MAY, 1945

THE ULSTER MEDICAL JOURNAL

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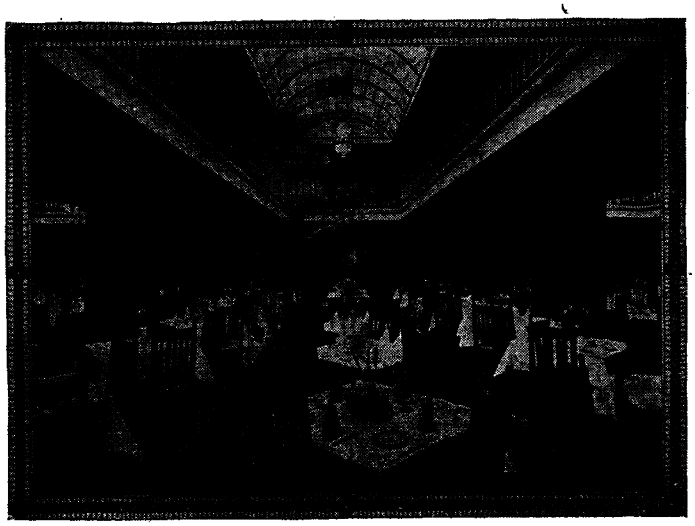

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No. 1. May, 1944

No. 2. November, 1944

The Ulster Medical Journal

VOL. XIII

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THE ULSTER MEDICAL JOURNAL
1944

CONTENTS

Fellows and Members of the Ulster Medical Society receive the Journal free.
Subscription to non-members, five shillings annually.

THE ULSTER MEDICAL JOURNAL

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To the Editor of the Ulster Medical Journal.

DEAR MR. EDITOR,—In the annual report of the Society for 1944, the Central Committee acknowledges the help given by the ULSTER MEDICAL JOURNAL by publishing appeals for funds. That help has been most graciously given and is truly appreciated, but I find myself wondering if these appeals are noticed by your readers.

Study of this latest annual report discloses that the Belfast and County Antrim Branch contributed £240. 11s. 6d. during the year, and in return derived benefit for seven widows and one family of orphans to the total sum of £201. 10s. True, it appears this year that we are at least paying our way, and this is only the second time we have done so, but it can be no cause for satisfaction that the widows' grants vary from £16. 10s. to £30 per annum and the orphans' grant was £25. There is no need to stress what pittances these amounts are in present times, but yet to the recipients they serve to make existence a bare possibility. Without exception these grants are applied to full advantage, and our Branch is proud of some of the educational results attained through this assistance.

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THE
ULSTER MEDICAL JOURNAL

:: PUBLISHED ON BEHALF OF THE ULSTER MEDICAL SOCIETY ::

Vol. XIV · 1st MAY, 1945 · No. 1

The Aetiology of Congenital Abnormalities

By J. EDGAR MORISON,

Department of Pathology, Queen's University, Belfast.

GROSS abnormalities are fortunately not common. Murphy (1940) in Philadelphia found that approximately 47 individuals possessing congenital malformations were born alive or dead per 10,000 live births. About one-quarter of these were reported as stillbirths. His data was collected mainly from death certificates and included only the grosser defects. Malpas (1937) recorded 294 cases in 13,964 consecutive births in Liverpool.

The occurrence of any congenital abnormality is especially painful to all concerned, and the parents will wish to know the cause of the condition, and whether it is likely to recur in subsequent pregnancies. It is not possible to give a satisfactory answer to these questions, but it may be useful to survey some recent contributions to the problem, to indicate in what directions progress may be expected, and to acknowledge the valuable contributions made in allied fields of biological science.

As an individual, developed from the fusion of the sex cells or gametes of his parents, grows through intra-uterine and extra-uterine life his whole being expresses the result of the interaction of his genetic pattern or constitution with the environment. The environment is at first the seemingly constant one of the uterus, and here the internal environment is determined primarily by such substances as can pass across the placenta. The genetic pattern is a mosaic inherited from his parents and more remote ancestors. It is composed of unit characteristics, or traits, all of which the geneticist hopes some day to recognise individually, and to trace as they are transmitted as physical entities, or genes, from generation to generation on the chromosomes of the sex cells. In accordance with the modern knowledge of Mendelian inheritance some of these characters or traits may not have been expressed for generations; either because they are recessive and have not been present as homozygotes, or because other genes or environmental factors have modified their expression. The present enquiry is concerned with the relative importance of genetic influences and the intra-uterine environment on the development of such variations from the normal as can be usefully recognised. These

variations are usually malformations or abnormalities of bodily form, but an increasing number of disturbances of physiological function will be recognised as biochemical and biophysical studies are pursued.

It is well known that in certain families abnormalities recur generation after generation in such a manner that the genetic mode of their inheritance can be demonstrated. One of the most striking examples is given by Drinkwater (1917). The skeleton and the effigy of the first Earl of Shrewsbury, a hero of the French wars of the fifteenth century, showed a fusion of the proximal and middle phalanges of certain digits. A lineal descendant fourteen generations later showed the same rare condition and knew of its existence in his father and grandfather. In the Nougaret pedigree dating from about 1637 there were 134 individuals affected with a form of night blindness (Roberts, 1940). Such abnormalities fail to interfere with reproduction and are among the more fundamental and elementary observations of medical genetics. The present problem is the occurrence of an individual, who is often so grossly malformed as to be described as a monster, in a family where there may be no previous history of any such disaster. Throughout his history mankind has questioned the meaning and significance of such visitations, and it may be of interest to describe some of the older beliefs. The relevant literature is fully listed by Ballantyne (1904).

Historical Review.

Three distinct trends of thought may be recognised, they were never necessarily exclusive of each other, but in different periods and countries varying emphasis was laid upon each of them, and they found expression in a diversity of terms.

The oldest, and at all times the most widespread, belief was in the Supernatural origin of monsters. Some have maintained that ancient peoples fashioned their gods in the shape of these human and animal monsters. Perhaps among the Greeks the Centaur was an infant born with two pairs of lower limbs or a hydrocephalic calf, Atlas a case of occipital encephalocele and the Gorgon's head an acormic placental parasite. The god Pthah of the Egyptians certainly appears to represent an achondroplasic dwarf. Some peoples believed that the gods amused themselves by creating such forms, others, however, looked upon such occurrences as portents of the future which were sent to warn or admonish them. A tablet from ancient Nineveh reveals that the birth of a baby with an imperforate anus meant famine, but that a child seeming to possess three legs indicated great prosperity. Many infants, and indeed many mothers, were sacrificed to such beliefs. In the early Christian era there was an increasing pre-occupation with the idea of sin, and the birth of such offspring was regarded as punishment for the sins of the parents. Sometimes the abnormality was thought to proclaim the greater glory of God. As the antithesis between good and evil, between the all good God and the evil one, became clearer malformations appeared rather to be the work of the Devil.

But while the ignorant mass subscribed to such doctrines there were those who looked for natural physical causes. Aristotle and the Greeks speculated on this

and their speculations were handed on through the Arab physicians of the pre-Renaissance period. Though based on no accurate knowledge of reproduction these doctrines influenced the physicians and philosophers of the sixteenth and seventeenth centuries. About this time there was a greater diversity of opinion as to the fundamental cause of these conditions than at any time in the world's history. Supernatural theories, theories of hybridity and the bestial origin of defects struggled with theories ascribing them to emotional strains and stresses.

The belief in the importance of mental or emotional causes is very ancient. According to the writer of the Genesis narrative (Gen. xxx) Jacob made use of it in stock rearing. Roman, Jewish and early Christian writers acknowledged the importance of mental impressions, especially at the time of conception. That emotional trauma to the mother at any time during pregnancy could serve as the cause of gross malformations was probably a contribution of the Revival of Learning in Europe and a revulsion from the crude beliefs in the Powers of Evil. The emotional incident was not necessarily specific, but hairy children occasioned by the sight of monkeys, and anencephalic infants produced by handling frogs, were attractive forms of this speculation. A few shrewd criticisms were made such as that few children should be born without defects. Doubt was also expressed as to whether these influences could operate after the child was fully formed about the seventh week after conception. The belief, however, gained wide acceptance and, even in the later half of the nineteenth century, it persisted in American medical literature.

It is apparent that no satisfactory explanations have been provided in the past. A belief in the importance of maternal emotional strain or shock persists even to-day among the laity. There is not one shred of evidence in its favour. Modern embryology has shown that the disturbances of normal growth responsible for the abnormalities described must occur in the early stages of embryonic development, and usually long before the eighth week of intra-uterine life. Perhaps this is an even more convincing argument than the absence of any nerve pathway between the mother and the fœtus, because the alleged psychic traumatisation usually occurred late in pregnancy and therefore could not have been significant. The enormous teratological literature of the seventeenth to nineteenth century is nothing but futile speculations over mere coincidences. Similar chronological considerations dispose of all but a fraction of cases where physical trauma to the pregnant woman has been alleged to produce fœtal abnormalities.

The Pre-Natal Environment.

The relative contribution to the development of the ovum made by the genetic constitution and by subtle, and as yet unknown, changes in the intra-uterine environment and nutrition remains a major problem in biology. Experimental embryologists, concerned with free living embryos of lower forms of life, have described the production of many monstrous forms by refrigeration and by the addition of magnesium chloride, alcohol and other substances to the medium (Stockard, 1921). Modern embryology conceives of the embryo as the site of

many loci of cells growing and differentiating at different rates at different periods in their development. This activity is directed by chemical substances called "organisers," and it is determined primarily by the genetic constitution of the individual. Especially in the lower forms of life an enormous mass of information has accumulated on the morphogenetic interrelationship of embryonic parts, but no coherent picture of the whole has emerged. It is not difficult to believe that an adverse environment will act selectively, probably on areas at the moment the site of most active growth, or that certain substances in very low concentration might interfere specifically with the activity of the organisers, either directly or by co-enzyme inactivation or substrate blockage. An inadequacy or omission of any stage in embryonic development cannot be repaired at a later stage. If determined by environmental changes these need only act for a short time. Experimental work on lowly forms of life can only be transferred to mammals, and especially to man, with very great caution. The mechanism of intra-uterine nutrition has been subjected to prolonged evolution and is well adapted to the preservation of a constant environment. For the embryo or fœtus this stability is of the highest survival value and it may be assumed that the mechanism has become highly efficient. That highly specific effects could be explained as due to changes in environment will not prove that human abnormalities are produced in this way. The production of abnormalities, even in mammals, and still less their production in lower forms, by highly artificial agents will not necessarily bear any relationship to their actual mode of production. Experimental embryology, like experimental carcinogenesis, is in some danger of mistaking the mere accumulation of facts for knowledge.

Mall (1908) produced evidence suggestive of the importance of the environment as modified by abnormalities of placental implantation. He found that 96 per cent. of the embryos in unruptured tubal gestations and 7 per cent. of those aborted from the uterus were abnormal. He considered that the argument against the germinal origin of pathological ova and monsters was overwhelming. While lethal genetic factors might determine abortion from the uterus it is more difficult to see how any genetic factor carried by the ovum could influence its implantation in the tube. This suggests that improper nutrition can produce abnormal embryos; it does not prove that monsters, associated with gestations which are better implanted and which proceed to term or near it, are produced in this way. Greenhill (1939) found an incidence of 2.5 per cent. of monsters in 4,446 cases of placenta prævia as compared with 0.94 per cent. for all obstetric cases. Before attaching importance to this as evidence of environmental influences it would be necessary to show that the low implantation interfered with transplacental nutrition early in pregnancy, and also that placenta prævia itself was not an associated genetic defect.

That specific insufficiencies in embryonic nutrition may sometimes determine congenital defects is strongly suggested by the work of Warkany (Warkany, Nelson and Schraffenberger, 1942, 1943; Warkany and Schraffenberger, 1944). Cleft palate and various bony deformities of the limbs were produced. These results

were obtained with a riboflavin deficient diet and in the Sprague-Dawley and Baltimore strains of rats, and by Noback and Kupperman (1944) in the Wistar strain. Genetic influences would, therefore, appear to play little part in these experiments. At most dietary surveys (Murphy, 1939, Burke and others, 1943) suggest a slightly higher incidence of dietary insufficiency among the mothers of malformed infants. The maternal reserves of most dietary constituents are unlikely to be as greatly strained during the early formative and critical period of embryonic development as later when the fœtal demands grow. Only occasionally have dietary deficiencies been recognised as the cause of disease in late fœtal life. Maxwell, Hu and Turnbull (1932) described fœtal rickets in the offspring of mothers with active osteomalacia. A search for other specific defects arising in late fœtal life should produce some results of interest, if maternal dietary deficiencies are of significance at any period.

In the past embryonic and fœtal inflammation, usually ascribed to intra-uterine infection, was thought to be frequent, and to be of great importance in the production of congenital abnormalities. It was thought to be of special importance in the amniotic sac, in the meninges and brain and in the heart. The histological evidence offered cannot be accepted. Streeter (1930) attacked the popular idea that amniotic inflammation, adhesions and mechanical constriction dictated intra-uterine amputations. He believed that the defects were due to imperfect development of limb-buds, comparable to doubling, hypertrophy and other defects of digits and limbs, and that the formation of adhesions and annular bands was secondary to nutritional changes. Very similar defects of limbs have been shown to be primary and due to hereditary factors.

Recent observations from Australia, described by Gregg (1941), Swan (1944) and Evans (1944), have shown what appears to be a significant association between maternal rubella in the first few months of pregnancy and the development of various congenital defects. These lesions include a hitherto undescribed form of congenital cataract (Gregg), deaf-mutism, heart disease, microcephaly and major dental anomalies (Evans, 1944). Reese (1944) and Erickson (1944) have already reported similar cases from America. Studies such as this depend on the collaboration of many outside the research itself, and are very liable to suffer from a failure to report negative cases. The association of the defect with illness in the early months of pregnancy is, however, very suggestive. It is possible that an aberrant form of German measles is responsible, but the probable penetration of the placental barrier by a virus disease in the early months of pregnancy is of very great interest. The only disease known to be spread from mother to child in utero with any frequency is syphilis, and here it is doubtful if infection of the fœtus can occur before the fourth month. The fœtus may be grossly affected, development may be retarded and it may die, but the incidence of malformations is not affected.

The author is not aware of any adequate scientific study of the effect of contraceptive techniques on the incidence of abnormalities. Several studies by partisans have appeared, but beliefs are no substitute for the accumulation and analysis of facts.

The marked increase in the incidence of defects, such as anencephaly (Malpas, 1937) and Mongolism (Penrose, 1932), with increase in maternal age is not evidence that the maternal environment produces the lesion. It suggests that it facilitates in varying degree the expression of a defect already present, and a possible genetic basis for Mongolism has been discussed by Penrose (1932). Studies on the incidence of abnormalities in different groups of the population must take such contributory factors into account.

Genetic Influences.

The science of modern genetics has progressed far beyond the study of simple dominant and recessive inheritance and the study of family trees. Statistical analysis has overcome some of the difficulties imposed by our inability to conduct selective breeding in man. Genetic considerations have been applied to conditions where the frequency of expression of a trait is low, compared to the frequency with which it is inherited, and to conditions which depend on interaction between inherited factors and the environment—for example, tuberculosis (Kallmann and Reisner, 1943).

It must be admitted that little real progress has yet been made with the analysis of the more common congenital abnormalities in man, such as anencephaly, spina bifida, some skeletal defects and Mongolism. Certain defects of the limbs, such as some forms of syndactyly, brachydactyly and polydactyly, some forms of hare-lip and cleft palate, and certain rare skin and nervous diseases are recognised as being determined, at least principally, by genetic factors. On the other hand Gruneberg (1943, 1944) has been able to study a wide range of comparable abnormalities in laboratory rodents, chiefly mice, and by selective breeding he has shown beyond doubt that many are genetic and often determined by simple recessive genes.

For the relative failure of genetic methods in the study of congenital abnormalities of man a number of causes must be considered. Some of these are common to any study of human genetics, such as the uncertainty as to whether the results produced by homozygous and heterozygous dominant genes are necessarily comparable. There is also uncertainty as to the relationship of certain abnormalities to one another. Not infrequently abnormalities are multiple and embryology does not yet enable us to refer them to a single developmental error, or to decide if they are necessarily related. Conditions such as anencephaly and various forms of spina bifida may be due to variations in the expression of a common defect. Again certain apparently similar end results may not be produced in the same way and may thus be fundamentally different. Surveys are also greatly hampered by the early death of many affected individuals, and by the extremely vague information which is usually available at the time of enquiry. A very serious source of difficulty is the probable loss of many of the affected individuals without any possible record by abortion and early miscarriage. The observations of Mall (1917) would suggest that many monsters fail to develop. He found that for each case appearing at term twelve others died and were aborted. Schultze (1940) believed that about one abortion occurred for every six live births, and that one abortion due to germ plasm defect might be expected for every thirteen live births. These monsters may not

all be identical ætiologically with those which survive to later in pregnancy, but the subject has been little studied and the position is very unsatisfactory. This problem of early intra-uterine death is a very pressing one and some geneticists (Penrose, 1932) have made assumptions which are in urgent need of proof, if they are to be applied to this field.

The construction of family trees is obviously useless in these cases. It might be thought that the brothers and sisters of the affected individuals would provide some information. These siblings are undoubtedly much more likely to be affected than non-related children. Macklin (1936) reviewed 1,420 cases from the literature and 311 of these were in families where more than one child was affected. In these affected siblings the defect was identical in 80 per cent. of cases. Murphy (1940) found the rate in families already having one defective child was approximately twenty-four times greater than in the general population, and that in about half of these cases the defects were identical in the siblings. Malpas found only twelve recurrences in 863 fraternities where one child was affected. He pointed out that recurrence only indicated that the maternal factors which determined malformations persisted, or recurred, in successive pregnancies, although it certainly showed that they were profound and permanent and far removed from the category of casual influences. On this view cyclic fluctuations in the conditions responsible in the maternal environment must occur, because normal children are often born between children with identical defects. It may well be urged that this requires an impossibly complex conception of these maternal or environmental factors.

There are a few observations on the occurrence of abnormalities and their duplication in near relatives (Murphy, 1940). The incidence recorded was three times as high on the maternal as on the paternal side, and this is not consistent with modern theories of inheritance. However, the information was obtained by home visiting and a questionnaire and was very probably incomplete. Important evidence pointing to inheritance of recessive traits is often afforded by an excess of cousin marriages among the parents. About 0.6 to 0.8 marriages are between cousins. However, unless a trait is much rarer than 1 in 3,000, a very large number of cases will have to be studied before any evidence can be provided in this way. When a trait is inherited by dominant or intermediate transmission, but only sometimes expressed, the frequency of expression remains constant when different generations are compared. It is evident that much larger samples must be accurately collected and correlated before either of these methods can be expected to yield results in the study of the inheritance of congenital defects.

A paramount difficulty when abnormal offspring are produced by normal parents, and do not themselves reproduce, is the impossibility of establishing a correlation between the defects of one generation and the next. It is here that the modern techniques of linkage study, especially those which may be applied to a single generation, such as the method described by Penrose (1935), will prove of value. It is necessary, however, first to determine a large number of readily detectable and particulate hereditary characters, preferably, at least one represented by a gene carried on each chromosome. It is here that the modern work on the genetics

of the blood groups is of the very greatest importance. Work on the identification and correlation of a multitude of normal hereditary characteristics is the first necessity. Afterwards, the study of a very large number of families with affected siblings will be necessary. If any progress is to be made in this subject it is becoming apparent that the study of defective individuals will have to be made, not by an individual, or even in one medical centre, but on a nation wide scale.

Genetic Mutations.

Haldane (1935) showed that in order to maintain the proportion of hæmophiliacs approximately constant it was necessary that fresh genes capable of producing the condition should spontaneously appear to replace those lost by the failure of many of the sufferers to produce offspring. If this did not occur the present incidence would require that the whole male population of England suffered from hæmophilia at the time of the Norman Conquest. He calculated that one mutation in 50,000 X-chromosomes was required to balance the elimination of the hæmophiliac gene. The rare disease epiloia is inherited as an autosomal dominant, yet cases occur with normal parents. Gunther and Penrose (1935) produced evidence that a gene mutation is responsible for this, and that it occurs in between one in 60,000 and one in 120,000 of the population. The occurrence of such apparently spontaneous mutations in the chromosomal structure of normal germ cells might seem to provide an explanation for the occurrence of congenital abnormalities. There is considerable evidence from lower animals that these figures for mutation rates are relatively high. It would seem that mutations could, at most, explain only a rather small percentage of abnormalities. Similar, but usually favourable, mutations are the basis of organic evolution, and the modern Mendelian system of evolution, unlike the Darwinian, does not require a high mutation rate. It is possible that some abnormalities appear as the result of gene mutations, and the loss of affected offspring without issue would require some such process, if the incidence of an abnormality is to remain constant. If abnormalities are determined by genetic factors any real change in their incidence carries with it important biological implications concerning the raw material of organic evolution.

The mutation rate can be greatly increased in an entirely non-selective manner by exposure to X-rays, radium, free electrons and neutrons. In mammals Bagg (1929) produced various deformities in mice by exposing the parents to X-rays. These malformations were transmitted to offspring for generations. It is, however, doubtful if defects are ever produced in this, or any comparable manner, in human beings.

Conclusions.

There seems little hope that the problem of the ætiology of congenital abnormalities will be solved within the near future. There is little evidence that changes in the maternal or intra-uterine environment, consistent with the maintenance of pregnancy, can have any specific effect. The evidence in favour of the importance of the environment is probably strongest when abnormalities, which may be explained as the result of incomplete twinning, are considered. There is satisfactory

evidence that many congenital abnormalities are due to the inheritance of hereditary taints carried on genes. Many other defects are probably also genetic in origin, but the evidence remains insufficient. The expression of these defects is perhaps modified sometimes by the intra-uterine environment, but it must be appreciated that very variable effects may be produced by an identical gene against the infinitely variable background of the different assortments of genes present in different individuals. Until large accumulations of data, accurately recorded at the time, and based upon very extensive analysis of the transmission of associated hereditary traits, are available little progress need be expected. Progress may also be delayed by lack of information concerning abortions and early miscarriages.

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Acute Monocytic Leukæmia

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Though in recent years there has been an increasing number of reports of cases of monocytic leukæmia, some doubt still exists about the actual mother cell of the circulating monocyte. Some authors seek its origin in the bone marrow; others in the littoral cells of the sinusoids of the spleen or lymph nodes, whilst for still others it arises from the reticulum cells of the medulla of the lymphoid tissue. As regards this problem the following case exhibits certain features which appear worthy of report.

Clinical History.

The patient, a young unmarried woman of twenty years, was admitted to the Royal Victoria Hospital on 16.10.43.

Apart from the usual childhood exanthemata and an occasional attack of bronchitis in her adolescence, the patient's medical history was irrelevant.

For the previous two months she had suffered from recurrent attacks of sore throat. Her general health had deteriorated, and at the time of admission her appetite and sleep were poor.

On admission the patient was seen to be a well-built girl. Apart from some pallor she did not appear very ill. The lymph nodes along the anterior border of the right sterno-mastoid muscle formed a prominent swelling extending upwards to the mandible, forwards to the submental region and backwards to the left submandibular region. Enlarged lymph nodes were also palpable in both axillæ and groins.

The spleen was palpable and liver dullness was increased, though the liver was not felt.

The heart was slightly enlarged and a mitral systolic murmur was present. The pulse rate was 112, and the temperature normal. The tongue was coated with a thick fur and the tonsils greatly enlarged and injected. This injection extended to the epiglottis and laryngeal mucosa.

The patient's temperature rose to 101°F. on the third day after admission and continued to swing until her death ten days later, the total duration of her illness being less than three months.

On the day after admission investigation of the blood picture showed a marked degree of anæmia with a colour index of 0.7. The white cell count was but little elevated, but the differential count revealed an almost complete agranulocytosis. The most striking feature, however, was the high percentage of somewhat peculiar mononuclear cells. Only an occasional cell conformed to the usual appearance of the monocyte of the circulating blood. The majority were larger, varying from 20-35 microns in diameter. Many were round or polygonal. Others showed long tails of cytoplasm, often three to four times as long as the diameter of the rounded forms. In others the cell margin was rendered indistinct by the occurrence of a fringe of small protoplasmic pseudopodia. The cytoplasm contained numerous

azurophilic granules, quite definitely coarser than those seen in the normal monocyte. These granules were grouped in greatest density around the nucleus, and were often absent in the pseudopodial projections. Auer's bodies were not observed. The nuclei were of varying shape: Some were ovoid, others kidney-shaped, whilst more rarely others were seen to have a lobed appearance. The nuclear chromatin had a sponge-like pattern without nucleoli.

TABLE I.

Date	R.B.C.	W.C.	P. %	L. %	E. %	M. %	Primitives %
17.10.43	2,320,000	13,400	1	23	0	55	22
18.10.43	2,000,000	11,875	1.5	11	0.5	72.5	14
21.10.43	1,625,000	20,000	2	14	0	72	14
25.10.43	1,475,000	26,700	1	21	1	62	15
27.10.43	—	45,865	—	—	—	—	—
28.10.43	—	63,650	1	14	0	70	15

These cells gave a negative peroxidase reaction. Differential cell counts on films stained by this method never gave more than three per cent. positively reacting cells, a figure which agreed with that obtained for the granulocytic series on films stained by Leishman's stain. Supra-vital stains demonstrated numerous neutral red granules, but these only rarely showed any tendency to be arranged in rosette form around the centrosome. Especially marked in the supra-vital preparations were numerous small intracytoplasmic vacuoles. These cells exhibited varying degrees of motility.

The appearance of the predominant cell in the blood films, therefore, corresponded closely to the descriptions of histiocytes given by Dameshek (1930), Clough (1932), Ford, Parsons and Butt (1933), and other authors.

Other mononuclear cells showed an even more primitive structure. Their cytoplasm was basophilic, contained no granules, and gave a negative peroxidase reaction. They possessed a rounded nucleus in which one or two small nucleoli were present. Hence they corresponded in structure to the "blast" type of cell. Whilst on morphological criteria alone it would be impossible to deny that they were myeloblasts, the absence of myelocytes and pre-myelocytes suggested that they might be the primitive forerunners of the histiocytic cells. Forms suggestive of transition from these primitive cells to the more mature granular histiocytes were occasionally seen.

Post-mortem.

The body appeared well developed. There was much swelling of the neck due to enlargement of lymph nodes, which, however, remained quite discrete. Areas of ulceration were present around the mouth and nostrils. Nodular elevations 0.5 cm. in diameter were noted in the skin, especially over the back.

The serous cavities showed no excess of fluid.

Heart.—Apart from pallor of the ventricular muscle and numerous small petechial hæmorrhages, no lesions were found.

Lungs.—There was gross enlargement of the lymph nodes at the hilum. On section, these presented a curious mottled appearance—dark red areas alternating

with fleshy pink areas. Few of these variations in colour were due to hæmorrhage. The alveolar tissue was œdematous.

Liver.—Weight 4¾ lb. The capsule was smooth and the underlying liver tissue had a mottled appearance. Numerous enlarged lymph nodes were present in the porta hepatis. On section, the viscus presented a most striking appearance. Around each portal tract and ramifying in this way throughout the liver substance was a thin white band of tissue. Around the larger tracts this measured more than 0.5 mm. in thickness.

Spleen.—Weight 12 oz. On section, the cut surface had a pink, fleshy appearance. The intimate structure of Malpighian bodies and trabeculæ was indistinct.

Pancreas.—Surrounding the head and body was a mass of lymph nodes, some of which measured 3-4 cm. in diameter. These formed a continuous chain with those at the hilum of the liver.

Kidneys.—These were enlarged. The capsule stripped easily, leaving a smooth but mottled surface, pale areas of ½ cm. in diameter being scattered diffusely. On section, the cortex was swollen. The cortical striæ were regular, but the general regularity was interrupted from place to place by whitish tissue.

Mesentery.—The whole mesentery was thickened and discoloured by the presence of very numerous enlarged dark-red lymph nodes.

Neck organs.—The lymphatic papillæ were prominent. The tonsils were enlarged, with superficial ulceration overlying yellow areas of necrosis. Ulcers were present on the thickened epiglottis. The cervical lymph nodes were similar to those seen in the thorax and abdomen. The thymus was enlarged and fleshy in consistence. It averaged over 1 cm. in thickness.

Bone marrow.—The vertebral marrow was a pale salmon-pink colour. The femoral marrow was hyperplastic but pale.

The adrenals, thyroid, stomach, intestines, bladder, and genital organs appeared quite normal.

Histology.

Heart.—There were many small areas of infiltration by leukæmic cells around the blood vessels and nerves in the epicardial fat and myocardium. Fatty change was present in the muscle fibres.

Lungs.—No leukæmic infiltrations were seen. In small groups of alveoli a fibrinous exudate was present, but this was almost completely acellular. Elsewhere the alveoli were distended with œdema fluid.

Liver.—There was a marked periportal infiltration by mononuclear cells. In frozen sections these cells gave a negative oxidase reaction, except for a very rare leucocyte. With Giemsa's stain they were seen to be granular with a morphology similar to those described on the blood films as monocytes or histiocytes. A few plasma cells were identified. Similar cells were scattered throughout the liver sinusoids and infiltrations were present around the hepatic veins. Mitotic figures were present in many of the infiltrating cells. The Kupffer cells were not prominent and the parenchymatous cells showed no lesions.

Spleen.—The whole architecture of the spleen was greatly disturbed by a dense

infiltration of mononuclear cells. The Malpighian bodies were small and without germinal centres. The littoral cells of the sinusoids were flat and showed no evidence of any excessive activity. As in the liver, the infiltrating cells were seen to be generally granular and negative to the oxidase reaction. Indeed, the scanty distribution of positively reacting cells was remarkable. The nuclei of the infiltrating cells were round, oval, or kidney-shaped with a fine vesicular chromatin network. Occasionally there were dense masses of chromatin at the intersections of the chromatin strands. Small groups of plasma cells were present. Some of these were binucleated. Occasionally vesicular nuclei similar to those seen in the monocytes were found in cells the cytoplasm of which stained red with pyronin. The trabeculæ and the subendothelial tissues of the veins were infiltrated. In the sections it was impossible to make any morphological distinction between the cells in the blood vessels and those infiltrating the tissues.

Pancreas.—The ducts, acinar and islet tissues showed no lesions. Around many of the blood vessels was a mantle of cellular infiltration. In a few areas this infiltration was more extensive and formed foci more than 1 mm. in diameter. Mitotic figures were not infrequent in these cell aggregates, which tended to spread in an invasive fashion into the adjacent adipose tissue.

Adrenals.—Foci of cellular infiltration were present in the zona glomerulosa, in the wall of the central vein, and around all the capsular blood vessels. From these perivascular foci the cells extended between the fat cells of the pericapsular tissue, producing a histological pattern more suggestive of sarcomatous than leukæmic infiltration.

Kidney.—Patchy diffuse cellular infiltration was present around the blood vessels and glomeruli. In some areas corresponding to the white areas noted at the post-mortem these infiltrations were extensive and often spread to the adjacent capsule.

Skin.—This showed cellular infiltration, especially marked around the vessels. Similar perivascular infiltrations were present in the somatic muscles.

Lymph nodes.—The architecture of these was completely destroyed, only the follicles being seen. Elsewhere the lymphoid tissue was replaced by a dense infiltration of large mononuclear cells with occasional plasma cells. Mitotic figures were not uncommon. Myeloid cells, as judged by the peroxidase reaction, were absent. The infiltrating cells were associated with an abundant reticulin. In many instances individual cells were in intimate relationship with this reticulin, but in other areas the reticulin strands surrounded an island of four or five cells. When the infiltrating cells extended, as they did frequently, to the adjacent fatty tissue they were seen to show the same pattern of relationship to the reticulin fibres. Studies of the reticulin in the spleen and liver gave similar results.

Tonsils.—These showed a histological picture similar to that seen in the lymph nodes. Plasma cells were more common. There were areas of necrosis extending deeply into the tissues from the surface, but around these practically no leucocytes of the polymorphonuclear type were demonstrated.

Thymus.—A few Hassall corpuscles surrounded by a little lymphoid tissue were seen. The great bulk of the thymic tissue was composed of masses of large mononuclear cells of the type already described. The impression was gained that

these cells were forming nodes of tissue, and the picture was that of a sarcomatous type of growth rather than of a diffuse infiltration of a pre-existing tissue. This resemblance to sarcoma was emphasised by the invasion of the mediastinal fat. Reticulin stains showed a pattern similar to that in the lymph nodes.

Marrow.—Smears and sections of rib, vertebræ, and femur were available. All showed a similar picture. Normal marrow was practically completely replaced by large mononuclear cells, the pattern of these often suggesting a syncytium. Stained by Giemsa, many of the cells were finely granular. On smears they were oxidase negative. Only a rare cell gave a positive reaction and belonged to the myeloid series. Red cell formation was greatly depleted. Reticulin stains gave the same pattern as was seen in the other organs and showed that reticulin was greatly in excess of that found in normal marrow.

Apart from small perivascular infiltrations, no lesions were noted in other tissues.

Anatomical Diagnosis.

Acute monocytic (histiocytic) leukæmia: agranulocytosis: infiltration of liver, spleen, kidney, thymus, lymph nodes and perivascular tissues generally: ulceration of tonsils, larynx, and epiglottis: œdema of lungs: terminal pneumonia.

Discussion.

This case conforms with the descriptions given by other authors of acute monocytic, acute histiocytic, or stem-cell leukæmia. The history of sore throat appears to have been due to the leukæmic infiltrations rather than to any preceding infection which might possibly be regarded as the trigger mechanism for the onset of the leukæmia. Indeed, in the reported cases infection of the mouth and throat has been the rule, and Forkner (1934) considers that the degree of involvement of these structures may be of use in the differential diagnosis of this type of leukæmia. Sternberg (1926) and Krahn (1926), however, consider such cases to be examples of an atypical response to infection, but this opinion is scarcely defensible in view of the widespread changes in the lymph nodes, liver, spleen, bone-marrow, and kidneys. Clough (1932) states that monocytic leukæmia should be characterised by (1) a pathological hyperplasia of the reticulo-endothelial system, from which it is believed the monocytes have their origin, (2) by the appearance of immature monocytes in the blood, and (3) by a relative, and usually absolute, increase in the number of monocytes. The case described fulfils all these requirements. It is true that the cell type is not the normal monocyte of the blood. It is larger: it contains more numerous azurophilic granules: it is oxidase negative: supra-vital stains reveal an absence of the rosette pattern of neutral red granules. Yet it is apparently more closely related to the monocytic series than to any other leucocyte. These variations from the normal monocytic characters have been recognised in other reported cases (Dameshek 1930, Clough 1932), and have led to their description as histiocytes or stem-cells. In general, cell types which appear to be transitional forms of the normal monocyte have been reported, and are present in this case. The degree of motility, of which there was both direct and indirect evidence from the blood films, was against these cells being of the myeloid series.

Perhaps the best evidence of the nature of the leukæmic cell is obtained from the study of the tissues at post-mortem. The actual morphological changes which may be deemed characteristic of monocytic leukæmia are as yet not clearly defined. Some authors have emphasised a proliferation of the littoral cells in the spleen, liver, and lymph nodes (Ewald 1923, Merklen and Wolf 1928, Schwirtschewskaja 1928, Bock and Wiede 1930) and interpret such changes as indicating an origin of the monocyte from these cells. In other cases (Clough 1932, Robb-Smith 1938, Campbell, Henderson and Croom 1936) the proliferation has been of the reticulum cells with or without any change in the littoral cells. In the present case no proliferation of littoral cells was seen, the splenic and lymphoid sinuses being compressed and lined by flattened, apparently inactive endothelium. On the other hand the reticulum cells showed a marked degree of proliferation with numerous mitotic figures.

The histological characters of this reticulum cell proliferation were suggestive of neoplasia. The cells tended to form nodules and to infiltrate adjacent fatty and connective tissues. Wherever they were present they formed a very intimate reticulin mesh. Such reticulin formation was usually peri-cellular, and on section of the lymph nodes or thymus it would be impossible to exclude a diagnosis of reticulo-sarcoma. This ability of the stem-cell of monocytic leukæmia to form reticulin appears to be a variable function. Campbell, Henderson and Croom found no reticulin formation in the cellular infiltrations, except possibly in the kidney. Clough mentions reticulin only in the cellular infiltrations of the intestine. Robb-Smith (1938) states that there is no increase in reticulin fibrils in this condition. In the majority of reported cases no studies on reticulin formation have been made. In what they interpreted as an aleukæmic monocytic leukæmia, Tschistowitsch and Bykowa (1928) did find a marked increase in reticulin with an intimate relationship to the infiltrating cells. Similar cases have been reported by Merklen and Wolf (1928). Whilst it is probable that such an aleukæmic state may exist its diagnosis is fraught with difficulty in view of the practically identical tissue changes in reticulo-sarcoma. The acute reticulosis of infants described by Oberling and Guerin (1934) shows much resemblance to such cases, but is not associated with reticulin formation.

It is therefore apparent that in proliferation of the medullary reticulum cells there is a variation in the power of the proliferating cells to form reticulin. In the present case the stem-cell of the leukæmia has apparently a twofold power of differentiation : (1) into a free motile histiocytic type of cell which appears in the circulating blood and which in turn may differentiate into a monocyte of the usual type, and (2) into a reticulin forming cell which appears to be a fixed tissue cell. In the tissues this results in appearances which are similar to those of a reticulum cell sarcoma, though the distribution of the infiltrations is leukæmic in type. To the blood it gives the appearance of a monocytic leukæmia. The possibility therefore seems to exist of gradations in the ability of the mother cell in the medulla of lymph nodes to form reticulin or freely circulating monocytes. In some cases only monocytes may be formed and there will occur tissue infiltration without reticulin formation. In others ability to differentiate either into free monocytes or

reticulin forming tissue cells will be manifested. Again, in others the production of a reticulin forming cellular tumour without changes in the circulating blood is conceivable. The twofold power of differentiation exhibited in the present case appears to suggest such a series of possibilities.

Many of the reported cases of monocytic leukæmia have shown varying numbers of myelocytes in the circulating blood and in the cellular infiltrations in the tissues. Such cases have raised important issues as regards the origin of the monocyte and its relationship to the granulocytic series of cells. Kracke in the discussion on the series of cases reported by Ford *et al.* (1933) suggests that there are two types of monocytic leukæmia—one in which there is a true reticulo-endotheliosis, a true monocytic leukæmia, and another which apparently has its origin in the marrow and which is more probably an acute myeloblastic leukæmia. The absence of myelocytes in the present case and the fact that only cells of the monocytic series are involved supports the idea of the origin of the monocyte from the reticulum cells, or rather their precursors in the medulla of the lymph nodes and also the existence of the monocytic series as a distinct entity, unrelated in their development to the granulocytes of the marrow.

Summary.

A case of monocytic leukæmia is reported. The cells infiltrating the tissues possessed the ability to form reticulin.

It is suggested that the stem-cell could evolve along one of two lines—either into a reticulum cell or into a free circulating monocyte.

I am indebted to Dr. Robert Marshall for the clinical notes and to Dr. Agatha Crawford for much help in the study of the blood films.

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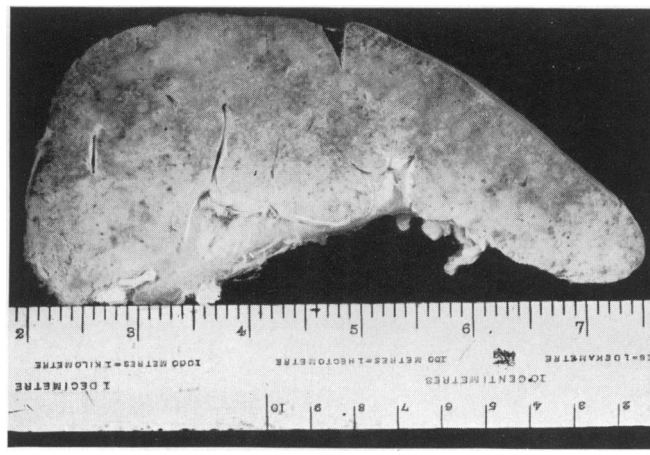

Plate I

Spleen. To show increase in size and general pallor.

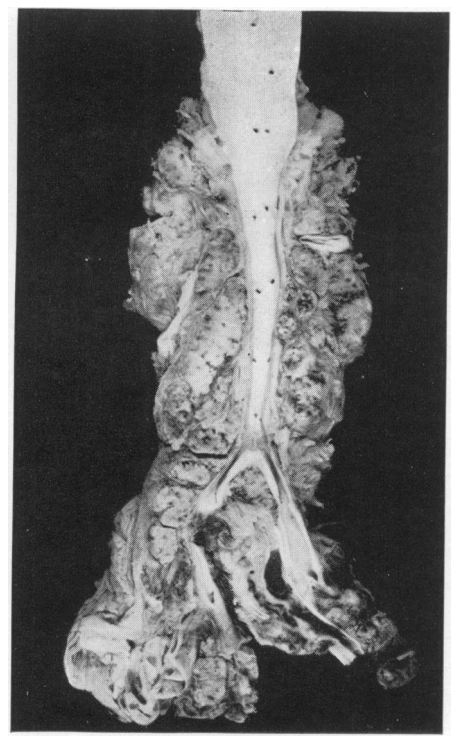

Plate II

To show the enlargement of the para-aortic lymph nodes.

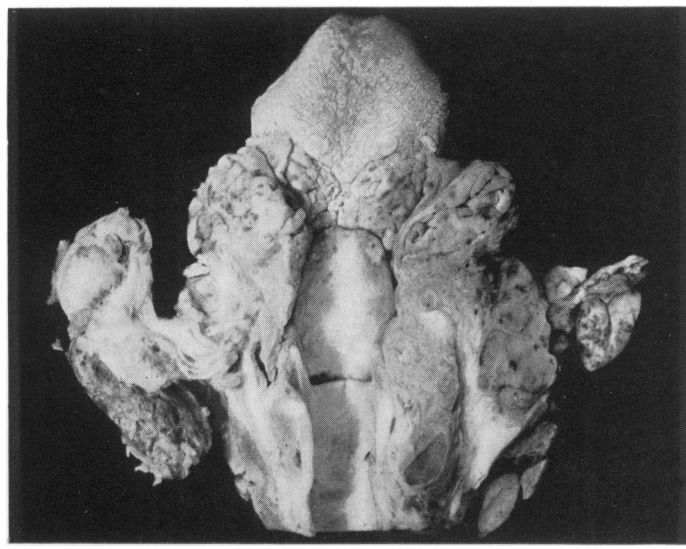

Plate III

To show the enlargement of the cervical lymph nodes, tonsils, and lymphoid tissues of the tongue. Patches of necrosis can be seen on the epiglottis.

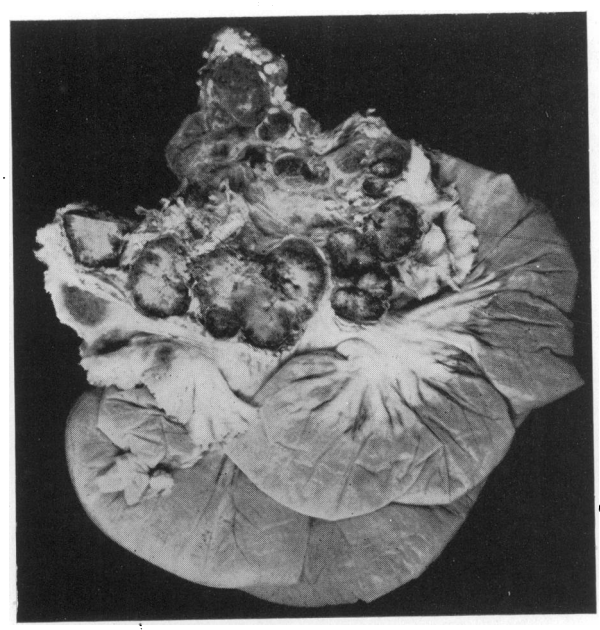

Plate IV

To show the enlargement of the mesenteric lymph nodes and their curious dark fleshy colour.

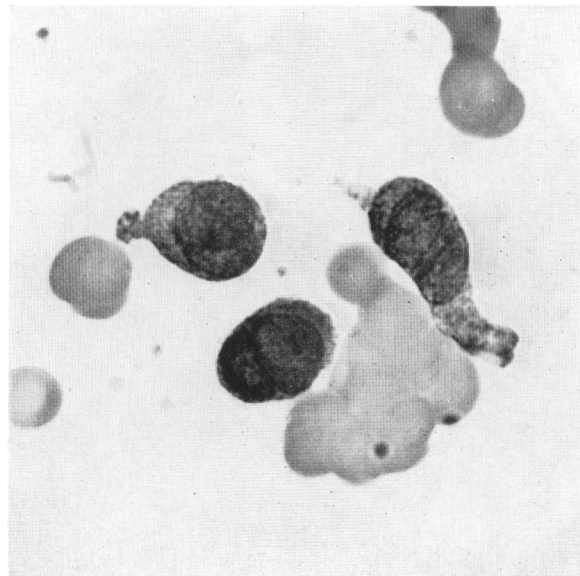

Plate V

Blood film. Three leukæmic cells showing the character of their nuclei, the granularity of their cytoplasm, and the pseudopodia. Leishman x 1200.

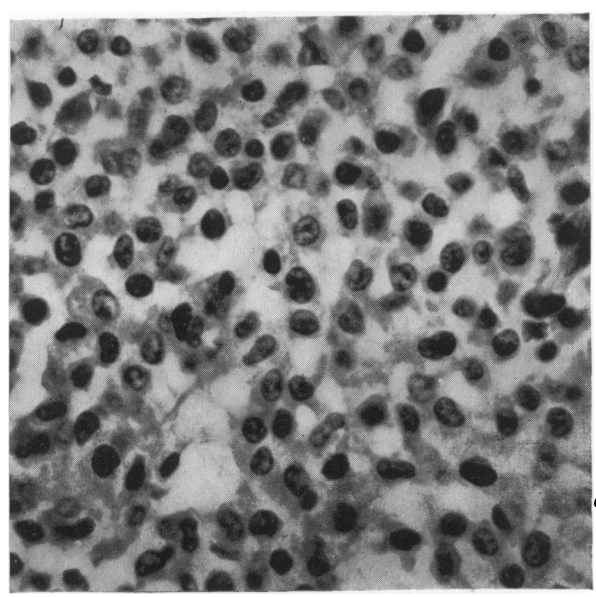

Plate VI

Section of femoral marrow showing the replacement of the normal myeloid tissue by primitive cells, which appear to be syncytical. H. & E. x 500.

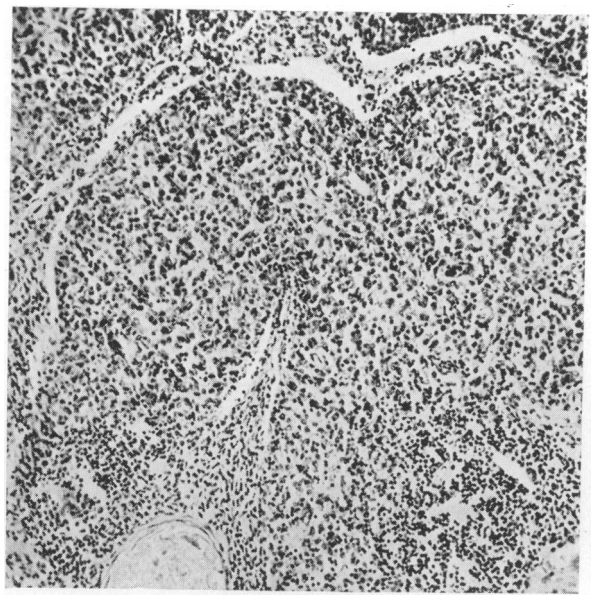

Plate VII

Section of thymus showing the invasion and replacement of lymphoid tissue by large mononuclear cells, which appear to form a tissue. H. & E. x 300.

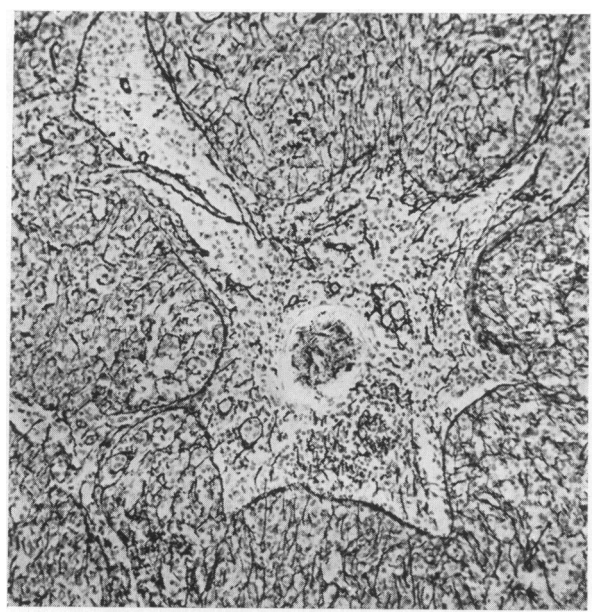

Plate VIII

Lymph node showing the formation of reticulin by the masses of leukæmic cells. H. & E. x 150.

A Study of Vitamin C Deficiency in Patients with Pulmonary Tuberculosis

By MARY ELIZABETH DUNN, M.D., D.P.H.

THE first experiments with regard to vitamin C and tuberculosis were carried out on guinea-pigs. As far back as 1924, Prausnitz and Schilf[1] showed that guinea-pigs with tuberculosis, if they were fed on a scurvy-producing diet, did not react to tuberculin in nearly as marked a degree as tuberculous guinea-pigs which were on a normal diet. The reactions caused by the tuberculin disappeared more quickly in scorbutic animals, and they had a less marked febrile reaction. Bieling[2] also found this true, but, nevertheless, discovered that when tuberculin was injected into guinea-pigs subcutaneously, those with scurvy died in greater numbers than those which had not scurvy.

In 1933 McConkey and Smith[3] fed 72 adult guinea-pigs on tuberculous sputum for periods from six weeks to four months. 37 animals were kept on a diet partially deficient in vitamin C. Of these, 26 developed ulcerative intestinal tuberculosis.

The other 35 animals were supplemented by an adequate amount of vitamin C, and of these only 2 developed tuberculous ulceration of the intestine. This seems to prove that in guinea-pigs vitamin C may have a protective power against infection with the tubercle bacillus.

Schröeder,[4] in 1935, investigated the requirement of vitamin C in 3 patients with tuberculosis, and reported that all needed more than the normal daily amount.

Next, Heise and Martin[5] studied the metabolism of vitamin C in tuberculosis in a series of 44 cases.

Of these cases, 6 patients, of whom 5 were active advanced cases, only excreted 0 to 5 mg. vitamin C daily. The next group of 14 cases excreted 5 to 8 mg. daily, and of these, 9 were active and 5 inactive. Seven active patients and 14 inactive comprised the third group, which excreted 8 to 14 mg., and the last group of 13 patients had 12 inactive and only 1 active. These patients excreted over 14 mg. daily.

Heise and Martin also showed that a group of 14 inactive tuberculous patients, when given 4 oz. orange juice (55 mg.) daily, excreted within two weeks at least 16 mg. vitamin C daily. On the other hand, a group of 10 cases, of which 8 were active, did not give a response when fed with the 4 oz. orange juice.

From these experiments Heise and Martin therefore concluded that although a normal person may only require from 15 to 20 mg. of vitamin C daily, tuberculous patients may require much more, and also that the excretion of vitamin C in the urine of tuberculous patients on the same diet, varies with the extent and activity of the disease.

These findings were substantiated by Abbasy, Harris and Ellman,[6] who made experiments on patients with pulmonary tuberculosis. These patients consisted of 19 active cases, 13 moderate, 6 quiescent, and 8 controls. All the patients were

standardised by being placed on a diet supplemented with orange juice (35 mg.) for four weeks.

They found that active cases excreted from 5 to 13 mg. per day, and quiescent from 18 to 28 mg. daily. The deficit in urinary excretion was parallel with the degree of severity of the tuberculous infection and of the sedimentation rate.

They concluded that in patients with pulmonary tuberculosis—

(1) The deficit in vitamin C is shown by low urinary excretion and diminished response to test doses.

(2) The daily excretion on a standardised diet falls to about one-third that of the controls.

(3) There is a good correlation between the severity of the cases as judged by the usual clinical standards (B.S.R., etc.), and the diminution in urine titre.

Previous to this, in 1936, Abbasy, Hill and Harris[7] had shown that in the case of 23 patients with active surgical tuberculosis, all had low rates of excretion of ascorbic acid (average 9 mg. daily); but 46 cases of quiescent surgical tuberculosis gave normal excretion of vitamin C. A group of 19 cases of "half-active" surgical tuberculosis gave intermediate readings.

The same year Green, Stein and Kramer,[8] working on guinea-pigs in America, seemed to get rather mixed results from their experiments. Their findings may be summarised thus—

(1) Chronic vitamin C deficiency plus progressive tuberculous infection causes shortening of survival period and decrease in body weight of guinea-pigs.

(2) Generalised tuberculosis develops more rapidly in chronic vitamin C deficient animals than in animals which are non-scorbutic, if the animals are infected with tuberculous sputum, either by the enteric route or by subcutaneous injection.

(3) Guinea-pigs maintained on a partially depleted vitamin C diet develop more lesions than do animals on a complete diet when fed with tubercle bacilli.

On the other hand, they found that—

(4) Animals infected with tuberculous sputum and allowed to develop acute scurvy, show no more tuberculous lesions than the control guinea-pigs.

Jetter and Bumbalo[9] showed that in Buffalo City Hospital children with tuberculosis all showed a vitamin C deficiency in their urine, although they were receiving 55 to 65 mg. daily.

Not only does the urine of tuberculous patients show a decrease of vitamin C, but the same has been shown of the blood plasma.

Getz and Koemer[10] have proved that ascorbic acid in the plasma is lowered with tuberculosis, and that it is lower in negroes than in white subjects, and also lower in males than females, while Pijoan and Sedlacek[11] report that 66 Navajo Indians with pulmonary tuberculosis all showed low ascorbic acid levels, although they had an average intake of 32 mg. vitamin C daily.

C. H. Behr,[12] Goggas and Scholz,[13] and Pilz, Heilstätte, Grafenhof[14] all have described a hypovitaminosis in patients with tuberculosis. Behr differs somewhat from the others in stating that it is only in cases of rapidly progressive tuberculosis

that there is a vitamin C deficiency. He also mentions that psychic disturbances cause an increased demand on vitamin C.

It is generally accepted, therefore, that people with tuberculosis show a deficiency of vitamin C both in the urinary excretion and in the blood plasma. The question then arises as to whether vitamin C has any therapeutic value in this disease.

German and American doctors have written in favour of using it as a therapeutic agent.

Hasselbach[15] [16] also confirms a vitamin C deficit in tuberculous patients, and says that clinically the administration of vitamin C causes a stimulation of the whole organism, an improvement in appetite, and an improvement of the general condition.

In a later work he claims good results by giving ascorbic acid in conjunction with gold therapy. He states that rashes and toxic effects, due to gold, can be dispersed by giving ascorbic acid.

Hasselbach treated 70 cases over a period of one year, and indicated three uses for vitamin C administration in tuberculosis—

(1) In special forms of hæmoptysis.

(2) As a general tonic: patients who had loss of appetite and were tired, improved on this treatment. As a special tonic to increase resistance. About 30 patients who had an unfavourable form of the disease were treated. All had vitamin C deficiency. Three cases who were positive became negative, but this group did not lead to any definite conclusions.

(3) Along with gold and tuberculin. Reduces toxic effects and rashes. Trautwein[17] also advocates the administration of vitamin C, especially along with adrenal hormone. He believes that many of the symptoms of acute infection are due to destruction of the adrenals, and points out that animals without adrenals show no resistance to diphtheria and tetanus toxins.

He claims that in experiments with adrenal hormones vitamin C always augmented the effect, and concludes that deficiency of vitamin C in acute and chronic infection affects the adrenals.

He states that in pulmonary tuberculosis various authors had found changes in the adrenals—amyloid, lipoid, etc.

Trautwein states that Thaddea got favourable results in pulmonary tuberculosis with cortical hormone and vitamin C, and that the Americans, Thompson and Whitehead, also got good results. He himself treated 20 cases. Ten cases were given hormone alone and 10 cases hormone plus 200 to 300 mg. ascorbic acid intravenously. He got good results in both groups, but better in the group that had been given ascorbic acid.

When patients were given daily doses 10 to 15 mg. of synthetic hormone with 500 mg. ascorbic acid over a period of five to six weeks, he found they improved in temperature, B.S.R., blood picture, hæmoglobin, Arneth count, and sputum.

In America, work has been done by McConkey and Smith[18] about the effect of vitamin C in intestinal tuberculosis. They state that of 774 patients, 411 patients in moderate and advanced stages of pulmonary tuberculosis did not get any cod-liver oil or tomato juice, and 11 per cent. developed intestinal tuberculosis. The

remaining 363 patients with similar type of disease received cod-liver oil and tomato juice, and only 4, or 1 per cent., developed tuberculosis.

In a later work McConkey[19] claims that cod-liver oil and tomato juice help to prevent the development of laryngeal tuberculosis in patients with moderately and far advanced pulmonary tuberculosis.

He states that of 371 patients who received cod-liver oil and malt, only 1 per cent. developed laryngeal tuberculosis, while of 420 patients who received neither cod-liver oil nor tomato juice, 3.3 per cent. developed laryngeal trouble.

Heise, Martin and Schwartz[20] deal with blood sedimentation, tuberculin sensitivity, and vitamin C. They found that nearly 50 per cent. of their cases of pulmonary tuberculosis showed a lowering of sedimentation rates after intravenous injection of vitamin C, and that tuberculin sensitivity was altered in a similar manner.

They suggested this was because either (1) the adrenalin action was increased by vitamin C, thereby lessening hypersensitivity in general, or (2) that, due to a hypovitaminosis C, the blood capillaries had lost their resistance and become more porous to substances elaborated at the site of disease. Giving increased vitamin C corrected this, leading to a fall in sedimentation rate and skin sensitivity.

Erwin, Wright and Doherty,[21] on the other hand, could find no evidence of any therapeutic value for vitamin C.

They had 13 patients, either acute cases or "bad chronics," and judged their reaction to vitamin C therapy by the difference in fever, pulse, weight, sputum, B.S.R., and X-ray.

At the end of the experiment 1 showed improvement in the X-ray and 12 were worse; 4 showed improvement in B.S.R. and 8 were worse.

One patient, although saturated, had a fatal hæmoptysis, and another died from broncho-pneumonia following hæmorrhage.

They conclude, therefore, that vitamin C is of no value in the treatment of pulmonary tuberculosis or its complications and that saturation neither contributes to recovery nor retards retrogression.

The Titration Test for Vitamin C in Urine.

In 1935 Abbasy, Harris, Ray and Marrack,[22] using the property of lemon juice and the active fractions derived from it, to reduce phenolindophenol, evolved a test by which the amount of vitamin C in the urine can be estimated, and as it is a modification of this test that was used when doing the following work, it is being described here.

The urine is collected over twenty-four hours and is titrated against 2 : 6 dichlorophenol-indophenol. The urine is collected in three-hourly periods and titrated as soon as possible after collection. If this cannot be done, the urine should be collected in dark bottles, and to it should be added 1/10 vol. glacial acetic acid, as vitamin C is destroyed rapidly by light and in an alkaline medium in the presence of air.

The volume of urine is measured and 1 cc. is put into a test tube, and to this is

added 1 cc. of glacial acetic acid. This is titrated against 2 : 6 dichlorophenol-indophenol; 1 cc. of the dye being standardised to be equivalent to .1 mg. of ascorbic acid. The total amount of vitamin C in the specimen of urine is thus calculated.

Harris and his colleagues found that there was little variation in the amount of vitamin C excreted between individual subjects, and that the amount of vitamin C excreted varied with the intake of vitamin C in the diet.

In normal subjects of ten stone weight the addition to the diet of—

90 mg. vitamin C gave an excretion of 50 mg.
45 mg. vitamin C gave an excretion of 30 mg.
15 mg. vitamin C gave an excretion of 15 mg.

They also showed that if healthy subjects excreting a sufficient amount of vitamin C were given a single large dose, the excretion of vitamin C rose rapidly, reaching a maximum in three hours of about eight to ten times the normal, then rapidly falling, and within a day reaching a normal resting level.

If, however, the subject is deficient in vitamin C, several large doses may have to be given before there is any appreciable rise in the vitamin excretion in the urine. The number of days taken to reach this level of excretion is known as the time taken for "saturation," and varies with the amount of hypovitaminosis in the subject previous to the test.

Harris recommends test doses of 700 mg. per ten stone of body weight.

People who have a sufficient amount of vitamin C should reach saturation level on the first or second day of the test.

In 1937 Harris and Abbasy[23] published a modification of this test. Instead of the urine being collected over twenty-four hours, a specimen was collected at 9 a.m. and disregarded. A second specimen was collected at 12 noon and titrated. Harris has shown that these three-hour morning specimens represent with sufficient accuracy about $\frac{1}{8}$ total day excretion, and furnish a record of the "resting level." To test for saturation, the test dose of vitamin C is given at 10 a.m., a specimen of urine from 2 to 5 p.m. is collected, and the amount of vitamin C in it is estimated. The collection in the afternoon, after the test dose, is arranged to coincide with the period of maximum response.

This modified method was used in the following work, owing to the difficulty experienced in collecting and measuring twenty-four-hour specimens, especially at night.

Vitamin C Observations in Patients with Pulmonary Tuberculosis in Whiteabbey Sanatorium.

The following work was carried out on 104 patients in Whiteabbey Sanatorium to determine as far as possible—

(1) Whether the patients were excreting a normal amount of vitamin C in the urine.

(2) Whether the addition of extra amounts of vitamin C to the diets of these patients made any demonstrable improvement in their condition.

The patients were divided into two groups. One group consisting of 45 patients was given extra vitamin C, and the other 59 patients were not.

Both groups consisted of early, moderately extensive, and advanced cases, and were chosen so that the two groups contained, as far as possible, the same type of cases. These two groups were again divided into cases which were having active treatment and cases which were having rest treatment only.

There were, therefore, four groups of patients—

(1) 13 patients who were having some form of active treatment, e.g., artificial pneumothorax or phrenic evulsion or crush plus extra vitamin C daily.

(2) 33 patients who were having active treatment but no extra vitamin C.

(3) 32 patients who were having extra vitamin C but no active treatment; and

(4) 26 patients who were having no active treatment and no extra vitamin C.

Ten probationer nurses of the Sanatorium, who were having practically the same diet as the patients, were used as controls.

First, the amount of vitamin C in the Sanatorium diet was estimated. This was done in the following manner :—

The food was collected from the dinner of the patients exactly as they received it. The amount of the dinner was found in mgs. A small specimen of the food was taken, e.g. potato. This was weighed, then put into a glass container, and covered with 5 per cent. sulphuric acid to extract the vitamin C. This specimen was allowed to stand for one hour. It was then made up to 100 c.c. with 5 per cent. sulphuric acid and 2 per cent. metaphosphoric acid, put into a dish and ground finely with quartz sand. This was then put into a centrifuge for fifteen minutes. The supernatant fluid was filtered through fairly coarse filter paper. Two test tubes were taken, and into each was put 1 c.c. of the filtrate. One was titrated with dichlorophenol-indophenol until it turned a faint pink colour, the colour not fading for at least thirty seconds. The second tube was now titrated, using the first tube as a control, and the average of the two readings was taken. From this was estimated the amount of vitamin C in the 100 c.c. of the specimen, and knowing the weight of the specimen, and the weight of an average dinner, it was simple to calculate the amount of vitamin C in a sanatorium dinner. As this was the meal at which almost all the vitamin C was received, it gave a reasonably accurate account of vitamin C these patients were receiving daily. It was found that the vitamin C intake was chiefly from potatoes and cooked green vegetables, with the addition of a small amount of fruit and fresh green vegetables during the summer months. The amount of vitamin C received daily was calculated to be from 15 to 20 mg. in winter and about 20 to 25 mg. in summer. This is somewhat below the standard set by the League of Nations as a minimum amount.

Next, the urinary excretions of the patients were determined, using the method described by Harris in 1937, which has been previously described.

The urines of the patients were tested on three consecutive mornings, and the amounts of vitamin C excreted daily were estimated. The patients were then given test doses of 700 mg. per 10 stone body weight, and these doses were repeated daily until the patients were saturated and were excreting at least 80 per cent. of

the test dose. The vitamin C used was in the form of "Celin" tablets and was given orally.

Next, the patients, who were chosen to have the extra vitamin C in addition to their diet, were put on daily doses of 50 to 100 mg. and the urinary excretion per day, and the "saturation" time were estimated every month for periods varying from three to nine months.

The other group of patients was not given any extra vitamin C, but a vitamin excretion test was done monthly.

The results are summarised in Tables A and B.

Discussion on Results of Treatment.

It will be seen that all the patients had some degree of vitamin C deficiency, but that this deficiency varied to a considerable extent. Early cases and less active moderately advanced cases had a higher excretion of vitamin C than the more active moderately advanced cases, and the advanced cases.

As the most advanced cases were in groups 3 and 4, i.e., the two groups which were not suitable for any form of active treatment, it was in those two groups that the lowest excretion of vitamin C was found. These two groups also had the cases with the highest sedimentation rates, and so it was found that the cases with the highest B.S.R. had also the lowest vitamin C excretion. This corresponds to the results obtained by Harris, Hasselbach, and others.

It was observed that very few patients, even in advanced cases, had a persistent temperature. Anyone admitted with a slight degree of temperature settled with a very short stay in bed, and it was only in those cases that were so advanced as to make any form of treatment hopeless, that a persistent temperature was noted. These extremely advanced cases were not included in the series of experiments.

With regard to the control group consisting of ten nurses, it was found that these showed a slight hypovitamosis C, but in a lesser degree than that shown by the patients. The nurses seemed perfectly healthy, and there was not any evidence of undue fatigue. This would agree with Fox, who found that miners could work satisfactorily on an amount of vitamin C below that considered a normal minimal amount.

It is interesting to observe that these control figures differ little from some of the figures obtained in patients with early or inactive lesions. This was also observed by Harris.

The results obtained will now be discussed in detail.

Group 1.—Of the 13 cases in this group, all were on active treatment. One was an early case, 9 moderately extensive, and 3 fairly advanced cases. The early case excreted 15 mg. vitamin C daily, while the moderate cases excreted from 11 to 14 mg., three of the more advanced cases only excreted 10 mg. daily. The average time for saturation in this group was four days. Ten of the cases were put on 50 mg. vitamin C (1 Celin tablet) daily, while the three who only excreted 10 mg. were put on 100 mg. daily. The duration of treatment varied from two to eight months (average six months). At the end of this period it was found that the

TABLE A.

	Amount Vitamin C Excreted in 24 hours before treatment.	Saturation Time	Amount of Extra Vitamin C given daily	Amount Vitamin C Excreted in 24 hours after treatment	Saturation Time
GROUP 1 Active Treatment + Vitamin C	10—15 mg.	4 days	50—100 mg.	20—30 mg.	1—2 days
GROUP 2 Active Treatment	10—15 mg.	4—5 days	—	10—15 mg.	4—5 days
GROUP 3 Rest Treatment + Vitamin C	9—16 mg.	3—6 days	50—100 mg.	20—40 mg.	1—2 days
GROUP 4	9—15 mg.	3—6 days	—	10—15 mg.	3—6 days
CONTROL GROUP	13—15 mg.	2—4 days	—	—	—

TABLE B.—RESULTS AT END OF TREATMENT.

	Weight		Sedimentation Rate			Sputum		X-Ray Findings		
	Gain	Loss	Imp.	I.S.Q.	Worse	Positive to Negative	Still Positive	Imp.	I.S.Q.	Worse
Group 1 13 Cases	12= 92%	1=8%	12= 92%	—	8%	10 Positive		8= 61.5%	2= 15.3%	3= 23.7%
						6= 60%	4= 40%			
Group 2 33 Cases	29= 87.8%	4= 12.2%	30= 90.9%	2=6%	1=3%	32 Positive		28= 84.8%	2= 6.2%	3=9%
						25= 75.7%	7= 24.3%			
Group 3 32 Cases	30= 93.7%	2= 6.3%	23= 71.8%	5= 15.6%	4= 12.5%	21 Positive		19= 59.3%	12= 37.5%	1= 3.2%
						7= 33.3%	14= 66.6%			
Group 4 26 Cases	25= 96.1%	1= 3.9%	15= 57.6%	7= 26.9%	4= 15.5%	21 Positive		12= 46.2%	12= 46.2%	2= 7.6%
						4= 19%	17= 81%			

average excretion was from 20 to 30 mg. daily, and the average saturation time was one to two days, i.e., practically all the patients were passing an average amount of vitamin C in urine, and responded to a test dose of 700 mg. vitamin per 10 stone body weight in one to two days.

The three fairly advanced cases excreted 30, 25, 20 mg. respectively when on 100 mg. daily, and while one was saturated in one day, the other two required two days. This means that it took three times the normal amount of vitamin C required for a healthy subject to saturate these patients.

With regard to the clinical conditions of the patients in this group, the following results were observed :—

Out of 13 patients 12 (92 per cent.) gained weight and one lost; the average gain was $10\frac{3}{4}$ lb.

The B.S.R. showed that 12 (92 per cent.) were improved and 1 worse. The B.S.R. in this group before treatment ranged from .5 to 22 mm. in one hour (Cutler). Seven cases had a B.S.R. not over 10 mm., and the other 6 cases were above 10 mm. The average fall in B.S.R. was 5.7 mm.

Only one of the patients had a rise in temperature, 99° to 101° at beginning of treatment, and this had fallen to normal before the end of the period.

Six cases (60 per cent.) who had positive sputum, became negative, 2 cases were always negative, 4 were still positive, and 1 positive on culture only.

The X-ray appearances of the patients' chests were used as the principal indication as to whether a patient had improved or not. It was found that 8 cases (61.5 per cent.) were definitely improved, 2 cases showed no improvement, and 3 were worse.

Two patients developed a pleural effusion after a pneumonolysis, and one patient later developed an empyema, although he was having 100 mg. vitamin C daily in addition to his diet.

One patient, while on treatment for his right lung, developed a cavity in his left. He had been having 50 mg. vitamin C daily for seven months.

The Second Group of cases consisted of 33 patients who had lesions similar to those of the patients in the first group. All these patients had an artificial pneumothorax performed and, in addition, 3 of the patients had interruption of the phrenic nerve. Of these 33 cases, 3 were early, 23 had moderately severe lesions, and 7 had fairly advanced lesions.

The amount of vitamin C excreted daily in the urine of these patients was estimated, and also the time taken for saturation; but these patients were not given any vitamin C apart from that which they received in their diet. At the end of the period of treatment the daily excretion of vitamin C and the saturation time were estimated again.

The findings in this group were very similar to those of the first group of patients. All showed some degree of hypovitaminosis C, and the amount excreted daily varied from 10 to 15 mg.

The amounts excreted by the early and less active moderate cases were from

12 to 15 mg. daily, slightly higher than those of the advanced and more active moderate cases, which varied from 10 to 12 mg.

When the vitamin C excretion was calculated at the end of the period of treatment, it was found that some of the patients were excreting a slightly higher amount in the twenty-four hours. These were mainly patients who, at the beginning of treatment, had shown a high sedimentation rate and often a positive sputum, but whose sedimentation rate had now improved, and in some cases the sputum had become negative.

One patient, who had a B.S.R. of 25 at the beginning of treatment and was excreting 10 mg. vitamin C daily with five days for saturation, at the end had a B.S.R. of 9 and was excreting 15 mg. daily with a saturation time of three days. This patient's sputum had also changed from positive to negative. Several other patients showed similar small improvement. It will be noted, however, that none of these patients was excreting a normal amount of vitamin C in the urine, and this may be understood, when it is remembered that they were receiving only the vitamin C furnished in their diet, which did not exceed 25 mg. daily. It seems reasonable, therefore, to conclude that the improvement in daily excretion and saturation time was due to improved conditions of their health, and a lessening of the activity of their lung condition.

With regard to the clinical condition of these patients, it can be seen that a large number showed a definite improvement after treatment.

Of the 3 early cases, all showed improvement, and of the moderate cases, 19 out of 23 were improved. Six out of the 7 fairly advanced cases were improved. The improvement was again gauged by the change in B.S.R., sputum, gain in weight, and X-ray appearance.

When the weights were examined after treatment, it was seen that out of 33 cases 29, or 87.8 per cent., had gained weight, and only 4 had lost. The average gain was $11\frac{3}{4}$ lb.

The B.S.R. before treatment was similar to those of the patients in the first group of cases, and varied from 30 to .5 mm. in one hour (Cutler). At the end of the treatment 30 patients, or 90.9 per cent., showed a decrease in the B.S.R., 1 patient showed an increase, and 2 patients showed no change.

The average decrease in the sedimentation rate was 8.7 mm. in one hour.

Thirty-two patients had a positive sputum before treatment and 25, or 75.7 per cent., became negative, while 7 cases still remained positive. One case had always been negative.

Only two cases had shown a rise of temperature at the commencement of treatment, and both of these had been afebrile within a short time of treatment having been begun. On the other hand, 3 patients who had been afebrile at the beginning later became worse, and had temperatures ranging from 99° to 101°.

The X-ray appearance of the lungs of these patients was again used as the principal evidence of progress. It was found that of the 33 cases, 28 cases, or 84.8 per cent., had definitely improved, 2 cases showed no apparent change, while 3 cases, or 9 per cent., had become worse.

One of these cases had a pneumothorax commenced and was waiting for a thoracoscopy, when he developed a temperature of 100° to 101°, headaches, rigidity of neck, and the obvious signs of a meningitis. A lumbar puncture showed that the fluid was clear, under pressure, and there were increased protein and cells, and diminished sugar and chlorides. Tubercle bacilli were found on culture. The patient died in about three weeks, and a post-mortem showed not only a lesion of lung, but a healed lesion in one kidney and an active lesion in testis and prostate, although there had been no symptoms to suggest this.

A second case was a patient who had a pneumothorax and internal pneumolysis, which gave a satisfactory hilar collapse. She suddenly took a severe pain in this side and her temperature rose to 101°.

Screening ruled out a spontaneous pneumothorax, but the patient became cyanotic, dyspnœic, and died three days later. A post-mortem was not available, but it is thought that the patient probably developed an acute tuberculous broncho-pneumonia.

Out of the 33 patients only 1 developed an effusion after the pneumothorax was induced. The same patient also developed a rectal abscess, and his condition deteriorated.

Another patient had a successful collapse of one lung, but still kept a high sedimentation rate and a positive sputum, and after about three months an X-ray showed a small cavity in the other lung, which had developed since his treatment had commenced.

In analysing the results in these two groups, it is rather difficult to determine if any of the improvement made was due to the extra vitamin C being added to the diet.

As the first group was much smaller than the second it is not very easy to make a comparison, but a few facts may be stated. With regard to the B.S.R., 91.5 per cent. in group 1 was improved as compared with 90.9 per cent. in group 2. This is not a very significant difference, especially as the average decrease in group 1 was only 5.7 mm., whereas that of group 2 was 8.7 mm.

Again, about 91.5 per cent. of the patients in group 1 showed an increase in weight, and only 87.8 per cent. in group 2, but the average gain in weight was only $10\frac{3}{4}$ lb. in group 1 and was $11\frac{1}{4}$ lb. in group 2.

Only 60 per cent. of the positive cases in group 1 became negative, and 75.7 per cent. in group 2 became negative.

On the whole, 61.5 per cent. of the cases in the first group were definitely improved and 84.8 per cent. in the second group.

It cannot be shown that the patients who were receiving extra vitamin C were any less liable to develop complications following active treatment, as one patient developed an empyema and two others got pleural effusions.

One cannot say, therefore, that the patients who received the extra vitamin C in addition to the active treatment showed any better progress than those who had the active treatment alone.

The next two groups of cases were composed entirely of patients who had no

form of active treatment, either because they were early cases which it was considered would clear up with rest alone, or because they were too far advanced for any active treatment. A few were cases on which an artificial pneumothorax had been attempted but which had not collapsed.

One group of 32 patients, in addition to the vitamin C in the diet, was given 50 to 100 mg. daily, while the other group of 26 cases was not given any extra vitamin C.

Both of these groups contained much more advanced cases than were to be found in the first two groups.

The first of these two groups consisted of 9 early cases, 14 moderately advanced cases, and 9 advanced cases.

The daily urinary excretion of vitamin C before treatment varied from 9 mg. to 15 mg. The early cases excreted from 12 mg. to 16 mg., the moderate cases from 11 to 14 mg., and the advanced cases excreted from 9 to 12 mg., with an average of 10 mg.

The early cases took an average of three days for saturation, the moderate took four to five days, and the advanced five to six days.

These cases were then put on 50 to 100 mg. vitamin C daily according to the amount they were excreting. At the end of the period of treatment the early cases were excreting from 25 to 40 mg. daily, the average being 30 mg.; the moderate cases were excreting from 20 to 35 mg., the average being about 25 mg.; and the advanced cases were excreting from 20 to 30 mg. daily, with an average of 25 mg. The advanced cases, however, had practically all got 100 mg. daily, while the early and most of the moderate had only been having 50 mg. After treatment all the cases were saturated in one to two days.

The clinical improvement in this group was not so marked as in groups 1 and 2, as it had more advanced cases, and was depending on rest only.

All the 9 early cases improved, 9 out of 14 of the moderately advanced cases improved, and 2 out of the 9 advanced cases. Eleven cases showed no improvement, and 1 case was worse.

With regard to weight, 30 out of the 32 cases, i.e., 93.7 per cent., all showed a gain in weight. The average gain was 12¾ lb.

This group showed rather a higher gain in weight than the first two groups, and it was noticed that patients having rest treatment, and usually in bed all day, were inclined to gain more weight than those on active treatment.

The blood sedimentation rate of this group showed a decrease in 23 cases, i.e., 71.8 per cent. Five cases showed no change and 4 cases showed an increase. The average decrease was 4.4 mm. in one hour.

At the beginning of treatment 21 cases had a positive sputum, and 7 of these had become negative at the end of the period of treatment (33⅓ per cent.). Eleven cases had always been negative, and 14 cases (66⅔ per cent.) were still positive.

Only one patient had a slight rise in temperature, 99.6°, and soon became afebrile.

X-ray photographs at the end of treatment showed that 19 cases were definitely improved, 12 cases were unchanged, and 1 case had become worse.

One case was very interesting, as previous to admission to the Whiteabbey Sanatorium, this patient had been three months in a general hospital undergoing an operation for appendicitis. It was after the operation that the patient developed a cough, and an X-ray of his chest revealed extensive infiltration of the right lung. When admitted to the Sanatorium his appendicectomy wound had not healed. His sedimentation rate was 26 mm. and he had a positive sputum.

An attempt was made to induce an artificial pneumothorax, but this was unsuccessful. His daily excretion of vitamin C was only 9 mg. daily, and the saturation time was six days. He was put on 100 mg. vitamin C daily. In about three weeks his wound had healed, and at the end of nine months his sedimentation rate had fallen to 3.5 mm., his sputum, although positive, was now only positive on concentration, he had put on weight, and his X-ray showed that the infiltration in the right lung was much less marked.

Another patient who had infiltration of the right lung with cavitation and also infiltration of the upper half of the left lung, showed a marked improvement after three months rest in bed and 50 mg. of vitamin C daily. His blood sedimentation rate had fallen from 21 to 1 mm., he had gained almost 2 stones in weight, his sputum had become negative, and his X-ray showed great improvement.

The other extensive cases did not show any marked improvement.

The FOURTH GROUP of cases contained patients with lesions similar to those in group 3. There were 26 cases, consisting of 6 early cases, 10 moderately advanced cases, and 10 advanced cases.

When the urines of these patients were tested, it was found that the daily excretions of vitamin C were similar to those in the third group.

The early cases excreted from 12 to 15 mg. daily, and were saturated in three to four days. The moderately advanced cases excreted from 10 to 12 mg., and the advanced cases from 9 to 11 mg. daily and took from five to six days for saturation. The exception was one advanced case who excreted 18 mg. daily, and no proof could be found of his taking more vitamin C than that supplied by the Sanatorium diet.

This group of patients was not given any extra vitamin C, and was on rest treatment only.

At the end of the period of treatment the excretion of vitamin C in the urine in twenty-four hours did not differ much from that before treatment, although a few showed a slight improvement. One early case, which at the beginning of treatment had been excreting 12 mg. daily and taking five days for saturation, was excreting 18 mg. at the end of treatment, and was saturated in three days. Another early case increased the daily excretion from 14 mg. to 16 mg. and took one day less for saturation. One patient who had an extensive lesion and was much improved at the end of treatment, also showed a rise in the daily excretion of vitamin C. At the beginning the amount excreted was only 9 mg. and the saturation time was

six days; while at the end of treatment it had risen to 12 mg. and the saturation time fallen to four days.

In this case the sedimentation rate had fallen from 20 mm. to 6 mm. in one hour.

In another case where the sedimentation rate had fallen from 22.5 mm. to 9 mm., there was a rise of daily excretion from 10 mg. to 14 mg., and a fall in saturation time from five days to three days. The remainder of the patients showed little change.

As in the previous three groups, all the early cases in this group were improved at the end of treatment. There were six of these cases.

Of the 10 moderately advanced cases 5 (50 per cent.) showed improvement, 4 (40 per cent.) were unchanged, and 1 (10 per cent.) was worse.

There were 10 advanced cases, and 2 (20 per cent.) improved, 7 (70 per cent.) were unchanged, and 1 (10 per cent.) was worse.

As was shown in the third group, a number of patients gained weight, although they showed no other improvement. Altogether, in this group, 25 cases (96.1 per cent.) showed a gain in weight. The average gain was $10\frac{3}{4}$ lb. Only one patient lost weight.

Fifteen patients (57.6 per cent.) showed a decrease in the blood sedimentation rate, 7 cases were unchanged, and 4 showed an increased rate. The average decrease was 3.6 mm. in one hour.

At the beginning of the treatment there were in this group 21 patients who had positive sputum, and 4 of these became negative (19 per cent.), while 17, or 81 per cent. were still positive. Five cases were always negative or had no sputum.

With regard to temperature, 3 patients who were febrile at the commencement of treatment became afebrile.

X-ray photographs showed that 12 cases were undoubtedly improved, 12 were practically unchanged, and 2 were worse.

There are no cases of outstanding interest in this group. One patient was admitted to hospital in a very advanced stage of pulmonary tuberculosis. His temperature was usually about 101°, he was dyspnœic, and was not expected to live more than a week. However, he improved and his temperature became normal, while his sedimentation rate fell to 17.5 mm. from 23 mm.

Unfortunately, after four months in bed he decided he was cured, and left hospital against medical advice, only to return in a few months very much worse, and this time he did die.

When the four groups of cases are considered together the following results may be seen. The patients in the second group showed more improvement than those in any of the other groups. As the first group is so much smaller than the second the comparison is difficult, but there is no evidence whatever to show that giving extra vitamin C to patients with active treatment made any improvement in their condition, nor did it help to prevent complications, e.g., pleural effusion or empyema.

It can be said that the patients on active treatment improved more than those with rest only, and a greater number became negative, e.g., 60 per cent. in group 1 and 75.7 per cent. in group 2, as compared with 33.3 per cent. in group 3 and 19 per cent. in group 4.

The sedimentation rates also showed a marked difference: 91.5 per cent. in group 1 and 90.9 per cent. in group 2 being improved, and only 71.5 per cent. in group 3 and 57.6 per cent. in group 4, and the average decreases in the first two groups were 5.7 mm. and 8.7 mm., while in the second two groups it was 4.4 mm. and 3.6 mm.

Patients on active treatment, however, did not gain more weight than those on rest treatment only, in fact the opposite was found, for whereas 91.5 per cent. in group 1 and 87.8 per cent. in group 2 showed gain in weight, 93.7 per cent. in group 3 and 96.1 per cent. in group 4 showed gains.

The average gain in the third group of patients was greater than that of either of the groups which had active treatment.

When comparing the first two groups of cases with the second two groups, it must be remembered that neither of the first two groups had such advanced cases as those found in the second two groups.

When the second two groups of cases were compared, it was found that patients which received extra vitamin C showed 62.5 per cent. of improved cases, and in group 4, 50 per cent. of the cases showed improvement. Although a slightly higher percentage of cases in group 4 showed a gain in weight (96.1 per cent. in group 4 and 93.7 per cent. in group 3), the average gain in weight in the group receiving the extra vitamin C was two pounds heavier than in the other group.

71.5 per cent. of the cases in the group receiving vitamin C showed a decrease in sedimentation rate and 57.6 per cent. improved in the other group, the average decrease being 4 and 3.6 mm. respectively. Sputum results showed that 33.3 per cent. of group 3 had become negative as compared to 19 per cent. in group 4.

In the group of patients receiving both rest treatment and vitamin C, 62.5 per cent. were improved, and in the group which had been resting only, 50 per cent. were improved. The sputum results, 33.3 per cent. as compared to 19 per cent., showed the most difference, i.e., 14.3 per cent. Analysed statistically, the standard error is $\pm$ 12.4, so the difference becomes almost insignificant, and thus it cannot be said that there was any definite improvement with extra vitamin C treatment.

Out of the 104 cases studied, none developed any signs of laryngeal tuberculosis or gastro-intestinal tuberculosis, so that McConkey's statement that cases deficient in vitamin C were more liable to develop these complications was not verified.

No effect could be noted of vitamin C on the incidence of hæmoptysis, as a few patients in both groups had staining.

With regard to the control group of patients, it was shown that they excreted an amount of vitamin C similar to early and inactive cases.

Getz, Westfall and Henderson,[24] in a recent article, have shown that the plasma ascorbic acid in non-tuberculous people on a low vitamin C diet corresponds to patients on a similar diet who have "arrested" tuberculosis.

Conclusions.

(1) All the patients showed a hypovitaminosis C, which was more marked in active cases and in those with advanced lesions and high sedimentation rates. These patients required a greater amount of vitamin C than normal to attain saturation, often 100 mg. daily.

(2) Improvement in the patients and decrease in sedimentation rate often led to a higher vitamin C excretion and a lowering of the saturation time.

(3) Patients on active treatment showed better results and a greater average sedimentation rate decrease than those on rest treatment.

(4) No evidence could be seen that patients having extra vitamin C and active treatment did better than those having only active treatment, nor did vitamin C prevent complications during treatment.

(5) There was no conclusive proof that patients on rest treatment who had extra vitamin C did better than those who had rest treatment only.

(6) The control group showed an excretion of vitamin C similar to that of patients with early or arrested tuberculosis.

It can be said, therefore, that there was no definite evidence from these results that vitamin C had any specific therapeutic value in pulmonary tuberculosis, but that these cases certainly require a greater amount than healthy subjects to give a normal urinary excretion.

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Pink Disease*

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THE condition of pink disease is so named because of the characteristic colour of the hands and feet. There are other synonyms which more accurately describe particular aspects of the clinical syndrome, but the title of this contribution is the one in popular use.

The disease is a distinctive one of infants and young children which, when once seen, is easily recognised. It is first recorded in medical literature in 1903, although it may have existed previously. There have been subsequent descriptions of its appearance, particularly in Australia, North America, and various countries in Europe, and it was noted in the United Kingdom in 1921 and 1922. So far as I am aware, the first case observed here was in 1929.

Symptomatology: The clinical picture is usually introduced by an indeterminate febrile illness associated with nasal catarrh. Some time afterwards the infant is noted to be irritable and peevish and the mother experiences difficulty in persuading it to take its feeds and to sleep restfully. There is often some degree of photophobia, and this may be extreme with very marked intolerance of light and consequent increased irritability suggestive in many ways of meningitis.

A rash is often found about this time, erythematous in nature and suggestive of scarlet fever. In fact, older infants have sometimes been sent to fever hospitals with a diagnosis of this infectious disease.

The loss of sleep and refusal of food become more marked, and flabbiness of muscles is noted, this being accentuated during succeeding days and weeks; but there is usually no enlargement of the costo-chondral junctions nor of the epiphyses of long bones such as occurs in rickets.

The child sweats profusely, throws off the bed-clothes and buries its head in one corner of the cot. The skin is irritable and there is constant scratching, but relief is obtained by tepid, or even cold, baths and by gentle massage. Owing to the loss of sleep and lack of nourishment there is considerable decrease in weight, and this, together with the increasing flabbiness of muscles, suggests a mortal disease associated with increasing paralysis. This may be so extreme that the child is much wasted and is unable to sit up, to hold up its head, or even to keep its mouth closed.

When the disease has been in existence for some weeks (or possibly earlier in a few cases) the hands and feet periodically display the characteristic pink colour associated with extreme coldness, just as if they had been placed in very hot water. The appearance in some respects resembles chilblains, but there is a distinct difference in the coldness of the extremities in contrast with the glowing warmth

*Read in introducing a colour cine-film of Pink Disease, Ulster Medical Society, 30th Nov., 1944.

of the former. It has been noted in most cases that the tip of the nose is also pink in colour.

Some time after the pinkness and swelling of the extremities develop, it will be noted that the skin desquamates (again suggestive of scarlet fever) and that the child rubs its hands to overcome the irritation.

The knee-jerks are frequently absent, there is constantly an increased pulse-rate, acceleration to 140 being frequently noted, and the blood pressure is raised. In one case in which the blood calcium was estimated, it was found to be raised to 120 mgm. per cent. The cerebro-spinal fluid is usually normal, although there may be a small increase in the cells in the initial stages of the disease.

Prognosis is good as regards the disease itself, but a general mortality of about twenty per cent. is usual owing to complications, particularly those of gastro-enteritis, broncho-pneumonia, and, in a few cases, encephalitis. The danger of the complications is accentuated by the general debility and lack of vitality of the patient. The course is a prolonged one; the shortest case of which I have notes being four months and the longest almost eleven months.

Aetiology: The disease, as far as can be ascertained, is not one of deficiency of vitamins or foodstuffs. One characteristic is that it occurs in infants and children who are well cared for and who have been given an ample and varied diet. It is almost certainly due to an infection, the nature of which has not been discovered, but which is probably of a virus type affecting the trophic nerves. I was fortunate in one of my early cases to have under my care an intelligent child of seven years who described the sensation she experienced as that of waves of pins and needles in her limbs and trunk. This is an illuminating suggestion, as it readily explains the discomfort felt by the infant, its crying, general miserableness, and refusal of food, as presumably the mucous membrane of the mouth and tongue is also subject to this sensory disturbance.

That the disease is an infection is supported by the fact that one case in a village is almost always succeeded by two or three others. But that the infection is not of an extremely contagious nature is indicated by the absence of any widespread epidemics.

Pathology: In some of the fatal cases which have been examined histologically there has been found a diffuse infiltration with small round cells in the spinal cord, along with degeneration of the myelin sheaths of the peripheral nerves. There has also been found a cellular infiltration in the cerebral cortex, basal ganglia, brain stem and medulla. It is estimated that the condition mainly affects the trophic nerves and is in some ways analogous to the so-called toxic polyneuritis in which there is loss of motor power.

Diagnosis: To those who are familiar with the appearance of the infant the diagnosis is easy in the fully developed case; in the early stages other possibilities may be considered first, of which I have mentioned the initial rash being mistaken for scarlet fever. An error is commonly made in assuming that the condition is due to teething, to otitis media, to pyelo-nephritis or rickets, but confirmation of

the presence of any of these diseases is not found. Some months ago I suspected an infant to be developing pink disease, but learned afterwards that the suspicious syndrome disappeared with the passage of a large mass of doll's hair which the infant had swallowed over ten months previously. Other cases, especially those associated with much photophobia, are mistaken for meningitis; and in the later stages the peeling of the hands and feet causes scarlet fever again to be suspected.

Treatment: There is no known line of treatment which is effective in producing a cure. All possibilities of substitution therapy by foodstuffs and vitamins have been tried without success. It is true that the intense administration of the vitamin B complex, particularly of B_1, by intramuscular injection of vitamin B preparations, liver, etc., has, when given at a certain stage, accelerated the rate of recovery. But there is no evidence that the administration of these preparations in the early stage will arrest the development of the disease.

Apart from the use of vitamin B preparations once recovery seems to be initiated, attention must be directed towards alleviation of the infant's discomfort and misery. Sedatives are necessary to procure sleep, and no one sovereign remedy is suitable in all cases. Some infants respond readily to a simple bromide and chloral mixture, whereas others require almost adult doses of phenobarbitone or one of the newer barbiturate preparations. Frequent bathing (three or four per day) in tepid or cool water is appreciated, and serves to relieve cutaneous irritation. A garment of artificial silk, linen, or cotton should be worn next to the skin, as it is more comfortable than woollens. Wool should be worn outside to keep the child warm and thus enable bed-clothes to be dispensed with. The sides of the cot should be padded with pillows.

A suitable diet and the maintenance of nutrition are extremely difficult, as no one ingredient is acceptable in all cases. The mother should be given full freedom of choice in trying any food preparation which will be taken by the infant and which will sustain its life until natural recovery takes place.

One's sympathy is generously bestowed on the mothers whose infants are suffering from pink disease, as the nursing care is particularly arduous. The disease frequently undergoes a downhill course week after week for four or more months, and when hope is all but abandoned slight signs of recovery appear, temporarily at first, but more constantly after a week or so. Then it is noted that recovery is maintained and progress is steady with full restoration (in the absence of complications) in two to three months, on an average.

A SYNOPSIS OF FORENSIC MEDICINE AND TOXICOLOGY. By E. W. Caryl Thomas, M.D., B.Sc., D.P.H., Barrister-at-Law. Bristol: John Wright & Sons. Pp. 179. 10s.

HERE, with an admirable economy of space and of cost, are to be found the essential facts of medical jurisprudence. The format is that of Tidy's synopsis of medicine and Hey Groves, and the subjects dealt with lend themselves admirably to this method of presentation.

This is an excellent short textbook both for the student in his fourth year and the practitioner who encounters a medico-legal problem, and who requires rapidly to renew his slender acquaintance with the proper procedure.

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A Case of Congenital Cystic Disease of the Lung

By D. G. F. HARRIMAN, M.B., B.CH., Lieut. R.A.M.C.
from the Belfast Hospital for Sick Children

THIS case is reported because it is assumed to be an example of the uncommon condition of unilateral congenital cystic disease of the lung.

CASE HISTORY.

E. McK., 14 months old, female. Admitted 26/3/44. The child was sent in as a case of pneumonia not responding to sulphonamide therapy. The onset had been six days previously, with cough, anorexia, laboured breathing. She had vomited once.

PREVIOUS HISTORY.

Cough developed two days after birth, and the child had been "chesty" ever since. No cyanosis had been noted.

On examination, the child was of good nutrition and in obvious respiratory distress. The temperature was 100.2°F., and the pulse-rate 134. There was cyanosis of lips, ears, and fingers. The respiratory rate was sixty per minute, with marked indrawing of rib interspaces and "heaving" of the chest. The apex beat was situated half an inch from the midline in the fourth left interspace, and cardiac dullness extended three inches to the right of the middle line.

On the left side, expansion was diminished and percussion yielded wooden dullness over the entire lung. Bronchial breathing, diminished in intensity, along with scattered rales and fine crepitations, was present.

On the right side there were also a few scattered rales and crepitations, but normal breath-sounds and percussion note. There were no abnormal signs in the other body systems.

The picture seemed to be that of a broncho-pneumonia with a left-sided empyema, both contributing to the marked respiratory embarrassment. Accordingly, oxygen was administered, a course of sulphamezathine initiated, and aspiration of the chest tried. Tapping was completely unsuccessful, however; only a few drops of blood-stained fluid came out of the needle.

Radiological examination showed marked mediastinal shift to the right, with numerous fairly well-defined cavities of varying size occupying the left lung (pl. I). A barium swallow confirmed the mediastinal shift to the right (pl. II). A bronchogram was done with great caution under general anæsthesia (pl. III). The lipiodol outlined the trachea and its bifurcation, but failed to enter either lung, possibly owing to compression of the main bronchial tubes or to use of an insufficient quantity of oil (6 cc. used).

Other investigations, such as culture of stomach washings for B. tuberculosis, Mantoux 1.5000 and 1.1000, and urinological examination, were all negative.

Subsequent Course.

During the first forty-eight hours the child's condition became worse, and oxygen had to be given continuously. The temperature rose to 105°F. on the third day, although cyanosis was much less marked. From this point, however, clinical recovery was gradual and complete, the temperature and pulse reaching normal limits by the eleventh day. The chest signs at this stage presented no change beyond disappearance of all adventitious sounds, and the development of resonance over the upper left zone anteriorly. The remainder of the left lung was dull as before.

The child was discharged and re-examined at intervals. There has been no recurrence of cough or dyspnœa, and the general condition is good. A further X-ray on 24/7/44 showed that there had been some alteration in the radiological picture; the cystic area was only visible in the left upper zone, and fluid now seemed to be present in the mid- and lower zones, except for the costo-phrenic angle which remained clear (pl. IV).

Discussion.

This is thought to be a case of congenital cystic disease of the lung, discovered during a severe attack of bronch-pneumonia which almost proved fatal. The diagnosis rests on the history and on radiological examination. The presence of a congenital abnormality is suggested by a history of attacks of cough and dyspnœa dating from birth. Schenck has pointed out that congenital cystic disease may occur in various forms; there may be a solitary cyst or multiple cysts, and they may or may not have communication with a bronchus. If there is no communication, the cysts remain fiuid-containing only; but if they open into a bronchus they will also contain air. The contained fluid may be expectorated. If the opening is free, the cysts are termed non-expansile, but if the air entry is by a one-way valve mechanism in the same manner as a tension pneumothorax, they are expansile air cysts.

So, there may be :

Solitary fluid cyst	Multiple fluid cysts
Solitary non-expansile air cyst	Multiple non-expansile air cysts
Solitary expansile air cyst	Multiple expansile air cysts.

In the present case, the condition is apparently one of multiple non-expansile air cysts along with multiple fluid cysts in which the contents are gradually increasing in amount.

The possibility that the cysts may not have a developmental origin must be considered. The view that pulmonary cysts at birth may be acquired in at least some cases has been put forward by Schultz, who groups such cases into the atelectatic variety of fœtal bronchiectasis. The mechanism of cyst production would be atelectasis at birth with subsequent pull on the bronchial tree and the formation of bronchial cysts. As inflammatory changes are often present in the bronchi, that, by its weakening influence on the wall, would also be an etiological factor. However, as Schultz himself points out, pathological studies have shown

that there is often a very great overgrowth of smooth muscle in the wall of the cysts, so that the tissue almost has the appearance of a leiomyoma. This would tend to point to a developmental origin, and that cystic disease of the lung in the infant really is congenital.

It is of some interest to note that this case shows mediastinal shift to the right: in a series of eleven cases reviewed by Young and Oswald, all lungs showing marked mediastinal displacement (five cases) were cystic on the left side, as is this case.

Summary.

A case of congenital cystic disease of the lung is described. Emphasis is laid on the fact that diagnosis rests on radiological grounds aided by a careful history; and the ease with which the condition may be confused with inflammatory conditions, including empyema, before X-ray evidence is available. The possibility of the condition being acquired and not congenital is considered.

I wish to offer my most grateful thanks to Dr. F. M. B. Allen, Honorary Physician to the Belfast Hospital for Sick Children, who was in charge of this case, for his invaluable help and encouragement in the preparation of this report; and to my commanding officer, who has kindly given his permission for this case to be published.

References.

Schenk: "Congenital Cystic Disease of the Lung," *Arch. Int. Med.*, July, 1937.

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REVIEW

PRACTICAL ANÆSTHETICS. By Ross Mackenzie, M.D., D.A. Baillière, Tindall & Cox. Pp. 136. 10s. 6d.

This book, as the title suggests, is essentially concerned with practical considerations of Anæsthesia. It should therefore prove of great help to the medical student or hospital resident who wants to know how to give an anæsthetic, what anæsthetic to give, or how to set about estimating the anæsthetic risk to the patient.

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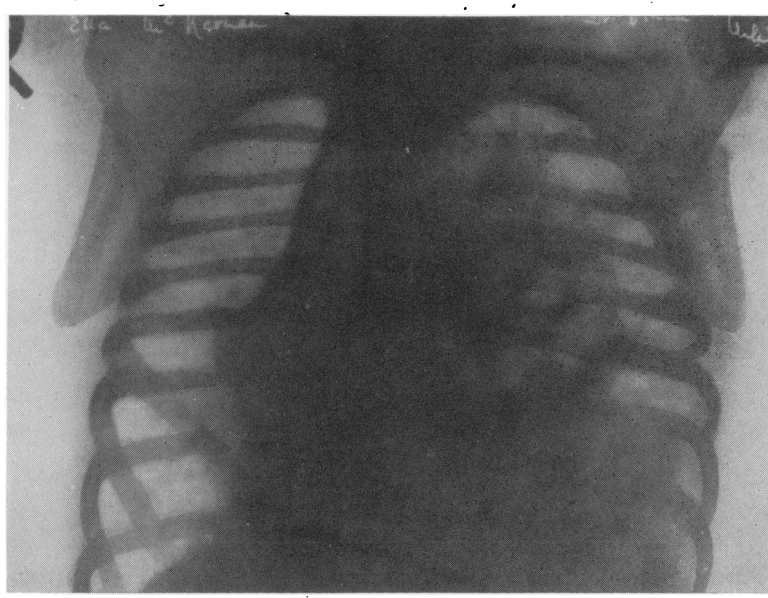
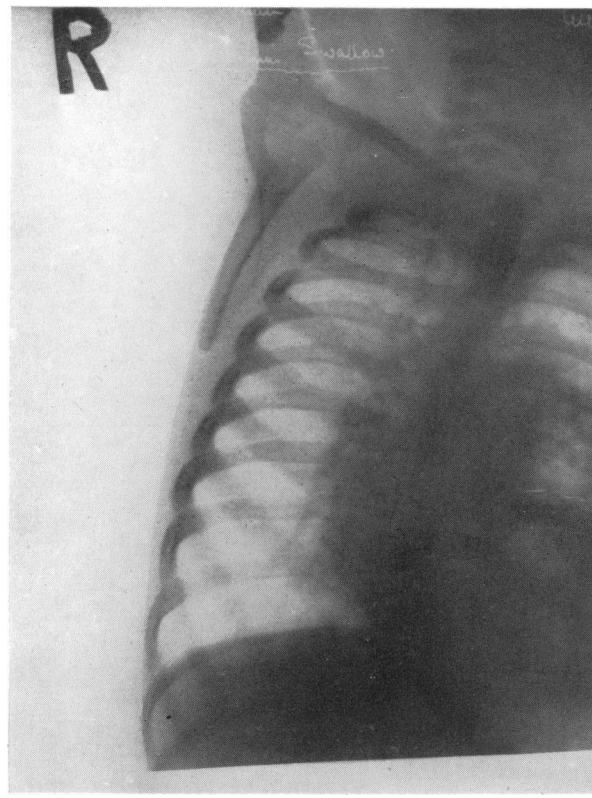


Plate I



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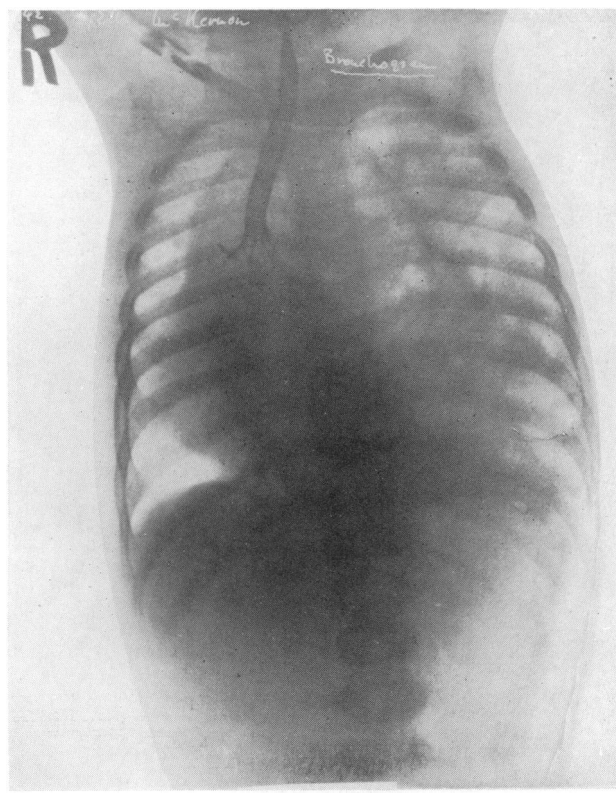

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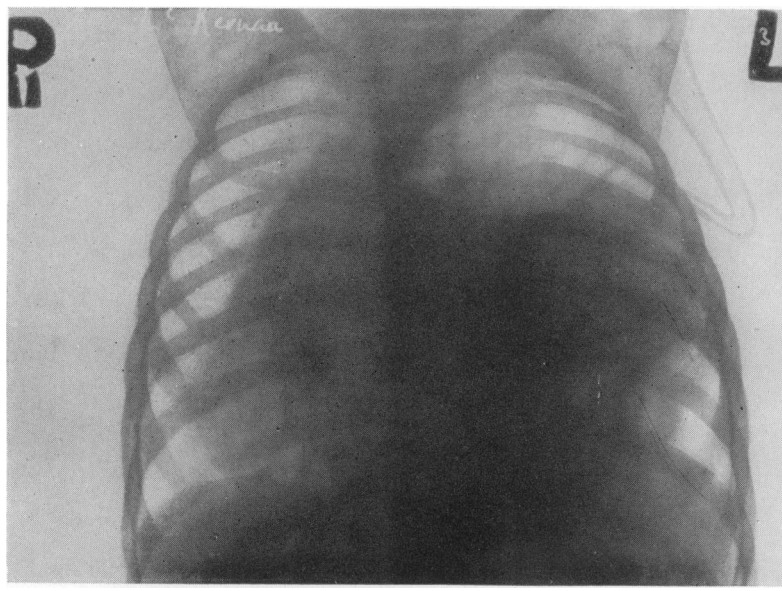

Plate IV

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The Diagnosis of Brucellosis

By C. R. MURDOCK, M.D.

from The Institute of Pathology, Queen's University

THE clinical diagnosis of undulant fever or brucellosis is frequently a matter of very great difficulty. This difficulty is made apparent by a short review of the opinions of various authors as they set them out in current textbooks of medicine. Thus, G. M. Low and N. H. Fairly in their contribution to Price's Textbook of Medicine (6th Edition) state that the differential diagnosis of undulant fever includes differentiation from "the enteric fevers, acute rheumatism, malaria, kala-azar, tuberculosis, subacute bacterial endocarditis, thoracic lymphadenoma associated with the Pel-Ebstein syndrome, amœbic abscess of the liver and occult pyogenic infections."

H. L. Amoss, in Cecil's Textbook of Medicine (6th Edition), lists, in addition to the conditions cited above, influenza, tularæmia, acute appendicitis and cholecystitis, gonorrhœal orchitis, arthritis, and neurasthenia as diseases, which infection with one of the brucella may simulate.

When the protean symptomatology of the foregoing diseases is considered, it can be readily understood that the term brucellosis can cover almost any symptom to which medical science can ascribe a name.

The textbooks lay great emphasis on the carrying out of agglutination tests in the detection of infection by the brucella. In practice, in the British Isles, it is sufficient only to consider those infections due to br. abortus, as the closely allied br. melitensis and br. suis do not occur. The agglutination test has a definite value, but further examination of the literature suggests that the investigation is not without its fallacies.

For example, Carpenter and Boak (1930) noted that in 6 per cent. of their cases in which the brucella had been isolated from the blood the agglutination test was negative. Many other authors have reported the presence of agglutinins to brucella in sera giving positive reactions with B. tularense (Francis and Evans, 1926), Pasteurella (Mallman, 1930), Vibrio choleræ (Wong and Chow, 1937), and B. typhosus and B. proteus X 19 (Shaughnessy and Grubb, 1938).

The culture of br. abortus from the blood is a matter of some difficulty and, in view of the high incidence of contagious abortion in the cattle in Northern Ireland, it was decided to attempt to evaluate the presence of agglutinins to br. abortus in the blood.

The sera of 2,073 apparently healthy blood donors were tested for specific agglutinins. Of these, 257 gave positive reactions to a titre of 1 in 10 or higher. This figure represents a percentage of 12.39.

Huddleson (1943) states that a serum agglutination in a dilution of 1 in 40 or higher should be considered to be indicative of a past infection with br. abortus. Accordingly, if the sera, reacting only in dilutions of 1 in 10 or 1 in 20, are ignored, the percentage of the population who have suffered from brucellosis is

6.5. This is slightly higher than the figure recorded for the State of Michigan (6.21 per cent.)

Cruikshank and Barbour (1931) found that less than 0.5 per cent. of the normal population give positive reactions, and similar figures are recorded by Marr (1933) in Scotland, and by Thompson (1931) in Ireland. The discrepancy between the results obtained in the present series and those for Michigan on the one hand, and those for England, Scotland, and Ireland on the other, may be due to the fact that in the case of the former the tests were all incubated for forty-eight hours, whereas there is no record, in the latter, of how long the tests were heated before being regarded as negative.

The importance of this point can be seen if reference be made to Table 4.

The distribution of the sera reacting to titres of 1 in 40 or higher between the sexes and between town and country dwellers is set out in Table 1.

TABLE 1.

	Male	Female	Town	Country
No. - -	22 ...	38 ...	65 ...	70
Percentage -	5.8 ...	7.2 ...	5.4 ...	8.0

This was all the analysis possible on the information supplied by the blood transfusion service, and so a circular letter was sent to each of the cases and, as a result, sixty of them were interviewed and further information was collected from them. Repeat agglutination tests were carried out and their sera were also tested against B. typhosus (O and H antigens), B. paratyphosus B, and enterococcus A and B. In each case the serum reacted in the same manner as before, and in no case was a positive result obtained with any of the other antigens.

Consideration of the histories of the individuals who were interviewed shows that the consumption of milk, which seems to be the most probable source of the infection, was very variable.

The daily consumption of milk by these individuals can be tabulated thus :—

TABLE 2.

Nil	Slight	½-1 Pint	1-2 Pints	More than 2 Pints
1 ...	12 ...	11 ...	26 ...	10

From this it can be seen that the majority of the cases were heavy consumers of milk, but that there was a considerable number who only took small amounts. One individual maintained that she never took milk in any form, and that she had ceased to take it from the time that she had had a severe pyrexial illness. No name for this disease had ever been given her by her doctor but, from her history, it seems probable that she had, in fact, suffered from an attack of brucellosis about nine months previously.

When the milk consumption was compared with the titre to which the corresponding serum reacted, it was found that there was no correlation whatsoever.

Professor G. S. Wilson states that the only people who show agglutinins to

br. abortus in the absence of the clinical disease are those who have direct contact with infected cattle or meat.

If the sixty persons are considered according to their employment and their contact, or possible contact, with infected cattle, the following table can be prepared.

TABLE 3.

Occupation	Number	Possible Contact with Cattle
Factory - - -	4 ...	Nil
R.U.C. - - -	1 ...	Nil
Farmer - - -	8 ...	8
Solicitor - - -	1 ...	Nil
W.R.N.S. - - -	1 ...	Nil
Schoolmaster - - -	1 ...	Nil
Housewives - - -	24 ...	1
Clerks - - -	16 ...	3
Labourers - - -	2 ...	Nil
Fishmonger - - -	1 ...	Nil
Student - - -	1 ...	Nil

The total number, who had any contact with direct infection from cattle by virtue of their employment or their private lives, is therefore twelve. That is, one-fifth of the total reacting.

Amongst the cases there were only five who gave a definite history which could be called brucellosis, and of these, none had had any contact with cattle.

It can be reasonably concluded, therefore, that occupation is not responsible, in all cases, for the appearance of agglutinins to br. abortus in the sera of these cases.

It was thought that the type of milk ingested might play a part in the production of antibodies, for, on enquiring into the source and grade of the milk consumed, it was revealed that, whereas none of the individuals drank pasteurised milk, all except three drank Grade B. The remaining three drank only Grade A.

Thus the only common denominator, so far apparent, was that all of the people concerned drank milk which was not treated or produced in such a way as to eliminate contamination.

On analysis of the histories of the cases, the most striking feature was that no less than twenty-two of them volunteered the information that they were bothered with what they called rheumatism. Four others complained of having arthritis. These observations, when compared with Huddleson's follow-up of cases which occurred in the Iowa epidemic, show a considerable degree of similarity. Huddleson states that about 40 per cent. of these positively diagnosed cases, who had recovered, complained of pains in muscles and joints. In this very small series twenty-six out of sixty (43 per cent.) made similar complaints.

In addition to the series of agglutination reactions reported above, sixty-three Widal reactions, including tests for agglutinins to br. abortus, were carried out

in the Clinical Pathology Laboratory of the Royal Victoria Hospital. In three of these there were found agglutinins to br. abortus, and these reacted in dilutions of 1 in 320, 1 in 2,560, and 1 in 2,560.

If these be included with the results of the tests on the donors' sera, the following table shows the number of positively reacting sera detected during the period of the investigation. It shows, also, the number of hours incubation in the water bath at 56°C. which were necessary to produce the reaction.

TABLE 4.

The titres to which specific serum agglutinins to br. abortus were obtained and the period of incubation necessary to produce the reaction.

Time in Hours	Highest Titre Attained						
	1/40	1/80	1/160	1/320	1/640	1/1280	1/2560
4	0	0	2	4	0	2	2
12	4	3	3	5	0	2	3
24	12	8	6	7	0	2	3
48	77	31	16	9	0	2	3

From this it can be seen that in the two highest dilutions the reaction was complete, in four of the five cases, in four hours, whereas in the lower dilutions no reaction had occurred at this stage.

Not all of these 138 cases were suffering from active brucellosis, and so an attempt was made to correlate the rapidity of reaction with the activity of the disease.

For this purpose the histories of the twenty individuals whose sera had completed the reaction in twelve hours or less, were examined more closely, and the findings are drawn up in table 5.

TABLE 5.

Histories, titres, and prozones of those cases with rapidly reacting sera.

Titre	Prozone	History
2560	Up to 160	Definite, with positive blood culture.
2560	80	Definite of infection.
2560	None	Rheumatism.
1280	160	Definite of infection.
1280	80	Typical attack three months before.
320	None	Not seen.
320	,,	Rheumatism.
320	,,	Rheumatism.
320	,,	Rheumatism.
320	,,	Not seen.
160	,,	Sciatica.
160	,,	Nil.

Titre		Prozone		History
160	...	None	...	Sciatica.
80	...	,,	...	Rheumatism.
80	...	,,	...	Rheumatism.
80	...	,,	...	Rheumatic fever.
40	...	,,	...	Positive history of undulant fever.
40	...	,,	...	Chorea.
40	...	,,	...	Nil.
40	...	,,	...	Nil.

Recently there have been three further cases, one of which has been confirmed by blood culture, in which the reaction was complete in twelve hours and in which there has been a prozone in the order of 1 in 160.

If the two tables above are considered, the question arises as to how the results of agglutination reactions are to be interpreted. Are all reactions which occur to be looked upon as indicative of active disease? This can only be denied, for, as has been shown, very few of the persons found to have specific serum agglutinins have had any history of the disease, and experience shows that the number of actively infected people does not amount to 6.5 per cent. of the population.

From the tables it seems that the sera showing a high titre react much more rapidly and that the majority of these people have, or have had, some illness which is suggestive of a clinical diagnosis of undulant fever. It seems that, when all the cases in which the reaction was complete in twelve hours are considered with regard to their histories, the majority of them show some evidence of an illness which might be due to infection with br. abortus.

If a serum reaction is to be considered to be diagnostic of undulant fever, it seems that the further conditions to be fulfilled are :—

1. The reaction must be complete in twelve hours or less.
2. The titre attained must be at least 1 in 40. (If marked prozone is present, it seems to indicate that the illness is acute.)
3. There must be some definite clinical evidence of the disease.

It remains to consider the case in which there is no agglutination reaction. Huddleson states that, in his experience, the majority of those cases which occur in children in the United States do not show any agglutinins in their blood during the course of the disease. One such case came under observation. This was a child who had completely unexplained pyrexia and who had a negative agglutination reaction. The physician in charge of the case remembered a previous case in which the milk supply was the same as that of the child under consideration. As this previous case was one of undulant fever, a blood culture was carried out, and after prolonged incubation it was positive.

It is therefore possible for a patient to be suffering from undulant fever in spite of a negative agglutination reaction.

Additional investigations which can be carried out in an attempt to establish such a diagnosis in obscure cases were also investigated.

Brucellergen.—This is the name given to a protein nucleate fraction of brucella organisms. It is a preparation made at the Michigan State College Agricultural Experiment Station by the method described by Huddleson. The test is designed to detect skin allergy to brucella, and it is claimed to be highly satisfactory and specific. Brucellergen is not available in British markets, and I am indebted to Dr. Huddleson for a supply.

The test is carried out by inoculation of 0.1 cc. of the material into the skin of the lateral surface of the forearm. In positive cases the local reaction consists of a circumscribed erythema, œdema, and induration. The area involved varies from 2 to 10 cm. in diameter. The reaction is read in twenty-four and forty-eight hours, and a positive result may persist for seven days. In the actively infected case the local reaction may be accompanied by a more marked manifestation of the symptoms already present. Those people who are hyper-sensitive show a marked systemic reaction in addition to the local reaction. Sometimes there is a small erythematous area around the site of inoculation, and this is considered to be a non-specific reaction.

The skin reactions to the brucellergen are recorded and are to be interpreted as follows :—

1. E. - Erythema—no significance.
2. + + - Oedema and erythema 2 cm. in diameter.
3. + + + - Oedema and erythema more than 2 cm.
4. + + + + - Oedema and erythema more than 2 cm. and mild systemic reaction.
5. + + + + + - Oedema and erythema more than 2 cm. and marked systemic reaction.

Some of the cases with specific serum agglutinins to br. abortus were subjected to intradermal tests with brucellergen. There was no correlation apparent between the titre attained in the agglutination test and the reaction obtained with brucellergen. On the other hand every one of the cases tested for skin sensitivity gave a positive reaction according to Huddleson's classification.

TABLE 6.

Allergic reactions according to Huddleson's technique.

	E.	+ +	+ + +	+ + + +	+ + + + +
Total -	0 ...	12 ...	10 ...	7 ...	1

Thus thirty cases were tested and they all gave positive reactions.

Further tests were carried out on a very small scale on persons who had not been tested for agglutinins. Twenty-seven in all were tested and they gave the following results :—

TABLE 7.

Allergic reactions of twenty-seven supposedly normal individuals.

	Nil	E.	+ +	+ + +	+ + + +	+ + + + +
Total -	12 ...	11 ...	4 ...	0 ...	0 ...	0

From the table it can be seen that 15 per cent. of these people gave positive

reactions to brucellergen. This figure is very close to that given for the State of Michigan by Huddleson (16.6 per cent.)

Agglutination reactions were subsequently carried out on these people and none of them had agglutinins in their sera.

It is evident then, that brucellergen skin-testing is of considerable use when applied at the same time as an agglutination reaction, and when both are carefully considered in conjunction with the clinical signs and symptoms. Care must be exercised in view of the very considerable numbers of individuals with allergy to brucellergen due to an acquired active immunity.

The Opsonophagocytic Test in the Diagnosis of Brucellosis.

This test was first used in the detection of meningococcal infection by Sir Thomas Houston and J. C. Rankin. Recently their technique has been modified and has been applied to cases suspected of being infected with brucella.

The test is carried out by adding 0.1 cc. of citrated blood (0.2 cc. 20 per cent. sodium citrate to 5 cc. blood) to 0.1 cc. of a bacterial suspension of br. abortus. After thorough mixing the suspension is heated in the water bath for thirty minutes at 37°C. After incubation the cells are again suspended by gentle shaking. Blood films are then made in the usual manner. The film should be dried as rapidly as possible in the air. The smears are then stained by one of the Romanovsky stains.

Twenty such tests were carried out and they were interpreted according to Huddleson. The system for recording results is :—

Negative	-	No bacteria ingested by the polymorphonuclear leucocytes.
Slight	-	1 to 20 bacteria ingested per cell (25 cells being examined and the average counted).
Moderate	-	20 to 40 bacteria ingested.
Marked	-	Over 40 bacteria ingested.

The percentage of cells showing phagocytic action is also estimated.

Table 8.

Allergic, agglutination, and opsonophagocytic reactions.

O-P Test Average Number of Bacteria Ingested	Percentage of Cells Showing Phagocytosis	Titre	Skin Allergy
33	27	1280	+ + + +
42	61	320	+ +
35	60	160	+ +
40	63	160	+ +
29	63	40	Nil
37	29	320	+ + +
41	26	320	+ + + + +
42	69	80	Nil
39	62	40	+ + +
30	80	40	+ +

O-P Test Average Number of Bacteria Ingested	Percentage of Cells Showing Phagocytosis	Titre	Skin Allergy
44	67	40	+ +
42	67	40	+ + +
46	60	40	+ +
42	21	2560	+ + + +
40	64	80	+ +
31	67	320	+ +
44	70	40	Nil
27	60	40	+ + +
29	63	40	Nil
31	39	320	+ + +

Huddleson, in an attempt to evaluate the conditions which can be diagnosed as brucellosis in the presence of the various laboratory findings, drew up the following scheme giving the possible combination of results.

Agglutination Reaction	Brucellergen Test	Opsonophagocytic Power of Blood	Status Toward Brucella
Negative	Negative	0 to 20% cells showing slight phagocytosis.	Susceptible
Negative	Positive	0 to 40% cells showing marked phagocytosis.	(?) Infected
Positive	Positive	0 to 40% cells showing marked phagocytosis.	Infected
Negative	Positive	60 to 100% cells showing marked phagocytosis.	Immune
Positive	Positive	60 to 100% cells showing marked phagocytosis.	Immune

If the cases on whom the opsonophagocytic tests were carried out are considered in this light, it can be seen that fifteen were immune, four were infected, and one was possibly infected. When their histories were referred to it was found that in fact these four were actively infected or had just recovered from an attack of undulant fever.

Of the remaining fifteen tested for their opsonophagocytic activity, three had histories which were, at least suggestive, of brucellosis. Four others gave the history that there had been outbreaks of contagious abortion among the cattle on the farms where they lived. It is probable that all seven of these individuals had acquired an immunity to br. abortus through active infection or through contact with infected animals.

From this small series of cases it is seen that the difficulty of laboratory diagnosis of undulant fever is considerable and that no one test is infallible. Agglutination reactions, while of help, may unfortunately give a positive result when, in fact, the patient has not got an active infection and, what is more important, if the frequency of the prozone phenomenon is not remembered, tests may be reported as negative when they really react only at a high titre. The test may be altogether negative when the patient, especially a child, is suffering from a severe reaction.

The employment of brucellergen would be of help, but the material is not commercially available in the British Isles and the manufacture of it is so complicated as to prevent its production in the routine laboratory.

The opsonophagocytic test, carried out in conjunction with the two other tests, is of some value, but it is very doubtful if the labour involved would be justified by the results obtained.

Blood culture is the only truly reliable positive finding and, unfortunately, the culture of the brucella from the blood is a matter of no little difficulty. The blood ought to be cultured in a special medium. The best of these would seem to be a product of the Difco Laboratories. It is a proprietary product and the trade name is bacto-tryptose digest.

Positive blood cultures will not be obtained even with this medium unless the cultivation is carried out under increased carbon dioxide tension.

These methods have been employed in a number of cases and four positive cultures obtained. One of these was in a child who never developed any agglutinins to the standard antigen or to her own infecting organism. All four of the cultures required at least fifteen days incubation before the brucella was isolated.

There ought to be many more blood cultures carried out on so-called pyrexias of unknown origin when undulant fever is suspected, but the suggestion must be put before the laboratory staff so that the proper methods, which cannot be employed as a routine, may be used.

I wish to express my indebtedness to Professor J. H. Biggart and Dr. N. C. Graham for their help and encouragement.

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REVIEWS

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The introductions at the beginning of the sections on gonorrhœa and syphilis are very fine, and give a rapid general picture of the conditions, which are further elaborated in the corresponding sections, whilst the various stages of the diseases themselves are illustrated by an excellent series of reproductions. Several small but important points have not been overlooked, such as the danger of transmission of venereal diseases before clinical evidence of the diseases has become manifest, and the importance of care and tact in history-taking. The importance of correct interpretation of Wasserman results is again brought out, and a particularly interesting chapter is written about the causation, pathology, and treatment of jaundice during arseno-therapy in syphilis. The treatment of the various conditions is well set out, though not all venereologists will agree with the dosage schemes suggested, especially in the chemotherapy of syphilis, whilst the suggested dosage of M.&B. 693 for the treatment of gonorrhœa in the female out-patient seems rather inadequate, even in spite of the danger of minor toxic effects produced by larger dosage of the drug.

The section on "Technique" is simple and to the point, the more elaborate procedures beyond the scope of the average practitioner being omitted. The Sociology of Venereal Diseases is stressed in a timely word, the importance of gaining the patient's co-operation and the follow-up of defaulters is pointed out and suggestions are outlined on possible means of improving the sociological aspect of venereology.

The newer methods of treatment of Venereal Diseases, such as penicillin and massive arseno-therapy, have purposely been given only a passing word, only those methods being described in detail which are within the reach and scope of the average medical practitioner.

As a whole, this is another excellent and attractive book which can be recommended with complete confidence to both the medical student reading for his final M.B., or to the busy practitioner who wishes to revise his knowledge of the Venereal Diseases. J. S. McC.

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In order to keep down the size of a book of this kind, written as it is for students and general practitioners, the introduction of new material calls for the deletion of old. The selection of what to include has been very successfully carried out, so that with its multitude of illustrations and many coloured plates, the new edition should easily maintain the position held by the earlier editions of this valuable textbook.

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