism. (included in the 5 cases of Swan et al, 1946). The maternal infection occurred at the end of the first trimester.

Ingalls (1947) later referred to another case of mongolism communicated to him by Benda. In this particular case, the mother had contracted German measles towards the end of the first month of gestation.

In a French survey (Gerard-Lefebvre et alter, 1948), where 2,247 foetal case histories were analysed, there was a definite history of an infective or toxic incident occurring during the first trimester in 20 cases. All these infants were abnormal and there were 2 cases of mongolism amongst them.

The present writer has also records of a case where maternal rubella was followed by mongolism:-

> A woman, aged 31 years, who had previously had a normal baby, contracted rubella between the tenth and twelfth week of her second pregnancy. The diagnosis seems to be definite, because her husband is a medical practitioner. When the child was born it was found to have the appearance of a mongolian idiot. It died, aged 2 weeks, apparently of a congenital cardiac condition. A subsequent pregnancy produced a normal child, and there is no history of any obvious congenital defects on either side of the family.

Analysing all the above information presented in this Chapter, the present writer comes to the conclusion that mongolism is the product of a combination of factors, partly genetic and partly environmental, ahd that rubella may be amongst the environmental factors operative in some instances, although the evidence to date on this point is not yet quite conclusive. Increased.

maternal age during conception does definitely seem to play a part in some instances, probably by affecting the metabolic environment of the developing organism.

CHAPTER XX.

M I C R O C E P H A L Y.

PATHOGENESIS: Apparently microcephaly is a phenotype with aetiology differing in different cases.

Spencer (1920) described the case of 2 microcephalic sisters born of normal parents who were first cousins - apparently a case of recessive inheritance. In this history, the development of the cerebrum appeared to be arrested. It is conceivable that in some cases, the brain may be intrinsically normal, but is hindered from developing by the shape of the skull, as occurs for instance in oxycephaly. Other cases are due to agenesis of the brain itself.

Recessive inheritance is also implied by Bernstein's family (1922) of German descent, where 5 cases of microcephaly occurred in a sibship of 10 with normal parents and grandparents. All the relatives were of normal intelligence, but the father is said to have had an abnormally low forehead.

Halperin (1944) reports on 3 sibships with 8 cases of microcephaly and 19 normals. The parents were normal (recessive inheritance). He also lists 89 recorded cases in 55 sibships.

Whitney (1930) gives a pedigree of 2 feeble-minded families, German and Swedish, who intermarried. In 4 generations, they produced at least 28 feeble-minded and 3 normal children, thus demonstrating an apparently recessive inheritance. There are doubts as to the legitimacy of the three normal children. In one sibship of this line, 11 were affected, 6 of whom were microcephalic and one was normal.

X-Radiation/....

X-radiation may also induce microcephaly, Haeber (1933) is said to have encountered microcephaly and eye defects in children of mothers exposed to X-radiation of non-pelvic regions during pregnancy. Goldstein & Murphy (1929) did not find any evidence of congenital defects in the offspring of mothers having had pre-conception radiation to non-pelvic organs.

In "true microcephaly", the brain remains abnormally small with mental development retarded, and often there are convulsive seizures associated.

The cranium is very small, rarely exceeding 18 inches in circumference while the face and remainder of head tend to approach normal size, thereby causing a characteristic disproportion between the lower and upper parts of the head. In many descriptions given of post-rubella defects, microcephaly is the term used merely to denote small circumference of the head, without regard to the mental status of the infant. In "true microcephaly" the fontanelles close prematurely, due usually to retarded cerebral development. The forehead is narrow, the vertex pointed, and the occiput flattened. The chin is receding, the ears are large and outstanding, while later in life the nose becomes prominent. Microcephalics are generally short-lived, and have a natural propensity to jump and climb like monkeys. There is, early in life, often a temporary spasticity, while later on there is a tendency to hold the head stretched forwards like a bird. Intelligence varies from idiocy to feeble-mindedness, and the disposition, in general, is unsavoury (Wyllie, 1949).

IN/.....

In the Australian series of 120 cases with post-rubella defects, 62 exhibited microcephaly, (Swan et al, 1946), but in the great majority of cases of microcephaly the aetiology is unknown, though almost certainly of genetic origin. Clayton-Jones (1947) examined 20 post-rubella deaf children and found that only 3 had normal sized heads, taking 20 inches as being the normal circumference.

Beswick et al (1949) saw 15 cases in the Paediatric Department of the University of Cincinnatti between 1944 and 1948, with a "post-rubella syndrome". Five of these cases, had microcephaly and by retrospective investigation, it was found that two mothers had been exposed to rubella early in pregnancy, but did not remember a rash; one mother had an exanthem in the sixth week of pregnancy which was probably rubella, and the remaining mothers gave a definite history of rubella in the 3rd week of pregnancy repsectively. The last case was a twin pregnancy and each twin, in addition to having congenital heart disease, bilateral cataracts, deafness and microcephaly, eventually developed epilepsy later on in life. The microcephaly was moderate, and at 17 years, the mental development of the twins did not exceed the 3 year level.

Many post-rubella children do not exhibit microcephaly and yet are mentally retarded, (Swan 1949[a]). Sometimes the diagnosis is given as "cerebral aplasia" or "cerebral agenesis".

CHAPTER XXI.

RUBELLA AND ABORTION. STILLBIRTH

1. ABORTION AND STILLBIRTH : GENERAL SURVEY.

Trauma, physical or psychic may cause abortion. Criminal abortion is one traumatic method. Mall (1917) showed that one of the most usual causes of early spontaneous abortion is abnormality in the foetus, which is inconsistent with life or normal development. A certain number of cases may be due to faulty implantation of the ovum, systemic disease in the mother such as diabetes, acute and chronic infections and rarely syphilis. Drugs such as lead are not abortifacient unless administered in poisonous doses. Erythroblastosis is not a cause of abortion, but may be of stillbirth. The question of hormonal unbalance is still not yet settled. Hain (1942) found in cases of threatened abortion, that the gonadotrophin and pregnanediol secretions were normal, and she suggests that utilisation, not production, is at fault. In rats, administration of progesterone is satisfactory in both threatened and habitual abortion. Mall (1917), Landtman (1948), and Worcester et al (1950) found a higher incidence of threatened abortion amongst mothers of malformed children.

Sutherland (1949), in an exhaustive survey, found that in the case of stillbirths, ante-natal influences are likely to be of more importance than obstetrical factors. He also found that there was a raised incidence of stillbirths associated with the following states or circumstances: sex of stillborn

children/....

children, males being more commonly affected; age of mother above 25 years; too long or short periods between pregnancies; multiplicity of births; previously high mortality rate in children of a particular mother; and poor environmental conditions. He found that maternal rubella in the early months of pregnancy, haemolytic disease and diabetes did not contribute substantially to the total stillbirth rate. Gilbert and Dunlop (1949) showed that there is not only evidence of raised stillbirth rates amongst diabetics, but also amongst those who subsequently develop the disease. Stillbirth, in general, represents a very considerable wastage of life, and in 1940-1942 varied in incidence from 21.9 per 1000 total births in Holland, to 43 per 1000 total births in Wales (Sutherland, 1949). Murphy (1940) found malformations in the stillborn to be 5.6 times more frequent than in the liveborn, and Worcester et al (1950) found malformed infants to account for 15.9 per cent of total stillbirths, and 13.2 per cent of total neonatal deaths.

2. CLINICAL AND AETIOLOGICAL ASPECT WITH REGARD TO MATERNAL INFECTIONS.

For a long time it has been known that maternal infections of smallpox, measles, poliomyelitis and influenza may cause abortion. Lande (1950) quotes the rate of abortion in smallpox as 80 per cent. The early Australian investigations gained the impression that rubella contracted during pregnancy, tended to raise the incidence of spontaneous abortion. (Gibson, 1945). Aycock and Ingalls (1946) mention one case

of Fox's, where a hydrocephalic stillborn foetus was delivered after rubella occurring in the first month of pregnancy. They, themselves, give 4 cases as follows:-

TABLE XIII.

MATERNAL RUBELLA AND STILLBIRTH OR ABORTION.

Case	Length of pregnancy before rubella	Estimated death of foetus	Haemorrhage before Delivery	Delivery of Dead Foetus
1	3 weeks	6 months	2 weeks	8 months
2	6 "	$5\frac{3}{4}$ "	1 "	6 "
3	Uncertain	Uncertain	none	9 "
4	4 weeks	immediate	none	6 weeks

Wesselhoeft (1947) describes another 5 cases. The present writer has had one case personally:

> A woman aged 27 had been married for five years and was unable to fall pregnant. Examination of the husband's semen failed to reveal any abnormality. Gynaecological examination also disclosed no gross or detectable abnormalities. She was treated for several weeks with thyroid sicca grss t.i.d., after which she refrained from treatment and was lost sight of for 6 months. At the end of this period she presented herself for examination because she was "overdue" with her periods by about 2 weeks. Pregnancy was presumed, and she was referred for re-examination after a months time. However, after a further fortnight, she was seen at home with rubella, i.e. when she was about 5 or 6 weeks pregnant. The rubella had been contracted from a child who was a neighbour. The infection passed over without a mishap or undue severity and she was acquainted of the possible danger of bearing a malformed child. She was also referred to a gynaecologist, who did not think that a therapeutic abortion was justifiable. The woman herself, also, stated that she preferred to "take a chance", in view of her difficulty in becoming pregnant in the first instance. When she was about 8 weeks pregnant, however, she began flooding and aborted within 13 hours. Unfortunately, the foetus had been disposed of, and hence could not be examined for evidence of malformations.

According to Wesselhoeft (1947), manifestations of rubella in pregnant women are apparently no worse than in other people. He points out that there is no evi-

dence yet as to what effect pregnancy has upon the incidence of rubella. It would seem that when rubella has become diagnosable in a pregnant woman, the virus has already attacked the foetus, so that administration of serum to the mother, once the diagnosis has been established, would appear to be of no use. Goodpasture noted the extreme susceptibility of embryonic tissue to virus infection, and hence the possibility also exists that rubella infection of the embryo may occur early during the mother's incubation period. In fact, Fenner's work on the mouse-pox virus (1948), the biological equivalent of human viruses, showing how that virus multiplies in the internal organs during the incubation period, rather suggests that the same may be happening in rubella, and that the placenta, even may be involved before clinical manifestation of the disease occur. If such is the case, then prophylactic use of serum products will not be effective unless administered early.

Goar & Potts (1946) described a case of rubella in the first month of pregnancy which was later followed by a twin birth. One of the twins had congenital cataract and heart disease, and the other was stillborn. Ober et al (1947) gave 4 instances of spontaneous emptying of the uterus, with rubella infection in pregnancy, in 2 cases during the 2nd month of gestation; in one during the 7th month, and one during the 8th month.

Swan (1948) undertook an aetiological survey of stillbirths recorded in South Australia during the seven years 1939-1945, with especial attention to the

incidence/....

incidence of infectious disease during pregnancy. A stillbirth was defined as a "baby of 28 weeks or more maturity since conception, who is delivered without showing any sign of life."

Of the 760 pregnancies, studied by Swan, infectious disease other than rubella occurred as follows:-

Morbilli	1 case
Mumps	2 cases
Mumps and whooping cough	1 case
Influenza or coryza	3 cases
Lobar pneumonia	1 case
Coryza	7 cases
Bronchitis	3 cases
Tonsillitis	1 case
"Gastric influenza"	1 case
Influenza	21 cases
Rubella	16 cases (One doubtful).

Thus the only infection which is comparable to rubella in producing miscarriage is influenza, a fairly common disease.

During the great influenza pandemic on 1918, there was a high rate of still-born foetuses and abortions, irrespective of the period of gestation (International Medical Digest, 1945).

None of the infectious diseases above listed, appeared to show any tendency to abortifacient action in the early months of pregnancy as is the case with rubella. As regards stillbirths, of the 16 instances (1 doubtful) of maternal rubella in pregnancy (Swan 1948), in 13 of these cases the infections occurred during the first four months of pregnancy. Only one mother in this series of 16 has had a stillbirth subsequently, the remaining 15 have had no other stillbirths, though 5 cases gave a history of miscarriages

either/....

either prior to, or subsequent to the stillbirths. In no instance was there a history of hereditary deformity or abnormality.

Swan (1948)(1949a) further indicates that when a woman contracts an infectious disease during pregnancy, several possibilities exist:-

(1) The embryo or foetus may be unaffected.

(2) The embryo or foetus may die due to a direct action of the organism, or its toxins, so that abortion, or stillbirth may occur according to the stage of gestation.

(3) Occurring early in pregnancy, the infection may damage the embryo by producing anomalies. The damaged foetus may either -

  (a) die and give rise to abortion or stillbirth; or

  (b) live to full term, but be unable to survive birth hazards and hence be delivered stillborn; or

  (c) survive to full term, being born alive with congenital defects.

In the 760 stillbirths investigated by Swan (1948), 15 or 16 were due to rubella, and in 13 of these the infection occurred during the first four months of gestation, thereby indicating that damage to the embryo or foetus may occur early, although it may survive for a variable period in utero thereafter. This conclusion is also strengthened by the case of Goar and Potts (1946) described above, and appears to explain the majority of stillbirths in maternal rubella. In a few cases (see Ober et al, 1947) stillbirth may be caused by rubella contracted later in pregnancy.

Swan (1949a) analysed 38 cases of abortions, miscarriages and stillbirths (collected from several sources in the literature), where the mother

had/....

had suffered from rubella during that particular pregnancy. This series was very small but the suggestion is, that, as with congenital malformations, the "critical period" is the first 4 months of pregnancy :-

4 abortions	:	Rubella occurred in : 2 the first month 2 the second month
9 miscarriages	:	Rubella occurred in : 2 the first month 2 the second month 3 the third month 2 the fourth month
25 stillbirths	:	Rubella occurred in : 3 the first month 7 the second month 4 the third month 3 the fourth month 2 the fifth month 1 the six, seventh and eighth months respectively 3 the month was indeterminate.

3. RUBELLA AND ABORTION: THERAPEUTIC AND MEDICO-LEGAL ASPECTS:

Wesselhoeft (1947[b]) states that after maternal rubella "any signs of miscarriage should be openly welcomed .... There is nothing in the dictates of the medical profession or in the common law of English-speaking countries that instructs a physician to attempt to prevent a miscarriage in the face of the evidence that has been presented .... Physicians are not bound to preserve life at all costs. Nothing is gained by saving a life, when agony and anguish lie ahead..... Because human life is sacred, there are exceptions to preserving it at all costs, and under all circumstances. Physicians are now faced with a new exception. No attempt should be made to prevent a

threatened/.....

threatened miscarriage in the course of, or after an attack of rubella, especially when that disease occurs in the early months. It is entirely up to the judgement of the attending physician to bring this to completion by surgical means. The medical profession is engaged in the prevention of disease, the preservation of life and the amelioration of suffering .... The problem presented by rubella in pregnancy, deals with the prevention of suffering in its broadest sense". Benda (1946) too, in his book expresses doubts as to the advisability of saving a foetus in an unexpected pregnancy, where abortion is threatened, and where the woman is near the menopause.

Wesselhoeft goes on to point out that even in Australia, there exist no legal grounds for termination of pregnancy complicated by rubella (Swan et al, 1943). In fact, all the early writers were not keen to recommend it. Fox and Bortin (1946) as a result of their investigation of 12 cases, in essence, condemned it. Wesselhoeft (1947[b]) is as we have seen, in favour of therapeutic abortion in such cases, as are Swan (1949[b]), Murphy, (1947), Cordes (1949), Scholes (1949), Abel and van Dellen (1949) and very many others.

The "Lancet" (1946) emphasises the fact that in England abortion is a felony, (1) if a woman with a child unlawfully takes a drug or uses an instrument to procure her own miscarriage; (2) if anybody else unlawfully gives her a drug or uses an instrument for that purpose. Note the word "unlawfully", interpretation of which is so very important; (3) "No person shall be guilty of an offence (under this section)....

unless it is proved that the act, which caused the death of the child, was not done in good faith, for the purpose, only of preserving the life of the mother."

In regard to the last point, the case of Rex vs. Bourne is cited. Bourne, a prominent gynaecologist, deliberately and openly procured an abortion in a minor female subject, pregnant as the result of rape. He was acquitted on the grounds, that by his operation, he was "preserving the life of the mother". The last phrase was interpreted "reasonably", i.e. the mother's health was spared, because if the pregnancy had continued, the mother would have become a "physical and mental wreck", due to the fact that her child would have been a living symbol of the indignity and violence to which she had been subjected. The same reaction of mind and body might occur to any woman who is assured that her child will be born with some terrible abnormality. Looking at the question from a purely medical viewpoint, it is the duty of the attending physician to remove all obstacles hindering the patient's recovery, and should a woman give birth to a malformed child, it might be argued that such an occurrence is a definite hindrance to her complete "recovery". According to the law, if an operation to terminate pregnancy is "justifiable" then the surgeon is not required to wait until the woman is in peril of immediate death, but it is his duty to perform the operation without delay.

To interpret the words, "preserving the life of the mother", more precisely, leads to difficulties

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in defence. Wesselhoeft (1947[b]) suggests that if tuberculosis is sufficient to terminate a pregnancy for the mother's safety, then so is rubella, because there always exists the possibility of the mother having a hydrocephalic infant, which may endanger her life at the time of birth. Such a possibility would of course be minimal, but nevertheless it is existent. Just as not every pregnant woman suffering from tuberculosis will die, (although there is a likelihood she will), so also an attack of rubella in the early months of pregnancy, is not invariably followed by malformations, but may be.

The Australian investigators showed that mothers who had produced such malformed children after rubella, either were so occupied with the case of such helpless children, or deterred by fear of recurrence in some future pregnancy, that they apparently refrained from having any more children in many cases, to the detriment of the State. A dead foetus in utero ordinarily offers no danger to the mother except the remote possibility of infection, or psychological trauma from the knowledge. Yet the Law allows in such cases, emptying of the uterus, because the issue of taking life is not raised. In the case of a pregnant woman with rubella, there is much more psychic trauma from the uncertainty in regard to the fate of the unborn child, such trauma being enough possibly to endanger the mother's health, and even her life. Liberality in the interpretation of the Law makes all the difference, and in 1938, Justice McNaughten urged just such liberal interpretation,

and/.....

and Bourne was acquitted.

Wesselhoeft also produced historical evidence to show how laws have been changed as a result of public opinion, but the fact still remains, that termination of pregnancy on the grounds just discussed is *prima facie* a felony, even though juries may be sympathetic. Conviction in such a charge of felony, implies fining, imprisonment, or removal of the doctor's name from the medical register. It is obvious that a change in the legal attitude would be greatly encouraged if adequate statistics were available, indicating that risk to the foetus were high (Swan 1949[b]).

Swan (1949[b]) analysed 656 cases from the literature. He found that the risk of a mother giving birth to a child with congenital anomalies following the contraction of rubella in the first 4 months of pregnancy ranges from 83.2 per cent in the first month to 74.4 per cent, whereas in the last 5 months of gestation the risk ranges from 11.2 per cent to 29.2 per cent, with an average of approximately 22.8 per cent. On this basis, Swan considers that contraction of rubella by a woman in the first four months of pregnancy offers suitable grounds for termination of pregnancy, as the knowledge of such a mother that there was a 3 to 1 chance of giving birth to a congenitally malformed child might turn her into a "physical or mental wreck". The possibly inaccurate grounds on which these figures may be based has however been discussed in Chapter XIV.

The mother might also become a "wreck" after the birth of a congenitally deformed child, as a result of the social implications, for the consequences are not

confined/....

confined to the affected child, but as Swan says, to the family, the other children, to the children yet unborn, and to the community as a whole.

The decision in England, in the case, Rex vs. Bourne, was not given by the highest tribunal, as it hinged on the interpretation of an English statute. For this reason, it is quite likely, that in South Africa, the courts will not necessarily follow such a decision, because the grounds for lawful abortion in this country, rest upon common law. (South African Medical Journal, 1949). The interpretation of the phrase, "preserving the life of the mother" is likely to be related to the dangers immediately and in escapably consequent on pregnancy. According to Masters (1947), even if the victim of a rape were to become a "physical or mental wreck", this would not provide legal grounds for performing an abortion. This also applies to undesired pregnancy resulting from criminal assault by Non-European upon a white woman. On the other hand, should an abortion be procured under such circumstances, the medical practitioner concerned, would no doubt be treated with leniency, even in South Africa, or the legal authorities would probably decline to prosecute.

The South African Medical Journal (1949) summarises the present position with regard to abortion in this country as follows: "It does seem clear, however, that although health as distinct from life, may be endangered by a pregnancy, or that the expectation of life may be shortened if the pregnancy is allowed to continue, legally the medical practitioner

would/.....

would not be technically within his rights to procure an abortion in such circumstances. In the strict sense, this probably applies in cases of Rh incompatibility and rubella in early pregnancy.

"The impeccable legal reasons for performing a lawful abortion do not seem to cover many instances which would today readily be approved as medically suitable for this operation. There is, therefore, much to be said for an urgent review of the position in this country."

Swan et al (1946) report 2 cases subjected to therapeutic abortion in Australia. One foetus subsequent to the operation, showed unilateral cataract. In this case, the mother had contracted rubella in the second month of gestation. The other case where abortion was procured, was one where the mother had contracted rubella just prior to conception, and the "foetus appeared normal". One would like to add, there, that had the foetus lived, the possibility of some malformation becoming evident at or near term, cannot be entirely excluded.

Some mothers who have given birth to a congenitally deformed child are nervous about having subsequent children because of the possibility of a "family taint". Where such abnormalities have followed on an infection with rubella in pregnancy, assurance can be given with fair certainty that the malformations will not be reproduced in later pregnancies. In this way, some cases of attempted criminal abortion may be forestalled.

CHAPTER XXII.

OTHER MATERNAL VIRUS INFECTIONS AND MORBID CONDITIONS

1. GENERAL SURVEY.

In Milwaukee, U.S.A., all common virus infections are legally notifiable, including rubella. Fox et al (1946), investigated measles, mumps and chicken pox from 1942 to 1945, as possible teratogenous agents. They chose these infections particularly, because they are much more often correctly diagnosed, and notified, than either rubella or poliomyelitis. They also occur commonly in the population at large and hence offer statistical material.

These authors surveyed the notifications and found that 100 cases of measles, 356 cases of mumps and 77 of chicken pox were entered for patients whose names were prefixed with "Mrs". Specially primed Public Health nurses armed with special forms interviewed the 64 per cent of these women who could actually be located. No dental or equivocal anomalies were recorded. Any children listed by these nurses as having a congenital anomaly, deafness, or any cardiac disorder were then subsequently examined by one of the authors. There were 589 live births before the onset of one of these three diseases, with 6 of the children exhibiting anomalies. A further 76 children had been born of pregnancies which had begun after the mother had recovered from one of these diseases. The number of children born of mothers who did not have any of these diseases in pregnancy was 589 plus 76, or 665, with 6 cases of.

congenital/...

congenital abnormalities, or a "normal" incidence of 0.9%per cent.

The above 589 women had borne 109 live children after recovery from one of these virus diseases. Of these 109 children, 33 had been born of mothers who had had one of these virus diseases during gestation, but there was only one congenital anomaly, namely a unilateral hare-lip. The above series is however, too small to formulate definite conclusions.

Swedish workers (Grönvall and Selander, 1948), extended their study from September, 1945, to cover several large cities as follows:-

(i) An examination of children whose mothers had suffered from such diseases as rubella, measles, chicken pox, mumps, infective hepatitis, or anterior poliomyelitis during pregnancy.

(ii) A search for virus diseases during the pregnancies of mothers of children suffering from certain deformities. Scarlatina, though not a virus disease was also included in this investigation, being regarded as a possible teratogenous agent. These authors give tables showing that of 354 mothers who had congenitally defective infants,

5 had had rubella,
1 had had measles,
1 had had chicken-pox
5 had had mumps) during pregnancy.

There were also at least 3 who had suffered from hepatitis and two from poliomyelitis. Thus 5.1%per cent of these mothers had suffered from virus disease during pregnancy. The "normal" incidence of congenital disease, based on controls, consisting of many thousands of mothers confined in maternity hospitals was 0.47 per cent. The suggestion is that the virus diseases in question were about 10 times more frequent among mothers of defective infants as among controls.

The writers conclude that rubella, mumps, infective hepatitis and anterior poliomyelitis may injure the foetus, although rubella in this respect may be much less dangerous in Sweden than it seems to have been in Australia.

Lande (1950) found amongst 16 institutional infants and children in Illonois with congenital malformations resembling the post-rubella syndrome, a history of rubella was present in 7 cases; but in 5 cases of the series, a history of common cold within the first trimester and in one case a history of virus influenza, was obtained. This writer concludes that approximately 6 per cent of institutionalised children with congenital malformations of heretofore unknown aetiology, may be attributable to early virus infection. The whole study group consisted of 252 preschool children of which 220 had congenital defects not due to birth injury, postnatal infection or known hereditary factors.

The present writer however, criticises this figure of 6 per cent on the grounds that the histories were obtained retrospectively, after repeated questioning, both by questionnaire and by personal interview. Yet these figures agree well with the statistics from Sweden above quoted (5.1 per cent). On the experimental side, it is interesting to note that Hamburger and Habel (1947) cultured the influenza virus on the chick embryo and found that anomalies could be produced in the 48 hour embryo.

Landtman (1948) found that apart from antepartum haemorrhage and toxaemia, various morbid states were observed during early pregnancy in 42.5 per cent

of the 73 mothers who gave birth to malformed children. Acute infectious diseases occurred in 12 cases (influenza, cold, bronchitis, sore throats, pneumonia, pyelitis) all in the first trimester of pregnancy. Or the 200 mothers with normal children who acted as controls, a total of 14.5 per cent had a corresponding history of various disorders during their pregnancy. There were 9 cases of acute infectious disease, of which however, six occurred after the first trimester of pregnancy. In none of these cases, was the acute infectious disease, rubella, however; nor were the listed malformations suggestive of the "rubella syndrome". The morbid conditions were varied and included conditions like mitral stenosis, diabetes, jaundice etc. From the data collected by Worcester and co-workers (1950), it is suggested that maternal infections other than syphilis and toxoplasmosis, late in pregnancy, may be important in the aetiology of hydrocephalus where this condition occurs as an isolated defect.

Worcester et al (1950) studied 677 congenitally malformed infants in Boston. They found that the number of births of infants whose anomalies required presumably more than one month for their development, was consistently high in the third and fourth quarters of the year. This dates their conceptions and organogenetic periods in the fourth and first quarters of the year, a time when respiratory diseases are common, These workers found, however, that only one per cent of mothers gave a history of febrile illness in the first trimester of pregnancy, and they note the probability of poor recollection on the part of mothers

regarding/...

regarding minor illnesses during gestation.

Miller (1950) emphasises the rarity of exanthemata other than rubella over the age of 15 years. He gives the following table :

INCIDENCE OF DEFECTIVE INFANTS FOLLOWING MATERNAL INFECTIONS IN EARLY PREGNANCY (EXCLUDING RUBELLA)

TABLE XIV.

Maternal Infection	1st 4 months of Pregnancy	
	Exposed Infants	Defective Infants
Rubeola (Measles)	13	4
Epidemic parotitis	24	6
Varicella	7	1
Infectious Mononucleosis	6	3
Poliomyelitis	36	2
TOTAL :	86	16

Seven of the children had cardiac defects; and there were 10 other defects found, including mental deficiency, pyloric stenosis, harelip, genu valgum, imperforate anus, absent auditory meatus, hypospadias, corneal opacities, clubfoot and cataracts. None of these defects occurred more than once except cataracts which were seen in 2 children. The value of these figures is questioned, because the method of collecting data favoured the reporting of defective children as compared to those who escaped, although the suggestion is that there is a higher incidence of defects in the offspring of mothers suffering from the above exanthemata in early pregnancy.

Landtman (1948) suggests maternal tuberculosis as a possible aetiological factor in malformations, and

Murphy (1947) reported a series of 109 malformed children where the parents had pulmonary tuberculosis in 16 instances.

Jones (1950) describes cases of congenital malarial infection by *P. falciparum* occurring in the infants of three European women in Lagos. Only one of the mothers admitted to any recent malarial infection, so it is possible that in the other two cases, infection may have occurred a considerable period before birth. No mention was made of any congenital anomalies being present in any of the three infants.

There appears to be no evidence that other bacterial infeetions during early pregnancy may cause congenital malformations. The writer had a case who contracted typhoid fever in the 10th week of gestation, was hospitalized for nearly two months and produced a normal full-time infant. Another of his cases who contracted typhoid between the sixth and eighth week, aborted 3 weeks later.

2. INFECTIOUS MONONUCLEOSIS.

Miller et al (1949), from questionnaires, noted five cases of infectious mononucleosis occurring during gestation. A sixth was later reported. Three of the children were born with malformations, two having cardiac lesions, and a third having cataracts with possibly a cardiac lesion as well. Prior to the birth of these 3 malformed children, the maternal infections diagnosed by a medico in each case all occurred in the first 16 weeks of pregnancy. Although this series is admittedly small, a relatively

strong/...

strong teratogenous effect is suggested for infectious mononucleosis and the lesions produced may be similar to those found in the post-rubella "syndrome". It is to be hoped that many more case reports will come to hand in the future, as infectious mononucleosis is not always a simple disease to diagnose, and confusion with rubella on clinical grounds is not inconceivable.

3. MATERNAL POLIOMYELITIS AND EFFECT ON FOETUS.

Aycock and Ingalls (1946) investigated 131 infants born of women who had poliomyelitis in pregnancy. In 33 cases, the pregnancy ended in abortion, miscarriage, stillbirth, or death shortly after birth. Of the 98 children remaining, there was one case of club-foot, and one case of heart disease, The mothers of the latter 2 children had had poliomyelitis in the second and third months of pregnancy respectively. The incidence of anomalies is 2 per cent in this series or about twice the normal rate. The normal rate of 0.9 per cent was obtained by Fox from cases reported to the Milwaukee Health authorities.

Fox and Waisman (1947) found that the total number of recorded instances where pregnancy and poliomyelitis, occurred coincidentally, was 175. The data for the 1945 and 1946 epidemics indicated that of 24 married women admitted to the South View Isolation Hospital with the diagnosis of poliomyelitis, 14 were pregnant. These workers gained the impression, without being able to produce figures, that the incidence of poliomyelitis was greater in pregnang than in non-pregnant women. The influence of

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the glandular changes in pregnancy which affect the physiological balance of the patient and therefore susceptibility to poliomyelitis apparently heightened susceptibility.

Setala (1947) investigated material consisting of 15 cases of poliomyelitis in pregnancy. In two-thirds of these cases, (10), the disease was contracted during the latter half of pregnancy. Five cases were fatal, 4 of these being where the disease had begun in the second half of pregnancy. There were NO miscarriages. In patients who survived, the poliomyelitis did not influence the course of the pregnancy except in some cases with paralysed abdominal musculature. All the surviving cases produced five children without any discernible symptoms of poliomyelitis, and apparently normally developed, with normal birth weights. A fatal case of meningo-polio-encephalitis is, however, actually reported in a three weeks old infant whose older sibling also contracted the disease, both cases probably originating from a common source of infection.

Gifford and Hullinghorst (1948) presented 170 cases of poliomyelitis in pregnancy. They did not find age, parity or stage of pregnancy to particularly influence susceptibility of women to this disease. Of the bulbar type, there was a 23 per cent incidence, incidence being increased in the last trimester. Bulbar poliomyelitis did not appear to induce abortion or premature delivery, or to cause precipitous delivery. A maternal mortality of 19 per cent and a foetal mortality of 26 per cent is ....

reported/....

reported. One-third of foetal deaths were intrauterine and undelivered, being associated with maternal death. Caesarean section offers a good opportunity to obtain a viable child, when death of the mother is imminent. Poliomyelitis may be transmitted to the newborn, but there is no definite clinical histological or virological evidence of its transmission in utero.

Taylor and Simmons (1948) observed 25 cases of poliomyelitis complicating pregnancy, during the Colorado epidemic in autumn, 1946. Nineteen of the 25 occurred in the first half of pregnancy. No case of congenital poliomyelitis has ever been recorded, although poliomyelitis has been seen in infants as early as the 11th day, and 3rd week of neonatal existence, (Horn et al 1948), thereby suggesting that the virus does not easily pass the placental barrier and that passive immunity is only short-lived.

In the above series of 25 cases : Spontaneous abortion occurred in one after 6 weeks of pregnancy. One stillborn twin was delivered post mortem by Caesarean section, the other of which died of pneumonia at 18 days. Poliomyelitis occurred when pregnancy was 37 weeks old. One male infant died 28 hours after birth. The diagnosis was that of pneumonia following spontaneous delivery. The poliomyelitis infection occurred when pregnancy was 19 weeks "gone". One abortion occurred after 6 weeks of pregnancy. Other women with poliomyelitis in the 4th to 6th weeks of pregnancy numbered four, and all these bore spontaneously and the children were "normal". In/...

mal". In fact the abortion was the first casualty out of 11 women who got poliomyelitis before the 16th week of gestation.

Fox et al (1948) emphasise the difficulty of ascertaining the incidence of foetal morbidity in relation to maternal poliomyelitis. They indicate the uncertainty of diagnosing and hence of notifying poliomyelitis in the pre-paralytic, non-paralytic and abortive forms. In fact, the given incidence of rubella too, is also subject to some error, because of the relative frequency of misdiagnoses. However, on their figures they estimate that for poliomyelitis in pregnancy, the over-all incidence of congenital anomalies is about twice the expected rate, and in the case of poliomyelitis in the first four months of pregnancy, nine times the normal rate.

Miller et al (1949), with their own cases, and those from the literature, collected 36 instances of poliomyelitis in the first four months of pregnancy diagnosed by a medico. Of these, only two defective children were observed, one with a clubfoot and the other with a cardiac lesion. Thirty-six cases collected from the world literature is a very small number on which to base accurate estimates regarding the incidence of congenital malformations in poliomyelitis.

4. MATERNAL MORBILLI.

Swan, Tostevan and Black (1946) investigated morbilli in pregnancy with the following results.

Total/.....

TABLE XV

MATERNAL MORBILLI AND CONGENITAL DEFECTS

Total Number of Cases - 18.

(Swan et al., 1946)

Period of Pregnancy	No. of Cases	Congenital Defect
1st month	1	0
2nd month	2	0
3rd month	4	2
4th month	3	2
5th month	3	0
7th month	1	0
8th month	2	0
9th month	1	0
Indeterminate	1 case	

They analysed the nature of the abnormalities as follows:

Spontaneous abortion, 10 days after onset of exanthem - 1 case

Heart disease - 1 case

Heart disease and pyloric stenosis - 1 case

Genu valgum - 1 case

Birth weights showed nothing significant.

Fox et al (1948) surveyed in Milwaukee, cases of measles notified during 1942 - 1945. There was one case of measles occurring in the first month of pregnancy with no anomalies. There was one case of measles in the fourth month of pregnancy with congenital unilateral hare-lip. There were five births from women contracting morbilli in the 5th month of pregnancy (included is a twin birth) - with no anomalies. The incidence of anomalies is therefore one in 7 or 14 per cent, i.e. more than 15 times the normal incidence which was found to be 0.9 per cent based on figures in this series from women without any history of virus infection co-incident with pregnancy. The

hare-lip/....

hare-lip anomaly occurred in one of 2 children born to mothers who had had morbilli in the first four months of pregnancy - an incidence of 50 per cent or 55 times more than normal. However, this series of 7 cases is too msall and the single anomaly may have been a chance occurrence; so here again the figures cannot be regarded as reliable.

Miller et al (1949) in a questionnaire to many thousand specialists and medicos in the United States, gathered 5 cases of maternal morbilli with only one defect noted, namely, mental deficiency in a child whose mother had had measles in the eighth week of pregnancy. A combined list from many investigators including Fox and his co-workers provided a total of 13 cases of morbilli occurring in the first four months of pregnancy, as diagnosed by a medical man. In this series there were 4 defective children born, an incidence of about 30 per cent. The anomalies included mental deficiency, congenital cardiac disease, hare-lip and genu valgum. It is conceivable, of course, that some normal children born after maternal morbilli were not reported, owing to the greater interest shown by doctors in reporting abnormalities.

The present writer feels that although morbilli in pregnancy may occasionally have teratogenous effects, the evidence to date is inconclusive.

5. MATERNAL MUMPS.

Swan et al (1946) found six cases of mumps recorded during pregnancy. The infection occurred in the first month (2 cases), the fourth month (1

case), fifth month (2 dases), and seventh month (1 case). These pregnancies were subsequently followed by a very high incidence of congenital abnormalities, in the light of investigations by other authors. The nature of the abnormalities was as follows:-

Mongolism 2 (one with heart disease, both with microcephaly).

Bilateral corneal opacities ($3\frac{1}{2}$ months of pregnancy)	1	The birth weights showed nothing of significance.
Naevus ..... (First month of pregnancy)	1	
Imperforate Anus ..... (First month of pregnancy)	1	

It must be emphasized that this information was obtained by retrospective study. One case had both rubella and mumps late in pregnancy and no defects of any kind were found in the baby.

Fox et al (1948) discovered 22 children whose mothers had suffered from mumps during pregnancy. In ten out of these cases, the disease had occurred in the first four months of gestation. (Six actually occurred in the first three months of pregnancy.) However, in this whole series of 22 children, there was not one congenital anomaly. These authors conclude that mumps does not affect to any marked degree the incidence of foetal abnormalities.

The present writer had one case of mumps during pregnancy:-

> A woman of 35 years (a 3-gravida) contracted mumps when she was justabout 4 months pregnant. She had contracted the infection from her children, two of whom had the disease. The parotid swelling was bilateral, very marked, and she was confined to bed. Nine days after the swelling had commenced, she began to haemorrhage slightly per vaginam. She was given 10 milligrams proluton intramuscularly for 3 successive days, when the....

bleeding/....

bleeding stopped. The baby who was born full time, was cyanotic at birth and weighed 10½ lbs. Her previous children had each weighed between 8½ and 9½ pounds. The cyanosis cleared up in a few hours, and the only abnormalities which the child had, were two naevi, one upon the scalp near the occiput about the size of a florin, and the other upon the upper left thigh about the size of a shilling piece. He is now three years old, and apart from the naevi, which may be a chance occurrence, is otherwise perfectly normal. In view of the progressively increasing size of her infants the mother is also under observation for the possible development of diabetes mellitus.

Miller et al (1949) from questionnaires, found eight cases of maternal mumps with defects in two children whose mothers had had respectively the disease in the thirteenth week (hypospadias), and the thirteenth week (pseudo-optic neuritis). A combined list is given from various investigators, showing 19 cases of maternal mumps diagnosed by a doctor in the first four months of pregnancy. Out of these 19 cases, three children were born with defects (imperforate anus, hypospadias, and corneal opacities).

Greenberg and Beilly (1949) report a case where a parotid swelling developed in a 31 year old female, who had previously had two spontaneous abortions. The parotid swelling was diagnosed as mumps and occurred nineteen days after the onset of the last menstrual period, and conception was estimated as having occurred on the 11th post-mentrual day according to the body temperature curves. She was delivered prematurely of a living child about 2 months before the expected date. The infant had a mere crater of skin where the right ear should have been and the external auditory meatus was absent. The other ear appaared normal in all respects.

Once again, more evidence is required before mumps can definitely be implicated as a teratogenous agent.

e. HERPES/....

Swan et al (1946) by retrospective study found 2 cases where herpes zoster had occurred during pregnancy. In the one case the disease occurred during the fourth month, but there was also a possibility of subclinical rubella infection in this case. The child was born with microcephaly, deaf mutism, and congenital cardiac disease. In the other case , herpes zoster was contracted in the sixth month and the child was born with myelocoele, bilateral talipes and right genu recurvatum. The birth weights of both were within normal limits.

The present writer records the following case which may prove to be not without significance.

> A woman gave the following history about a previous pregnancy. She was about 25 years old, and had developed a rash on the left buttock when she was 6 weeks pregnant. This rash had never been definitely diagnosed, although she had seen more than one dermatologist. The original rash apparently disappeared within a few days, and after receiving injections and local treatment, the secondary erythema and irritation subsided in a matter of weeks. The child was born at full term, was perfectly normal, and is now 3 years old and free from any defects. She was not attended by Dr.E. up to this time.
>
> She came under Dr. E.'s care for her second pregnancy. At about the sixth week of gestation, she developed a vesicular rash on the left buttock again. The vesicles had an erythematous base, and were diagnosed both by her medical attendant, and a dermatologist as being an obvious herpes simplex, apparently recurrent, because as she stated, the original rash during her first pregnancy had been of a similar nature when it had first started. She was given local X-ray treatment, and the rash cleared up very quickly without recurrence. At about the 28th week of gestation she aborted spontaneously in a nursing home. Unfortunately the foetus was not seen by any doctor and no autopsy was performed upon it. A nursing sister, who, however, did see the foetus, said that there were no obvious abnormalities.
>
> Five months prior to the date of writing, this woman again fell pregnant and once again developed the same type of rash at about 6 weeks. The rash cleared up after 24 hours, with aureomycin treatment. There has been no recurrence and the patient is at present under the care and observation of a specialist obstetrician.

More/....

More case records are required before herpes can be assessed as a teratogeneous agent.

7. MATERNAL VARICELLA.

Swan et al (1946) encountered two cases, both occurring during the 7th month of pregnancy. Both children were female, but only one was abnormal, evidencing heart disease and a naevus. The weights were within normal limits.

Fox et al (1948), in their Milwaukee survey of married women contracting chicken pox during the years 1942-1945, found only 4 cases where the disease occurred in pregnancy. In none of these mothers was the exanthem contracted during the first two months of pregnancy. Two had however, suffered from the infection in the first four months (one in the 3rd month; one in the 4th month). The other two had varicella in the fifth month. There were NO congenital anomalies at all. Conte et al (1945) records the case of a normal male infant being born after the mother had contracted varicella in the second week of pregnancy.

The low incidence of chicken pox in pregnant women, or in adults for that matter, is probably related to the general endemicity of the disease which offers opportunity for infection before maturity.

Miller et al (1949), extracted from questionnaires (to some 6,000 specialists in the United States, and to Kansas medicos,) 6 cases of maternal varicella definitely diagnosed by doctors. One child had cataracts whose mother contracted the infection in

the/.....

the 5th week of pregnancy. In the collective list, including cases from the world literature, they found maternal chicken pox in the first four months of pregnancy, (definitely diagnosed) reported 4 times with one case of congenital cataracts.

Here again, the suggestion is that maternal varicella may occasionally produce cataracts in the children, but much more evidence is required.

The present writer here also records a case of chicken pox occurring in the first trimester, the child being born normal.

> The woman, 24 years old, is the wife of a dermatologist, so the diagnosis of chicken pox was not in doubt. She was three months pregnant at the time of infection and this pregnancy was her first. The child, a girl, was born at full term and weighed 6 pounds 10 ounces and seemed perfectly normal. At the time of writing, the child weighs 15½ lbs. and has been pronounced by a paediatrician to be clinically normal except for slight underweight.

Greenthal (1945) refers to a chicken pox infection occurring in a mother during the latter months of pregnancy. The child was born normal and later contracted chicken pox at the age of two years. If the foetus is not immunized when the mother contracts a contagious disease during pregnancy, then presumably the foetus is not harmed by the disease.

8. MATERNAL VACCINATION IN FIRST TRIMESTER OF PREGNANCY.

VACCINIA is a general infection. Various investigators have shown that the virus enters into the blood stream and becomes widely disseminated throughout the tissues. (Greenberg and Appelbaum, 1948). The possibility, therefore, of the virus attacking the human embryo was studied. Following an outbreak of variola in New York City in 1947, more than five million people were vaccinated. Greenberg et al (1949) conducted two parallel studies, one in child health stations, and one in

maternity/...

maternity wards of hospitals. The two investigations complemented each other as there is a higher incidence of congenital malformations found immediately after birth and many infants die of such anomalies during the neonatal period. Other congenital defects which are unrecognisable early in life, become obvious somewhat later in childhood, and are recognised at child health centres. Duplication of cases was eliminated.

Greenberg and his co-workers found 4,172 women to have been vaccinated during the first trimester of pregnancy, with a 1.63 per cent incidence of congenital malformations. A control non-vaccinated group of 2,186 women in the same period of pregnancy, had a 1.37 per cent incidence of congenital anomalies. Thus there were no significant differences in the figures for each group.

The vaccinated group gave birth to 343 premature infants, or a rate of 8.2 per cent while the unvaccinated group gave birth to 185 premature infants or a 8.5 per cent incidence.

The death rate from congenital malformations in New York City during the four months representing the first trimester of pregnancy of the observed women, was compared with the corresponding months the previous year, and no significant difference was found. (48.8 per 10,000 live births as against 47.2 per 10,000 live births). There was no apparent increase in the ratio of stillbirths to total births in 1947, during the months when the stillbirths may have been conceived, over the ratios of the corres-

ponding/.....

ponding months of the previous year.

The above workers conclude, therefore, that smallpox vaccinations of women in the first trimester of pregnancy has no demonstrably deleterious effect on the developing embryo.

9. CHILDREN WITH SO-CALLED RUBELLA SYNDROME WHOSE MOTHERS HAD NO KNOWN INFECTION DURING PREGNANCY.

Cases of congenital anomalies apparently identical with the post-rubella types, are described, where the mothers denied any infection during pregnancy (Swan et al 1943; the New South Wales Committee, 1945; Carruthers, 1945; Goar and Potts, 1946; Hopkins, 1946).

Miller et al, (1949) in a questionnaire covering the United States, found 14 cases of children with the so-called rubella syndrome, whose mothers had no known infection during pregnancy. To be considered under this heading, the children had to show two or more of the common defects commonly associated with the "rubella syndrome", namely cataracts, deafness, microcephaly, mental deficiency and congenital heart disease. One of these cases had, in his family, 3 siblings, all of whom had congenital cardiac disease. Another case had a dwarf sibling. The remaining 36 had normal siblings. Only in two cases, did birthdays correspond with the peak of births associated with the rubella epidemics. The conclusion drawn, was that either the rubella syndrome has more than one aetiology, or the mothers had had rubella without knowing it. In this connection, it may be mentioned that the diagnosis of rubella is not always easy or obvious.

Beswick et al (1949) describe three cases of the post-rubella syndrome, where the mother was actually exposed to rubella, but did not remember having had a rash. Presumably in these cases, the rubella had been contracted unnoticed.

Lande (1950) mentions cataracts and severe ocular defects in children following infections of influenza and the common cold incurred during early pregnancy. All of these cases had severe mental deficiency, with some degree of microcephaly in a few cases. Some were dystrophic and one appeared deaf. The whole series consisted only of 6 cases and cannot therefore be regarded as very convincing, in view of the fact that mothers retrospectively may tend to exaggerate any infection during a pregnancy which is followed by an abnormal child. On the other hand, if the common cold and influenza virus do occasionally produce teratogenous effects, many cases of children with "rubella syndrome" whose mothers had no known specific infection during pregnancy, might be explained on the basis of infection by the above viral agents.

10. PRECONCEPTUAL VIRUS INFECTION.

Gillman et al (1948) injected trypan blue into female rats 16 days before conception and obtained abnormally jaundiced pups. Rats injected the day before conception yielded a 25 per cent incidence of abnormal offspring. Apparently some metabolic disturbance remains operative when conception occurs.

It is well known that viruses persist in the tissues for long periods and hence may be present when the embryo comes into being, thus exerting a teratogenous

effect/...

effect during the stage of rapid multiplication by susceptible embryonic cells. In the case of rubella, the power of persistence is suggested by the occurrence of relapse in this disease (Swan, 1949[b]).

Gregg (1941) found a congenital cataract in a child whose mother had had rubella three months before conception.

Swan et al (1946) found two mothers who had contracted rubella 13 days and 6 days before conception respectively. The first gave birth to a normal child, while the second was therapeutically aborted at three months and seemed normal.

Hall (1946) described a syndrome of congenital cataracts, deafness and heart disease encountered in a child whose mother was treated for a "sharp attack" of rubella 6 weeks before conception.

Wesselhoeft (1947) mentions a case, personally communicated to him, of a woman who had contracted rubella 10 days preconceptually. Her offspring suffered from bilateral cataracts, patent ductus and hydrocephalus.

Fox et al (1948) surveyed 76 children born of pregnancies, where conception had taken place from 3 weeks to slightly more than 4 years after the onset of measles, mumps and chicken pox. In this series, there were no anomalies. The impression gained by these investigators was that conception taking place after recovery from these three diseases is not significantly followed by a raised incidence of congenital anomalies in the offspring.

A case/....

A case is here recorded:

> A woman was admitted to the City Hospital Edinburgh on the 9th March. 1945. The Medical Superintendant communicated in a letter of the present writer :
>
> "The diagnosis of measles was confirmed, the patient showing the characteristic acute febrile disturbance with rash, Koplik spots and catarrh. There was no adenopathy and there were definite signs of bronchitis. You can take it beyond question that the case was one of measles and not rubella. The patient made a good recovery and was discharged from Hospital on the 17th March, 1945".
>
> She subsequently gave birth to a child in February, 1947, which was seen in South Africa and found to have bilateral cataract, and interventricular septal defect without cyanosis. As the child grew older, it was regarded as being most likely deaf. It died in Rhodesia as the result of a pulmonary infection before the age of three years.

The above patient probably conceived about May, 1946, a period of about 14-15 months after the attack of measles. It is possible that during that interim period she may also have contracted an unnoticed infection or rubella; or the preconceptual morbilli attack may have been purely coincidental without any aetiological significance. The writer feels, it is worth while recording the case on account of the meagre reports of preconceptual infections. He admits however, that the case reported by him, and the other cases taken from the available literature do not provide sufficient evidence as yet, to incriminate preconceptual virus infection as an aetiological agent in the production of congenital deformities. The cases quoted by Hall and Wesselhoeft may well contain an element of error, because it is so often difficult to fix the exact time of conception.

> During January of 1947, the present writer treated a 26 year old woman for a typical condition of unilateral herpes zoster, involving the pudendal region. She fell pregnant in April, 1947, and was delivered of a perfectly normal infant at term after an uncomplicated labour. Her previous child aged two and a half, had had a moderate

degree/....

degree of knock-knees which was ultimately cured by prolonged treatment with plaster of paris casts. Apparently the herpes which occurred about 4 months prior to the second conception, produced no ill effects upon the second child. She has had no recurrence of the herpes.

If persistence of virus in the tissues can affect a subsequent pregnancy, then the question that arises is for how long a period prior to conception can this teratogenous effect be effectual? Almost certainly not over a period of years. These conclusions are based upon the following grounds. Swan et al (1946) investigated 19 mothers with post-rubella defective children who had subsequent children, and only one case showed a congenital defect, namely, talipes valgus. Had the virus been still present in the maternal tissues, subsequent children should also have been affected. The fact that the series was small, and that there was actually one deformity (not of the usual post-rubella type) leaves the door open for further light to enter upon the subject.

CHAPTER XXIII

GENERAL DISCUSSION AND CONCLUSIONS

1. An outline of genetic processes of inheritance is given. Also various environmental factors are shown to play an important part in the aetiology of congenital malformations. Foetal abnormalities which result are not necessarily of any characteristic type in relation to various aetiological factors. The most important factor appears to be the stage at which foetal development is disturbed. Due to the lack of specificity of teratogenic factors, malformations caused by environmental factors may simulate anomalies of genetical origin and are designated by the term, phenocopies. The possible future role of actinic radiation in the production of genetic changes is mentioned, and reference is made to the role of Rh and possibly of ABO - isoagglutination in the production of mental deficiency and neurological abnormalities. Such environmental factors as maternal diabetes and maternal isoimmunisation, however, play a very insignificant part in the over-all incidence of congenital malformations. If the mother of a deformed child did not receive therapeutic pelvic radiation during pregnancy, or was not attacked by rubella in the early part of gestation, then, as Murphy (1947) says, the probability is that the defect in the child is of genetic origin. If such is the case, the probability of a subsequent child being born defective, is twenty to thirty times greater than is the case in the children of parents where the

previous/.....

previous offspring have all been normal. The chances of any subsequent child being born defective, increases with maternal age above 30, and after 40, the chance that a child will be born malformed, is three times greater than when conception occurs before 30. There is at least one chance in 200 that the child of any couple will be malformed, and this also applies to the subsequent pregnancies occurring after the birth of post-rubella defective infants.

2. Not only are congenital abnormalities produced by an interaction of genetic and environmental factors, but so also are disease processes. Every possible ailment in childhood, adult life or senility is influenced in greater or lesser degree by the genetic constitution of the individual. Environmental factors provided by age, parity, climate, diet, occupation, infection, etc., interact with different genetic factors provided by the individual, such as its sex and various modes of inheritance or transmission, some known, some unknown.

3. Because a disease is hereditary, it is not necessarily incurable. Many diseases based on genetic defects may be treated as for instance, inborn methaemoglobinaemia and the de Toni-Fanconi syndrome. The former is treated by ascorbic acid or methylene blue, and the latter by vitamin D and alkali. If a definite diathesis can be discovered in an individual by biochemical, serological or other means, then prophylactic measures may possibly be initiated before overt symptoms appear. In diabetes and gout, it is possible that only the diathesis is determined

genetically,/....

genetically, but not the disease. The environment probably plays a not insignificant part.

4. Some attention has been drawn to the importance of serology, physiology and bio-chemistry in the investigation of genetic problems, and in fact the study of human genetics has contributed much to the progress in these branches of medical science. But the future elucidation of bio-chemical and bio-physical processes involved in inborn diseases may help us understand the treatment of other conditions (Penrose, 1950). For instance, a comprehension of the distorted bone metabolism occurring in osteopsy-arthyrosis (which is associated with blue sclerotics), may open up the road to speeding up healing of fractures. If we know why in phenylketonuria (where there is a block in phenyl-alanine metabolism affecting the whole body), only the brain function is grossly disturbed; or if we understand what combination of factors, genetic and/or otherwise produce mongolism, then we shall open up a new world in the study of brain metabolism. An attempt is made to analyse factors in the production of mongolism and it would appear that this condition results from the interaction between genetic and various environmental factors.

5. The genes are likened not to particles but to physiological units or enzymes. Genetic differences in pathogenic organisms are often dependant on, or related to loss of particular enzymes. Genes may also be regarded as playing the same roles in the

physiology/....

physiology of the cell as organs do in the body. Hence the study of metabolic diseases may lay bare many secrets of metabolism in the same way as the study of Graves' or Addison's disease led to the discovery of thyroxine, cortisone and ACTH. Even the study of bacterial genetics is producing considerable results in Medicine today.

6. There is some evidence that constitutional weaknesses may not only affect a part of an organ, but actually a whole organ or even a complete system. Here again, the explanation probably is to be found in the level at which embryonic metabolism is disturbed, the further back in the embryonic life-track, the more profound, widespread and complicated are the sequelae.

7. There is no reliable estimate of the extent to which the health of the population is jeopardised by pre-natal factors. Prolonged epidemiological and statistical study extending over many years, and involving the combined efforts of many branches of Medicine, is essential to uncover various aetiological factors concerned in the production of congenital defects.

8. Only in the case of maternal syphilis, maternal toxoplasmosis and maternal rubella is there sufficient evidence for a definite causal factor in the production of congenitally defective infants. Other maternal exanthemata such as mumps, morbilli, varicella, and virus infection such as poliomyelitis have not yet conclusively been shown to produce a

higher/.....

higher incidence of congenital defects in children. Infectious mononucleosis during gestation is also on the suspect list. Exanthemata other than rubella are rare after 15 years of age, and particularly so in pregnant women. There is as yet no great body of evidence to show that maternal infections of non-specific origin, have any injurious effect upon the unborn child, and there is no real evidence that bacterial infections are concerned in the production of congenital malformations. On statistical grounds, vaccination of pregnant women has not been found to have any determinable effects on the foetus.

9. Rubella is a disease which by virtue of its innocuous character, is frequently missed. Diagnosis is not infrequently very difficult. Second attacks must be very rare, but relapse occurs more commonly than is generally known.

10. The rubella virus is filtrable through a millemicron membrane and is transmissible to Macaca mulatta monkeys. It can be kept active for a considerable period when collected from infective throat washings by a suitable technique and stored immediately at - 70°C. The virus is viable in the presence of penicillin and is not the same agent as that responsible for roseola infantum.

11. The diagnosis of rubella is based on adenopathy (especially of the post-auricular glands), morbilliform rash, absence of severe constitutional symptoms, long incubation period (over 14 days), non-appearance of Koplik's spots, and initial leucopenia. The rash tends to be morbilliform on the first day

and/....

and scarlatiniform on the second. This kalaedoscopic characteristic is emphasized as well as the occasional irregular distribution of the exanthem. A leucocyte count will help distinguish between rubella and scarlatina, but not between rubella and measles. Complications of rubella are rare, but are of the nature of polyarthritis, neuritis and encephalomyelitis. The mortality rate for rubella is low (estimated as 1 in 60,000, and for encephalitis as 1 in 30,000). Recovery from encephalitis may occur, but sequelae often persist, although the general tendency is to clear up, as in mumps encephalitis in contrast to measles encephalitis. The onset of encephalitis occurs when the usual symptoms of rubella are subsiding, and is accompanied by a leucocytosis in the blood. All age groups appear to be susceptible. Neuritis appears only to occur in adults.

12. It is well to remember that rubella is infectious during the invasion period, prior to the appearance of the exanthem, and hence may be spread before precautionary measures can be taken. As regards maternal rubella, many points remain to be settled, namely (1) the epidemiology of the disease, (2) the methods of prevention, (3) the risk to the foetal population, and (4) the period of risk. In regard to the last point, the question of preconceptual infection in the mother and possible effects on the foetus, need further study. Although rubella was first implicated as a teratagenous agent in 1941, it has been found by retrospective investigation, to have played a similar, but unrecognised role prior to that date.

13./.....

13. Maternal rubella may produce abortion, stillbirth or a congenitally defective infant. There appears to be a certain critical period in the development of the embryo when noxae are most likely to cause disturbances leading to persistent anatomical defects. In the course of rubella, it is now clear, that the foetus is susceptible to injury during the first trimester, and although by questionnaire methods, data suggest that the foetus may be damaged in the fourth and fifth months of pregnancy, the possibility of error due to the very nature of a retrospective investigation, cannot be excluded. The extent of the anomalies, and the types, are to a great extent, related to the stage of pregnancy at which rubella was contracted, i.e. to the particular system or systems which happen to be undergoing the greatest development at that particular time.

14. The extent to which the foetus is damaged, bears no relation to the clinical intensity of rubella in the mother, and in some cases the maternal disease may even have been missed, while the foetus bears the scars.

15. It is not known whether the maternal infection passes across the placenta into the embryo directly, or whether some other mechanism is involved, such as disturbance of maternal or placental metabolism. It would be of great assistance to find out whether any defective child born after maternal rubella, is immune to infection when German measles is introduced into the body by experimental methods such as inoculation or insufflation of infective material.

16./.....

16. Infection by rubella may occur in the first trimester, and yet the mother may be delivered of a perfectly normal infant. The risk of rubella to the foetal population is not known, but probably appears higher in statistics as post-rubella normal children are often not reported. The risk for the first trimester varies from over 90 per cent, (as determined by the early Australian investigators), to 27 per cent (as determined by some American workers), and probably approaches towards the lower figure. Questionnaire and retrospective investigations are also subject to error. Better statistical material will be provided for future studies by cases of maternal rubella actually observed by medicos, followed up, and fully reported on, whether followed by defective infants or not.

17. The commonest defects present in congenitally defective children born after maternal rubella, are cataracts, deafness, congenital cardiac disease and microcephaly, but a host of other defects of a more or less serious nature are often found spread out amongst post rubella children. Severe dystrophy may be marked feature of such post-rubella children, and dental anomalies are quite frequent. In analysing the less common congenital defects after maternal rubella, it is difficult to assess whether some are purely incidental or not. Hence an appeal is made to determine the population frequencies of all diseases significantly based on genetical factors. A false incidence of defects is got by reporting interesting defects and malformations, to the exclusion of normal cases, and factors,

allegedly noxious, are seen in false perspective and relationships.

18. The congenital cataract following maternal rubella is usually bilateral and seems to differ from other types of congenital opacities. It has been suggested that congenital cataract may be produced by the operation of the virus of influenza, common cold, or chicken pox during early pregnancy, but the evidence is inconclusive. Early operation is recommended for post-rubella cataract and success is dependant on the severity and nature of concomitant defects such as deafness or mental retardation.

19. The deafness is usually bilateral and may be partial or complete. It is of the nerve type and in most cases is not associated with cataract. It is emphasized that the diagnosis of deaf-mutism may be delayed due to the difficulties in diagnosis, and early treatment, which is so necessary, may consequently be deferred. The personality of deaf mutes tends to be coloured by frustration, and behaviour difficulties are apparent.

20. Congenital cardiac disease of post-rubella aetiology may be acyanotic or cyanotic, and it is usually of the type where foetal physiological patterns tend to persist, for example, Fallot's tetralogy, patent ductus, etc. It is apparent that only a small percentage of cases of congenital morbus cordis, probably about one per cent, is caused by maternal rubella; and in fact, maternal rubella appears to be responsible for a very small proportion of congenital defects in general. In some cases the diagnosis of congenital cardiac disease can only be established

by special methods.

21. Dental anomalies include delay in eruption, abnormal tooth forms, absence of incisors, etc. and an apparently greater tendency towards caries. Most cases with dental defects showed defects in other parts of the body as well. This is in keeping with the embryological facts that the dental lamina appears in the sixth week of embryonic life, and calcification in the ninth week, i.e. during period of organogenesis.

22. The critical period of pregnancy for the production of cataract by the rubella agent appears to be 6 weeks; for deafness, 9 weeks; for cardiac abnormalities, 5 to 10 weeks; for deformed teeth, 6 to 9 weeks; for combined cataract and deafness, 8 weeks.

23. Microcephaly and mental defects are not infrequent types of anomaly found in post-rubella children. Major and minor epileptic phenomena may be associated. Mongolism has been ascribed in some cases, to maternal rubella, but the evidence is as yet inconclusive.

24. Rubella is most likely to produce abortion if contracted in the first four months of pregnancy. Although the foetus may be damaged at this stage, it may not necessarily be killed, however, and the mother may be delivered of a stillborn child, at or near term. Although the Law will probably not consider the grounds for termination of pregnancy, justifiable in the case of maternal rubella, yet should a miscarriage or abortion threaten in the course of rubella, or after rubella, no attempt should be made to prevent the ...

expulsion/...

expulsion of the embryo, and in fact surgical means should be resorted to in order to complete the process if conditions demand. Most medical writers on the subject, consider that an infection by rubella, incurred during the first trimester of pregnancy, offers reasonable or justifiable grounds for therapeutic abortion.

25. The health of the mother during pregnancy and her freedom from infections and morbid conditions of all kinds, especially if she is over 30, appears to be important, particularly during the first trimester, which is the organogenetic period for the embryo. A plea is made for all doctors to record any pathological atate or abnormal circumstances during early pregnancy, and to examine and follow up the children subsequently born. It is important to note absence of defects as well as their presence. The family history on both sides should also be investigated. An intensified study of foetal and placental physiology will help to establish a new branch of Medicine, namely, "ante-natal paediatrics."

26. The risk for recurrence of anomalies in children born subsequent to a post-rubella congenitally defective child is apparently not greater than for the population at large.

27. All congenitally defective children, such as post-rubella deaf mutes are social problems, and treatment devolves not only upon the affected child, but also upon the sibs, the parents and the community as a whole.

COLLECTED CASES.

OFFSPRING AFTER VARIOUS MORBID CONDITIONS

CONDITIONS DURING PREGNANCY.

Below are tabulated cases investigated by the present writer. In common with other investigators, he found that retrospective history obtained from mothers is not reliable. Two of the mothers (cases 10, 17) stated that they had had "German measles" during pregnancy, whereas in point of fact, the former had had morbilli. (information obtained from her medical attendant), and the latter had had a rash which probably was rubella, but was not definitely diagnosed as such. Apparently "German measles" is becoming known to the laity as a teratogenous agent, and mothers make mistakes in retrospective histories. Thus it behoves the investigator to check the veracity of the mothers' statements in all cases, where possible. There are three definite cases of rubella, and one probable one, all occurring in the first trimester of pregnancy. Out of these four cases, there was one abortion (case 14), one case of combined mongolism and congenital morbus cordis (case 16), and one case of congenital cyanotic cardiac disease. (case 17). The fourth case showed no abnormalities. The incidence of lost or defective offspring in this small series of cases is 50 per cent (or 75 per cent, if the doubtful case of rubella is included). The case of mongolism is of interest in view of the doubt which still exists as to whether rubella can act as an aetiological factor in this condition.

TABLE XVI.

OFFSPRING AFTER VARIOUS MORBID CONDITIONS DURING PREGNANCY.

No.	Morbid State	Stage of Pregnancy.	Age of Mother	Parity	R E S U L T
1	Typhoid Fever	6 weeks	Yrs. 34	4 previous children (all normal)	Inevitable abortion at 9 weeks, terminated surgically.
2	Typhoid Fever (Fairly severe, hospitalised 6 weeks).	10 weeks	34	6 previous children (all normal)	Full time normal labour. Child free from defects.
3	Whooping Cough	18–20 weeks	32	4 previous children	F.T.N.L. Child free from defects
4.	Septic subungual whitlow on finger, drained by removal of fingernail under local (2% novocaine) anaesthesia. Morphine gr.¼ given post-operatively for pain.	+ – 7 weeks	25	First Pregnancy	F.T.N.L. Child born with 1) pre-aural sinus right side of face. 2) poor development left cheek. 3) lack of motor power lower half left lip. Subsequent child free from defects.

TABLE XVI (Contd.)

No.	Morbid State	Stage of Pregnancy	Age of Mother	Parity	R E S U L T
			Yrs.		
5	Dermatitis both hands followed by sepsis, pyrexia	+ 8 weeks	24	Second Pregnancy (First child normal)	F.T.N.L. Child born with persistent ptosis left upper eyelid and weakness left side of face, the latter condition responding somewhat to treatment.
6	Mumps	16 - 18 weeks	35	Fourth Pregnancy (previous children normal, all boys.)	Child cyanotic at birth but recovered completely. Has naevus about size of florin on head and on thigh. A first cousin has recently been successfully operated upon for patent ductus arteriosus.
7	Chicken Pox	3 months	24	First pregnancy	F.T.N.L. Child free from defects.
8	Chicken Pox	4 - 6 weeks	+ 30	3rd Pregnancy (2nd Pregnancy twin) all children normal.	Threatened abortion at 8 weeks; terminated surgically.

TABLE XVI (Contd.)

No.	Morbid State	Stage of Pregnancy	Age of Mother	Parity	RESULT
9	Measles	14 - 15 months pre-conceptually	± 25 ?	First Pregnancy	Bilateral cataract; Interventricular septal defect without cyanosis, ? deafness. Died of pulmonary infection.
10	Measles	4 - 6 weeks	26	First Pregnancy	Cyanotic from birth; basal systotic murmur; attack of unconsciousness; weakness of lower extremities. Died at age of 19 months. Probably Fallot's tetralogy. Subsequent child normal.
11	Herpes genitalis (Zoster)	4 months pre-conceptual	26	1 child act. 2½ with moderate knock-knee	F.T.N.L. Child free from defects.
12	Recurrent herpes of buttock	6 weeks	28	1 previous child normal	Abortion at ± 28th week

TABLE XVI (Contd.)

No.	Morbid State	Stage of Pregnancy	Age of Mother	Parity	RESULT
13	"Allergic rash", fine maculo-papular, involving body, but not face. One post-auricular gland enlarged. Also sore throat. The rash recurred after 3 weeks and once more after several months.	10 - 12 weeks	Yrs. 24	No previous children.	F.T.N.L. Child free from defects.
14	Rubella	± 6 weeks	27	No previous children: great difficulty in falling pregnant.	Abortion within 13 hours.
15	Rubella	10-12 weeks	36	3rd Pregnancy Other children normal	F.T.N.L. Child free from defects. Father is a radiographer
16	Rubella	10-12 weeks	31	First Pregnancy.	Mongolism; congenital morbus cordis, died at 2 weeks.
17	? Rubella (blotchy rash over body and face and extremities subsiding in a few days).	8 - 10 weeks	22	First Pregnancy	Mild cyanosis aggravated by exertion. ? Eisenmenger. ? Fallot's.

B I B L I O G R A P H Y.

"A"

ABEL, S. and VAN DELLEN, T.R. (1949): J.Am.Med.Ass., 15, 1210 - 1212.

ABBOTT, Maud (1932) : Nelson's Loose Leaf Living Medicine, 4, 284.

ABBOTT, M.E. (1936) : Atlas of Congenital Cardiac Disease, N.Y. Am. Heart. Ass., p.50.

ADAMS, F.H. (1945) : Journal-Lancet, 65, 197-198.

ALARCON, G.A. (1949) : Am. J. Dis. Child., 78, 914-916.

ALBAUGH, C.H. (1945) : J.Am. Med.Ass., 129, 719-723.

ALLBRIGHT, F., et al. (1942) : Am. J. Med. Sci., 204, 625.

ANDERSON, S.G. (1949) : J. of Immunology; 62, 29-40.

ANDREWS, C.H. (1948) : Practitioner, 160, 82.

AREY, L.B. (1946) : Developmental Anatomy, Saunders, Philadelphia, 5th Ed.

ARKWRIGHT, J.A. (1921): J. Path and Bact., 24, 31.

ATLEE, W.H.W. (1937): Brit. Encycl. Med. Pract., Vol. 5 p. 549; Butterworth and Co. London.

AUERBACH, C. and ROBSON, J.M. (1946): Nature, 158, 878-9.

AYCOCK, W.L. and INGALLS, T.H. (1946): Am.J. Med. Sci., 212, 366-379.

"B"

BAIRD, D. (1945): J. Obstet. Gynaec.Brit.Emp., 52, 217, 339.

BAKWIN, R.M. (1950): J. Pediat., 36, 668-681.

BANKS, H.S.(1949): Diseases of Children, Ed. by Paterson and Monorieff, Edward Arnold and Co., London, Vol.2 4th Ed., p.847.

BARDRAM et alter (1947): Acta Ophth., 25, 353-367, (cited by Ear, Nose and Throat Year Book.1948, the Year Book Publishers, Chicago.)

BARENBERG, L.H., et al (1940): Am. J. Dis. Child., 60, 36.

BARENBERG, L.H., LEVY, W., GREENSTEIN, N.M., and GREENBERG, B. (1942): Am. J. Dis. Child., 63, 1101-1109.

BARCROFT, J. (1947): Child Health and Development, Ed. by R.W. Ellis; J. and A. Churchill, London, p.58.

BARNS, H.H.F. (1941): J. Obstet. and Gynaec.Brit. Emp., 48, 707.

BARTON, Mary, and WIESNER, B.P. (1946): Brit. Med.J., 2, 606.

BAUER, J. (1945): Constitution and Disease, Grune and Stratton, New York, 2nd Ed.

BEADLE, G.W., and TATUM, E.L. (1941): Proc. Nat. Acad. Sci., 27, 499.

BEDFORD, D.E., and BROWN, J.W.(1937): Brit.Encycl. Med. Pract., 6, 206. (Butterworth & Co. London.)

BENDA, C.E. (1939): Arch. Neur. and Pschyiat, 41, 83-97.

BENDA, C.E.(1946): Mongolism and Cretinism, Grune and Stratton, New York.

BENNETT, R.A., and GORMAN, M.D.(1940): Brit. Med.J., 1, 924-926.

BERNSTEIN, C.(1922):J. Heredity, 13, 36-39.

BESWICK, R.C., et al (1949): Am.J.Dis.Child., 78, 334-34

BIRCH-JENSEN, A.(1949): Congenital Deformities of the Upper Extremities: Andelsbogtrykkeriet i Odense, pp 27.- 45.

BLALOCK, A.(1946): Bull. N.Y. Acad. Med., 22, 57-80.

BLEYER, A. (1934): Am. J. Dis. Child., 47, 342-348.

BOYD, W. (1944): The Pathology of Internal Diseases, Lea and Febiger, Philadelphia, 4th Ed., p.298.

BOYD, W. (1944[a]): Ibid, p. 457.

BRADFORD (1944): Brennerman's Practice of Pediatrics, Vol. 2, Ch.12.

BRIGGS, J.F.(1935): J. Pediat., 7, 609.

BROCK, G. (1940): Brit. Med.J., 2, 818.

BROWN, E.E.(1947): Northw. Med., 46, 288.

BROWNE, Dennis (1947): Diseases of Children, Ed. by Paterson and Moncrieff, 4th Ed., Vol. 1. Edward Arnold and Co., London.

BRUCH, H., and McCUNE, D.J. (1944): Am.J. Dis. Child., 67, 205.

BRUSHFIELD, T. (1924): Brit. J. Ch. Dis., 21, 241-258.

BRUSHFIELD, T. (1925): Brit. J. Ch. Dis., 22, 274-280.

BURNET, F.M., and LUSH, D. (1936): Austral J. Exp. Biol. 14, 27.

BURNET, F.M. (1945): Virus as Organism, Harvard University Press, MASS.

BURNET, F.M., ANDERSON, et al (1948): Report, Director of Walter and Eliza Hall Institute of Melbourne, Lancet, 2, 936.

BYERLEY, T.C. (1946): Anat. Rec., 32, 249.

"C"

CAIRNS, J.M. (1941): J. Exper. Zool. 88, 481

CAMPBELL, Dorothy, A.(1936): Brit. Med. J., 2, 1133-1136

CANDIOTTI, A. (1949): Rev. Laryng. Paris, 70, 346-383 (cited in J. Obstet. Gyanec. Brit. Emp., 57, 497, 1950).

CANTAROW, A., and TRUMPAR, M. (1944): Lead Poisoning pp.84 - 87, The Williams and Wilkins Co., Baltimore.

CARROL, J.V. (1934): Lancet, 226, 182-184.

CARRUTHERS, D.G. (1945): Med. J. Austral, 1, 315-320.

CHAPPLE, C. (1947): Mitchell-Nelson Textbook of Pediatrics, 4th Ed. pp.1202-1217.

CLAYTON-JONES, E. (1947): Lancet, 1, 56-61.

CONTE, W.R.; McCAMMON, C.S., and CHRISTIE, A.(1945): Am.J. dis.child., 70, 301-306.

CORDES, F.C., and BARBER, A (1946): Arch. Ophth., 36, 135.

CORDES, F.C., (1949): Arch. Ophth., 42, 596-605.

CORLETT, W.P. (1902): A treatise on acute infectious exanthemata, cited by Wesselhoeft (1947a)

COWAN, D., et al (1942): Arch. Neurol. and Psychiat., 48, 689.

CREWE, F.A.E. (1947): Genetics in relation to clinical medicine, Oliver and Boyd, Edinburgh and London, p.101.

CROOKS, J. (1947): Diseases of Children, Ed. by Paterson and Moncrieff, Edward Arnold, London, Vol. 1, p. 565.

"D"

DAVIDOFF, L.M. (1928): Arch. Neurol and Psychiat., 20, 1229-1257.

DAVIDSOHN, I. (1937): J.Am.Med.Ass., 108, 289.

DAVISON, C., and FRIEDFELD, L.(1938): Am.J.Dis.Child: 55, 496-510.

DE KRUIF, P.H. (1921): J.Exp.Med., 33, 773.

DELBRUCK, M., and DELBRUCK (1948): Scient.Am., 179, 46. (cited in J.Am.Med.Ass., 6,541, 1949).

D.G.M.S. (Director General Medical Services, South Africa)(1939-1945): Access to records, by courtesy Major Dreisenstock.

DOGRAMACI, I., and GREEN, H. (1947): J.Pediat; 30, 295-301.

DUNN, L.C. (1941): Third Growth Symposium, pp.147-161.

DUKES, C. (1900): Lancet, 2, 89.

"E"

EHRLICH, L.H. (1948): Arch. Ophthmal., 39, 205-209.

EISEN, D.(1944): Radiology, 42, 570-578.

ENGLER, M.(1944): J. Neurol., Neurosurg., and Psychiat., N.S., 7, 27-29.

ERIKSON, C.A. (1944): J. Pediat., 25, 281.

EVANS, W. (1933): Quart. J. Med., 26, 1-31.

EVANS, M.W. (1944): Med. J. Austral., 2, 225-228.

EVANS, M.W. (1947): Med. J. Austral., 1, 786.

"F"

FAEBER (1933): Jahr.Kinderh., cited by Gillman, Jetal (1948).

FANTHAM, H., (1925): S.Afric.J. Scien., 22, 400-424.

FARBER, S., and HUBBARD, J. (1933): A m.J.Med.Sci., 186, 705.

FENNER, F. (1947): Australian J. Exp. Biol. and Med. Sci., 25, 257-274

FENNER, F. (1948) Lancet, 255, 915-920.

FISHER, R.A. and RACE, R.R. (1946): Nature, 157, 48.

FORD, F.R. (1938): Bull. Johns Hopkins Hosp., 43, 140.

FOX, M.J. and BORTIN, N.M. (1946): J.Am.Med.Ass., 130, 568.

FOX, M.J. and WAISMAN, H.A. (1947): Am.J.Med.Sci., 214, 142-148.

FOX, M.J., et al (1948): Lancet, 1, 748.

FOX, M.J., et al (1949): Pediat., 35, 561.

FRANCIS, I., and STUART-HARRIS, C.H. (1938): J.Exp. Med. 68, 789-813.

FRANESCHETTI, A. (1947): Ophthalmologica, 114, 332-339. cited by Eye, E.N & T. Year Book, 1948, The Year Book Publishers, Chicago).

FRIEDMAN and COHEN, P. (1947) Am.J. Dis. Child., 73, 178-188.

"G"

GALLAGHER, F.W.,,and WOOLPERT, O.C. (1940): J. of Exp. Med., 72, 99.

GAMBLE, R.C. (1946): Am. J. Ophthal., 29, 737.

GATES, R.R. (1946): Human Genetics, The MacMillan Co., New York, Vols. 1.

GATES, R.R. (1946a): Ibid, Vol. 2.
Cataract: Vol. 1, pp.196-204
Deafness: Vol. 2, pp.256-267
Mongolism: Vol. 2, pp.1111-1119
Congenital Cardiac Disease, Vol. 2, pp.1301-1305.

GEAR, J. (1941): Leech, 12, 7-15.

GEIGER, J.C, (1918): J. of Am. Med. Ass., 70, 1818-1820.

GEORGE, J.P. (1945): Canad. Med. Ass. J., 53, 167-168.

GERARD-LEFEBVRE and MERLEN, J. (1948): Sem. Hôp. Paris, 24, 2541-2546. (cited by J.Obstet. and Gynaec. Brit. Emp., 1949, 56, 703).

GESELL, A. (1940): First Five Years of Life. Harper and Bros., London, p. 288.

GESELL, A. (1946): Volta Rev., Nov. 1946.

GIBSON, A.J. (1945): Med. J. Austral., 1, 332.

GIBSON, S. (1950): Pediat., 6, 300-302.

GIFFORD, H., and HULLINGHORST, R.L. (1948): Am. J. Obstet and Gynaec., 55, 1030-1036

GILBERT, J.A.L., and DUNLOP, D.M. (1949): Brit. Med.J. 1, 48.

GILCHRIST, A.R. (1946): Brit. Med. J., 1, 515-519.

GILLMAN, J.; GILBERT, Christine; GILLMAN, T., and SPENCE, Isobel (1948): South Afr. J.Med.Sci., 13, 47-90.

GLASER, R.W. (1930): Arch. Path., 9, 71,557.

GOAR, E.L., and POTTS, C.R. (1946): Am.J. Ophthalmol., 29, 566.

GOLDSTEIN and MURPHY (1929): Am. J. Roentgenol., 22, 322.

GOODPASTURE (1942): Science, 45, 391.

GRASSET, E.G. (1929): South Afr. Inst. Med. Res. (S.A.I.M.R.) Publ. No. 24.

GREGG (1941): Tr. Ophth. Soc. Australia, 3, 35-46.

GREGG, N.M. et al (1945): Med. J. Australia, 2, 122-126.

GREENBERG, M. et al. (1940): J. of Am. Med. Ass. 126, 944-947.

GREENBERG, M. (1947): Med. Clinics of N. America, 31, 603.

GREENBERG, M., and APPELBAUM, E. (1948): Am. J. Med. Sci., 216, 565.

GREENBERG, M.W., and BEILLY, J.S. (1949): Am. J. Obstet. and Gynaec., 57, 805-806.

GREENBERG, M. ,.et al (1949). Pediat., 3, 456-467.

GREENE et al, (1938): Science, 87, 396.

GREENE, H.J. and HOBBY, G.L. (1944): Proc. Soc. Exper. Biol. and Med., 57, 282.

GREENTHAL, R.M. (1945): Arch. Pediat., 62, 53-56.

GRIFFITH, C.C., et al (1948): Am. Heart J. 35, 438-443.

GRONVALL, H., and SELANDER, P. (1948): Nordisk Medicin., 37, 409-415. (cited by Abstracts of World Medicine, November, December, 1948).

GROSS, P. (1941): Arch. Path., 31, 163.

GROSS, R.E. (1946): Surgery, 20, 1.

GRÜENEBERG, H. (1943): The Genetics of the House Mouse: London, Cambridge Univ. Press.

GRUENWALD, P. (1946): Anat. Rec., 94, 518.

GRUENWALD, P. (1947) Arch. Path. 44, 398-436; 495-559. Ibid. (1947a) Arch. Path., 44, 648-664.

GRÜNEBERG (1938): Proc. Royal Soc. Biol., 125, 123.

GUNN, W. (1933): Brit. J. Dis. Child., 30, 111-117.

"H"

HABEL, K. (1942): Public Health Reports, 57, 1193.

HADFIELD, S.J. (1940): Brit. Med. J. 1, 878.

HAIN, A.M. (1942): J. Endocrinol., 3, 10.

HALDANE, J.B.S. (1938): Heredity and Politics, 2nd Ed., Henderson and Spalding, London, p. 114.).

HALE, F. (1937): Texas State J. Med., 33, 228.

HALL, M.B. (1946): Brit. Med. J., 1, 737.

HALPERIN, S.L. (1940): J. Heredity, 31, 2118.
Ibid. (1944): J. Heredity, 35, 211-214.

HAMBURGER, M. (1944): J. Infect. Dis., 75, 58-70.

HAMBURGER, and HABEL, K. (1947): Proc. Soc. Exper. Biol. and Med. 66, 608.

HANHART, E. (1941): Schweiz. Med. Wochens, 71, 861-864 (cited by Gates, R.R. in "Human Genetics" Vol 2, p. 17).

HARRIES, E.H.R., and MITMAN, M. (1947): Clinical Practice in Infectious Diseases, E. & S. Livingstone, Edinburgh.

HARRISON, B.L. (1940). Brit. Med. J., 1, 637.

HILL, W.B. (1908-9): Quart. J. Med., 2, 49.

HIRO, Y. and TASAKA, S. (1938): Monatschr. f. Kinderh., 76, 328-332 (cited by Habel, K., 1942).

HODGES, G.M.W. (1940): Brit. Med. J., 1, 548.

HODGES, G.M.W., and WITNEY, W. (1940): Brit. Med. J. 1, 830.

HOLLIDAY, P.B. (1950): J. Pediat., 36, 185.

HOPKINS, L.A. (1946): Am. J. Dis. Child., 72, 377.

HOPKINS, L.A. (1949): Ibid., 78, 182-200.

HORN et al, (1948): J. Pediat., 33, 484-488.

HOSKINS, R.G. (1941) : Endocrinology: The glands and their functions. Norton, New York.

HUGHES, E.W. and RUMORE (1944): Arch. Path., 37, 364-366.

HUGHSON et al (1939): Arch. Otolaryngol, 29, 403.

HUMPHREY, T.F. and EKERMEYER (1937): Ohio State Med. J. 33, 406-408.

HURWITZ, D., and IRVING, F.C. (1937): Am. J. Med. Sci., 194, 85.

HUXLEY, J.S. (1942): Evolution: The Modern Synthesis. Cambridge.

HYNES, M. (1940): Lancet, 2, 679.

"I"

INGALLS, T.H. (1947): Am.J. Dis. Child., 73, 279-292.

INGALLS, T.H. and DAVIES, J.A.V. (1947): New.Eng. J. Med., 236, 437-438.

INGALLS, T.H. (1948): Pediat., 1, 315-320.

INTERNATIONAL MEDICAL DIGEST (1945): 47, 244.

JAMES, V., and FREIER, A (1949): Arch. Dis. Child., 24, 54-58.

JAVERT, C.T. (1942): Surg., Gynaec. Obstet., 74, 1.

JENNINGS (1935): Genetics, Faber and Faber Ltd. London, p. 156.

JENNINGS, R.E. (1940): J. Med. Soc. New Jersey, 37, 577.

JONES, B.S. (1950): Brit. Med. J., Aug. 19.

JOSLIN, E.P. et al. (1940): Treatment of Diabetes Mellitu Lea and Febiger, Philadelphia.

Journal Am. Med. Ass., (1949): Leading Article, 6, 541.

"K"

KENNEDY, J.M. (1942): Lancet, 2, 543.

KOLETSKY, S. (1941): Arch. Int. Med., 67, 129-176.

Ibid. (1941a): Arch. Path., 31, 338-353.

KRAATZ, J. (1925): J. Heredity, 16, 265-270.

KRAUSE, A.C. (1945): Annals of Surgery, 122, 1049.

KRONFELD, R. (1939): Histopathology of teeth and their secondary structures, 2nd Ed., (p.99, Lea and Febiger, Philadelphia.

KRYNAUW, R.A. (1950): South African Med. J., 24, 539-544.

"L"

LADD, W.E., and Gross, R.E. (1934): Am. J. Surg., 23, 167.

LANCET (1946): Leading Article, 1, 208.

LANCET (1947): Editorial, 1, 639.

LANCET (1948): Leading Article, 2, 933-934, 936.

LANDAUER, W. (1945): J. Exper.Zool., 98, 65.

LANDAUER, and DUNN (1930): J. Genetics, 23, 397.

LANDE, L. (1950): J. Pediat., 36, 625-634.

LANDSTEINER, K., and WIENER, A.S.(1941): J. Exper.Med. 74, 309.

LANDTMAN, B. (1948): Arch. Dis.Child., 23, 237-246.

LAWRENCE, R.D., and OAKLEY (1942): Quarterly J.Med., 11,45.

L'ETANG, H. (1947): Lancet, 1, 849.

LEVIN, P.M. and MOORE, H. (1942): J. Pediat., 21, 673.

LEVY, S. and PERRY, H1A. (1948): Am. J. Ment. Deficiency, 53, 2.

LINDBERG, G. (1924): Acta. Paediat., 4, 1-19. (cited by Wesselhoeft, 1947a).

LIPITZKY, S.J. and BOSHES, B. (1942): J. Heredity. 83, 155-156.

LITTLE, C.C. and BAGG, H.J. (1924): J. Exper. Zool., 41, 45.

LOVE, J.K. (1920): J. Laryng. Rhinol. and Otol., 35, 263-270.

LURIA (1948): cited by J. Am.Med. Ass. (1949), 6, 541.

LYON, R.A. (1945): Congenital Heart Disease, Mitchell-Nelson Textbook of Pediatrics, W.B. Saunders Co., Philadelphia and London.

"M"

MacBRYDE and CHARLES (1935): Arch. Int. Med., 56, 935-943.

McFARLAND, J. and MEADE, T.S. (1932): Am. J. Med. Sci. 184, 66-80.

MACKLIN, M.T. (1929): Human Biol., 1, 382-405.

MACKLIN, M.T. (1929a): Am.J. Med. Sci., 178, 315-337.

MACKLIN, M.T. (1936): Am. J. Obstet. and Gynae., 32, 258-265.

McLORINAN, H.(1949): Med. J. Austral., 1, 600.

MALL, F.P. (1917): Am. J. Anat., 22, 49-72.

MARGOLIS, F.J.; WILSON, J.L.; and TOP, F.H. (1943): J. Pediat., 23, 158-165.

MARTIN, S.M. (1945): Brit. Med. J., 1, 865.

MARTIN, S.M. (1946): Ibid., 1, 588.

MARX, L. (1942): J. Exper. Zool., 91, 365.

MASTERS (1947): Clinical Proc., 6, 300.

MAXWELL, J.P. et al (1939): Proc. Roy.Soc. Med., 32, 287.

MELLANBY, May, and COUMALOS (1946): Brit. Med. J., 2, 565.

METROPOLITAN LIFE INSURANCE CO. (1948): Statistical Bulletin, 29, 2.

MEYER, K.F. (1950): J. Pediat., 37, 627.

MILLER, L. (1936): Lancet, 230, 1197.

MICHAEL, May (1908) : Arch. Pediat. 25, 598-606.

MILLER, H.C. et al, (1944): J. Pediat., 24, 603.

MILLER, H.C. (1945): Am. J. Med. Sci., 209, 447.

MILLER, H.C. et al. (1949): Pediat., 3, 259-270.

MILLER? H.C. et al (1950): Pediat., 2, 322.

MITCHELL NELSON TEXTBOOK OF PEDIATRICS (1948) Ed. by W.E. Nelson, W.E. Saunders Co., Philadelphia and London.

MOHN, J.F. and WITEBSKY, E. (1948): New York State J. Med., 48, 287-290.

MOORE, L.A. et al (1935): J. Nutrition, 9, 533.

MORLET, C. (1949): Med. J. Austral., 2, 760.

MUIR, D.C. and BROWN, J.W. (1935): Brit. Med. J., 1, 966-971.

MULLER, H.J. (1948): The Bulletin of N.Y. Acad. of Med., 24, 447-469.

MURPHY, D.P. (1940): Congenital Malformations. Lippencott & Co., Philadelphia.

MURPHY, D.P. (1947): Ibid., 2nd Ed.

MURRAY, M.M., and WILSON, D.C. (1945): Nature, 155, 79.

"N"

NATIONAL COUNCIL FOR THE BLIND, South Africa (1950): Records, by courtesy Mr. Wentworth.

NATIONAL RESEARCH COUNCIL (1938): Monograph: H.M. Stationary Office, London.

NEEDHAM, J. (1942): Biochemistry and Morphogenesis. Cambridge Press.

NEUHAUSER, E.B.D. (1946): Am. J. Roentgenol., 56, 1

NEW SOUTH WALES COMMITTEE (1945): Med. J. Austral., 2, 122.

"O"

OBER, R.E. et al (1947): Am. J. Publ. Health., 37, 1328-1333.

OSLER AND MACRAE (1926): Modern Medicine. Henry Ximptor London, Vol. 2, p. 117.

OWENS, A.B.S., and GREENWAY (1940): Med. J. Austral, 2, 536.

OWENS, W.S. and OWENS E.V. (1949): Am. J. Ophthalmol., 32, 1631.

PARSONS, J.H. (1936): Diseases of the Eye. London, Churchill, 8th Ed.

PARSONS, L.G. (1946) : Canad. Med. Ass. J., 55, 327.

PATRICK, P.R. (1948) : Med. J. Austral., 1, 421.

PATTON, J.L. (1947) : Lancet, 2, 451

PENROSE, L.S. (1933) : J. Genet., 27, 219-224.

PENROSE, L.S. (1934) : Proc. Roy. Soc. Biol., 117, 431 431-450.

PENROSE, L.S. (1950) : Brit. Med. J., Oct. 21, pp. pp. 903-905.

PERERA, C.A. (1945) : Am. J. Ophthalmol., 28, 186.

PERERA, C. (1948) : Ibid., 31, 96.

PERRY, C.B. (1931): Arch. Dis. Child., 6, 265-272.

PINTNER, R., and PATERSON (1923): A Scale of Performance Tests, D.C. Appelton, New York.

PLAUT, A., and SCHARNOFF, G. (1935): Arch. Path., 20, 582.

PLAUT, A. (1939) : Am. J. Path., 15, 649.

POST, L.J. (1950) : J. Pediat., 36, 834.

POTTER, C. (1930): Brit. Med. J., 2, 1084.

POTTS, W.J. (1950): Pediat., 6, 302-304.

PRENDERGAST, J.C. (1946): Arch. Ophth., 35, 39-41.

PUTNAM, T.J. (1941) : Bull.N.Y. Acad. Med., 17, 337-347.

"R"

REESE, H.B. (1944) : Am.J. Ophthal. 27, 483-387.

REESE, A.B. (1949): Arch. Ophthal., 41, 527.

RIDE, L. (1938): Genetics and the Clinician. John Wright and Sons, Ltd. Bristol, p.50.

RIVERS, T.M. (1943) : Viral and Rickettsial Infection of Man, Lippincott, Philadelphia, pp. 3-31.

ROMANOFF, A.L. (1930): J. Morphol., 50, 517.

RONES, B. (1944) : Med. Ann.Dist. Columbia, 13, 285-287 (cited by Aycock and Ingalls (1946).

SCHAMBERG, J.F. and KOLMER, J.A. (1928): Acute Infectious Diseases, Lea and Febiger, Philadelphia, 2nd Ed., pp. 545-573.

SCHLAPP, M.G. (1925): J. Heredity, 16, 161-170.

SCHOLES, F.V. (1949) : Med. J. Austral., 1, 601.

SCHRÖDER, H. (1939): Zeits. f. Neurol., 164, 286-310 (cited by Gates 1946a p. 1113).

SEIB, G.A. (1934) : Am. J. Anal. 55, 511-525.

SETALA, A. (1947): Ann.Chir. et Gynaec. fenn., 36, 117-127 (cited in Poliomyelatis Current Literature. Vol. I. No. 14, p.160, 1947).

Sherman, et al (1940) : J. Exper. Med. 72, 611.

SHULL, A.F. (1948): Heredity, McGraw-Hill Book Co., New York, 4th Ed.

SHUTTLEWORTH, G.E. (1909): Brit. Med. J. 2, 661-665.

SILVER, A.A. (1950): J. Pediat. 37, 134.

SIMPSON, R.E.H. (1940): Brit. Med. J., 1, 835.

SKIPPER, E. (1933): Quart. J. Med., 2, 353.

SMITH, P.E., and MacDOWELL, E.C. (1930): Anat.Rec. 46, 249.

SMITH, F.R. (1939): Am. J. Syph., Gonorr., and Ven. Dis., 23, 165.

SMITH, Clement (1945): The physiology of the newborn Infant, c.c. Thomas, Springfield, Ill.

SMITH, Clement (1947): Am. J. Dis. Child., 73, 243.

SMITH, (1948): Am. J. Ophthalmol., 31, 96.

SNELL G.D. (1941): Radiography, 36, 189.

SOUTH AFRICAN MED. J. (1949): Editorial : Abortion in South Africa, 23, 223.

SPEART, H. (1940): Bull. Johns Hopkins Hosp., 66, 139.

SPEMANN, H. (1938): Embryonic Development and Induction. New Haven, Conn., Yale Press.

SPENCE, J.C., and MILLER, F.J.W. (1939), cited by R.W. Ellis in "Child Health and Development", Churchill, London, 1947, Chap. 13.

SPENCER, W.G. (1920) : Proc. Royal Soc. Med. 13 (clin. sect.) 73-78.

SPRAGINS, M., et al (1950): Pediat., 5, 600.

STADLER, H.E., et al (1950): J. Pediat., 36, 370-375.

STEIN, J., and BARBER, D.J. (1945) : Am. Heart J., 30, 118.

STEINMAURER, H. (1938): Monatschr. f. Kinderh., 75, 98-102 (cited by Habel, 1942).

STERN, C. (1950): Pediat., 5, 324-328.

STOCKARD, C.R. (1920-1): Am. J. Anat., 28, 115.

STOCKARD, C.R. (1931) : Physical Basis of Personality. W.W. Norton and Co. N.Y.

STOKES, J.Jr. (1948): Mitchell-Nelson Textbook of Pediatrics. W.B. Saunders and Co., Philadelphia and London, 4th Ed., pp.449-450.

STOLOFF, E.G. (1928): Am. J. Dis. Child., 36, 1204.

STONE, W.S. et al. (1947) : Proc. Nat. Acad., 33, 59.

SUTHERLAND, I. (1949): Stillbirths. Oxford University Press.

SWAN, C., TOSTEVIN, A.L., MOORE, B., MAYOR, H., and BLACK (1943): Med. J. Austral., 2, 201-210.

SWAN, C., TOSTEVIN, A.L., MAYO, H., and BLACK, G.H.B. (1944) : Med. J. Austral., 1, 409-413.

SWAN, C. (1944) : J. Path. and Bact., 56, 289.

SWAN, C., and TOSTEVIN, A.L. and BLACK, G.H.B. (1946) : Med. J. Austral. 1, 889-908.

SWAN, C., and TOSTEVIN, A.L. (1946[a]): Med. J. Austral. 1, 645-659.

SWAN, C., (1948): Lancet, 1, 744.

SWAN, C., (1949[a]): J. Obstet. Gynaec.Brit. Emp., 56, 341-366.

SWAN, C. (1949[b]): Ibid. 56, 591-605.

"T"

TAUSSIG, Helen, D. (1947): Congenital Malformations of the Heart. Oxford University Press, London.

TAYLOR and SIMMONS (1948) : Am. J. Obstet. Gynaec., 56, 143.

TERRY, T.L. (1942) : Am. J. Ophth., 25, 203, 1409.

TIDY, H. Letheby (1940): Brit. Med. J., 1, 869.

TIDY, H.L. (1948): Blood, 3, 823-829.

TINKLE, W.J. (1933): J. Heredity, 24, 13-18.

TITUS and ELLIS et al (1935): Proc. Soc. Exper. Biol. and Med. 32, 1542.

"V"

UNITED STATES BUREAU OF CENSUS (Children's Bureau, 1941): Mitchell-Nelson Textbook of Pediatrics (1948), Robert A. Lyon, Chapter: Care and Evaluation of Well Children.

VAN ROOYEN (1946) : South Afr. Med. J., 20, 772.

VARNEY, R.F. et al (1942) : J. Clinical Endocrinol., 2, 137.

VEEDER, B.S., and HEMPELMAN, T.C. (1921) : Arch. Pediat., 38, 437.

VERSE (1909) : cited by R.R. Gates (1946) Human Genetics, Vol. 2, pp. 1301-1305.

VICKERY, D. (1945) : Med. J. Australia, 1, 332.

VISONHALER, F. and COSGROVE K.W. (1936) : Arch. Ophth., 15, 222-224.

"W"

WALTER and LEVINE (1944): Science, 100, 453-454.

WARKANY, J., and SCHRAFFENBERGER, E. (1946): Arch. Ophthalmol., 35, 150.

WARKANY, Josef (1947): Advances in Pediatrics. Interscience Publishers, New York, Vol 2 pp 1 -63

WARREN et al (1946): Med. Clin. of North America, 30, 401-404.

WEBER, F.P., and SCHOLTZ, M. (1939): Brit. J. Child. Dis., 36, 131.

WELCH, L. St. V. (1945): Med. J. Austral., 1, 574.

WELLER (1917): Proc. Soc. Exper. Biol. and Med., 14, 14.

WERTHEMANN, A. (1948): Annales Pediatrics, 171, 187 (cited by International Med. Dig., 54, 101 - 106, 1949).

WESSELHOEFT, C.: (1939): Arch. Int. Med., 12, 1473-1485.

WESSELHOEFT, C. (1946) : Med. Clin. of North America, 30, 1016.

WESSELHOEFT, C. (1947a) : New Eng. J. Med., 236, 943-950.

WESSELHOEFT, C. (1947b) : Ibid, 236, 978-988.

WHIPPLE, D.V., and DANHORN, E.C. (1938): J. Pediat., 12, 386.

WHITBY, L.E.H. and BRITTON, C.J.C. (1942): Disorders of the Blood, 4th Ed., The Blackiston Co., Philadelphia.

WHITE HOUSE CONFERENCE ON CHILD HEALTH AND PROTECTION, D. Appelton - Century Co., N.Y. and London, Vol.ib, p. 338.

WHITNEY, E.A. (1930): Eugenics, 3, 105-106; 208-222.

WIENER, A.S. (1937): N.Y. State J. Med., 47, 985.

WIENER, A.S. (1943) : Blood Groups and Transfusion : C. Thomas, Springfield, Ill. 3rd Ed..

WILDMAN, W.W. and TEASEY, W.B. (1940): Brit. Med. J., 1, 851.

WINCKEL (1902): cited by J. Warkany, Advances in Pediatris, Vol. 2, p.47.

WINTERBOTHAM, L.P. (1946): Med. J. Austral., 2, 16.

WITSCHI (1939): Sex and Internal Secretions, Ed. by E. Allen, The Williams and Wilkins Co., 2nd Ed., p. 145..

WORCESTER, J., et al (1950): Pediat., 6, 37, 208.

WRIGHT, S, (1926) : American Nature, 60, 552-559.

WYLLIE, W.G. (1949): Diseases of Children, Ed. by Paterson and Moncrieff, Edward Arnold and Co., London, 4th Ed., Vol. 2, pp. 241-243.

WYLLIE, W.G. and McKISSOCK, W. (1949): Ibid., pp.98-99.

"Y"

YANNET, H., and LIEBERMAN, R. (1948): Am. J. Dis. Child., 76, 176.

YANNET, H. (1950): Pediat., 5, 335.

"Z"

ZAHORSKY, J. (1940): Arch. Pediat., 57, 405.

ZAHORSKY, J. (1948): Brennerman's Practice of Pediatrics, Vol. 2, Chap. 21., Prior Co. Maryland.

ZINGG, R.M. (1942): Wolf-children and Feral Man, Harpers.
